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Synthesis and structure analysis of the novel 4-(2-aminoethyl)morpholine substituted cyclotriphosphazene

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Abstract: In this study, the reaction of hexachlorocyclotriphosphazene with 4-(2-aminoethyl) morpholine which is a primary amine was carried out in the presence of Trimethylamine in THF. The molecular structure of the final compound was confirmed by mass spectrometry, FT-IR, ^{31}P, ^{1}H and ^{13}C NMR spectroscopies. The possible progress mechanism of the reaction was proposed using the structure analysis of the product formed.

Keywords: Cyclotriphosphazene, aminoethylmorpholine, NMR

Yeni 4-(2-aminoetil)morfolin substitüe siklotrifosfazenin sentezi ve yapı analizi

Özet: Bu çalışmada, hekzaklorosiklotrifosfazenin primer bir amin olan 4-(2-aminoetil) morfolin ile reaksiyonu THF içerisinde trimetilamin varlığında gerçekleştirilmiştir. Final bileşiğin moleküler yapısı, kütle spektrometresi, FT-IR ^{31}P, ^{1}H ve ^{13}C NMR spektroskopi teknikleri ile doğrulandı. Oluşan ürünün yapı analizi kullanılarak, reaksiyon için olası ilerleme mekanizması önerildi.

Anahtar Kelimeler: Siklotrifosfazen, aminoetilmorfolin, NMR

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1 INTRODUCTION

Hexachlorocyclotriphosphazene ring is an important member of inorganic ring systems [1-3]. This ring is renowned for the robustness of the phosphorus-nitrogen backbone and active phosphorus-chlorine bonds that enable nucleophilic substitution reactions [1-5]. The planar molecular geometry of the cyclotriphosphazene ring, its resistance to heat, light and different reaction conditions, and its ability to combine multiple groups with the same or different properties in the same molecule make this ring an indispensable carrier framework for new material designs [1, 2, 6-8]. Depending on the number, type and properties of the functional group carried by the cyclotriphosphazene ring, fluorescence chemosensor [6, 7], anticancer [8, 9], antimicrobial agents [10], organic light emitting diodes [11,12], biosensor [13] and photosensitizer [14, 15] applications have been successfully demonstrated. Therefore, the nucleophilic substitution reactions of the cyclotriphosphazene ring with different functional groups, the diversity of the products formed and the potential application areas attract attention.

The progression pathway of the substitution reactions in the cyclotriphosphazene ring depends on many parameters, especially electronic, steric and mechanistic effects [16-21]. Thus, a great deal of effort has been devoted to elucidate the preference of geminal and non-geminal reaction pathways in cyclotriphosphazene derivatives [4, 19, 20, 22-24]. When electron-donating units are attached to the cyclotriphosphazene core, the positive charge on the P atoms decreases and then their reaction with monofunctional alkoxy groups proceeds in the non-geminal route [19]. The substitution reactions of cyclotriphosphazenes with secondary amines generally tend to form non-geminal product, while the formation of geminal products with primary amines predominate due to polar environment or steric factor [4, 18, 24-26].

Morpholine is a heterocyclic ring containing oxygen and nitrogen atoms in its structure, and it is a bioactive molecule often preferred in medical applications [27-29]. The reactions of morpholine, a secondary amine, and cyclotriphosphazene were investigated and it was reported that non-geminal products were dominant [23]. The di-, tri- and tetra-non-geminal replacements in cyclotriphosphazenes often lead to a mixture of *cis*- and *trans*- isomers [19, 23, 26, 30]. In this study, the reaction of hexachlorocyclotriphosphazene (**1**) with 4-(2-aminoethyl) morpholine (**2**) which is a primary amine was carried out and the progression route of the reaction was investigated from the structure analysis of the obtained product.

2 MATERIALS VE METHODS

2.1. General methods

All the precursors chemical reagents and solvents were procured from commercial suppliers. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck, Kieselgel 60 Å, 0.25 mm thickness) with F_{254} indicator. Column chromatography was performed on silica gel (200-400 mesh). Mass spectra were acquired in linear modes with average of 50 shots on a Bruker Daltonics Microflex mass spectrometer (Bremen, Germany) equipped with a nitrogen UV- Laser operating at 337 nm. ^{31}P, ^{1}H and ^{13}C NMR spectra were measured with a 400 MHz spectrometer (Varian 400 MHz).

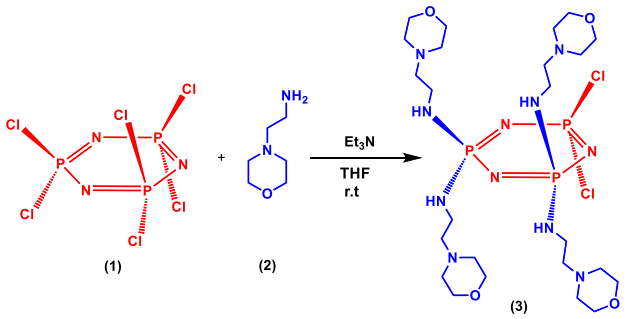
2.2. Synthesis of 4-(2-aminoethyl)morpholine substituted cyclotriphosphazene (3)

4-(2-aminoethyl)morpholine (**2**) (3 mL, 23.0 mmol) was dissolved in 20 mL of dry THF in a 100 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and triethylamine (3.2 mL, 23.0 mmol) was quickly added to the stirred solution. Then, hexachlorocyclotriphosphazene (**1**) (1.0 g, 2.9 mmol) in dry THF (10.0 mL) was added to the medium. The reaction mixture was stirred for 4 days at room temperature and followed by TLC silica gel plate. The triethylamine hydrochloride (NEt_3.HCl) and any other in soluble materials were filtered off. The solvent was removed under reduced pressure. The crude product was subjected to column chromatography using THF:methanole: *n* - hexane (90:9:1) as the mobile phase. The product (0.40 g, 17 %) was obtained as oily. MALDI TOF (m/z) Calc. 721.08, Found: 721.28 $[M]^+$, 1076.85. ^{31}P NMR (162 MHz, $CDCl_3$, ppm) δ_P 24.1 (t, 1P), 14.3 (d, 2P). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ_H 3.6 (m, 16H) ($-OCH_2$), 3.1 (s, 4H) (-NH), 3.0 (m, 8H) ($-NCH_2$), 2.4 (m, 8H) ($-NCH_2$), 2.4 (m, 16H) ($-NCH_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C 66.8, 58.9, 53.3, 37.0. FT-IR (ν : cm^{-1}): 3110.13 (N-H); 2954.91, 2856.20 and 2813.54 $(C-H)_{aliphatic}$; 1655.19 (N-H); 1222.77 and 1176.74 (P=N) ; 1116.48 (C-O) and 971.69 (P-N-C).

3 RESULT AND DISCUSSION

3.1. Synthesis and structural characterization of 4-(2-aminoethyl)morpholine substituted cyclotriphosphazene derivative

Cyclotriphosphazene ring is an important class of molecules consisting of six peripheral arms [1-3]. Cyclotriphosphazene derivatives are easily prepared by the nucleophilic substitution of reactive chlorine atoms with different reagents, and their structural, physical and chemical properties can be easily modulated by substituents [4, 5, 19-23]. In this study, the 4-(2-aminoethyl)morpholine substituted cyclotriphosphazene derivative (**3**) was synthesized (Scheme 1). The compound **3** was prepared by treating hexachlorocyclotriphosphazene (**1**) with 4-(2-aminoethyl) morpholine (**2**) in the presence of Et_3N in THF. The product was purified by column chromatography and then the molecular structure of the final compound was confirmed by mass spectrometry, FT-IR, ^{31}P, ^{1}H and ^{13}C NMR spectroscopies. The molecular ion peak of the compound was marked as 721.07 Da by MALDI-TOF mass spectrometer (Fig.1). The MS data of the novel compound confirmed that the four chlorine atoms on the cyclotriphosphazene core had been replaced by the morpholine group.



Scheme 1. Synthesis pathway of 4-(2-aminoethyl) morpholine substituted cyclotriphosphazene derivative

FT-IR spectrum of compound **3** exhibited characteristic stretching bands for P=N- at 1222.77 and 1176.74 cm^{-1}. The vibration band assignable to the stretching of the N-H was observed at 3110.13 cm^{-1}. The stretching bands of aliphatic C-H was seen about 2856 cm^{-1} and peaks of C-O was observed about 1116.48 cm^{-1} (Fig.2). However, these analyses were insufficient about whether the displacement occurred via geminal or non-geminal. The NMR spectra of the novel compound were examined to explain this situation. The proton decoupled ^{31}P NMR spectrum of the compound **3** was observed as an AX_2 spin system due to two different phosphorus environments within the molecule (Fig. 3). The signals of the compound **3** consisted of one triplet for the $[PCl_2]$ group at 24.1 ppm and a doublet for the $[P(NR)_2]$ groups at 14.3 ppm. The coupling constant for phosphorus atoms was calculated as 47.5 Hz. The ^{31}P NMR data confirmed the geminal displacement of four 4-(2-aminoethyl) morpholine groups with chlorine atoms. Further structural verification was obtained via ^{1}H and ^{13}C NMR spectroscopies. The -OCH_2 and -NCH_2 protons of morpholine ring were marked at 3.6 and 2.4 ppm, respectively. The characteristic -NH protons were observed at 3.1 ppm as broad signal. The other aliphatic -NCH_2 protons gave signals at 3.0 and 2.4 ppm (Fig. 4).

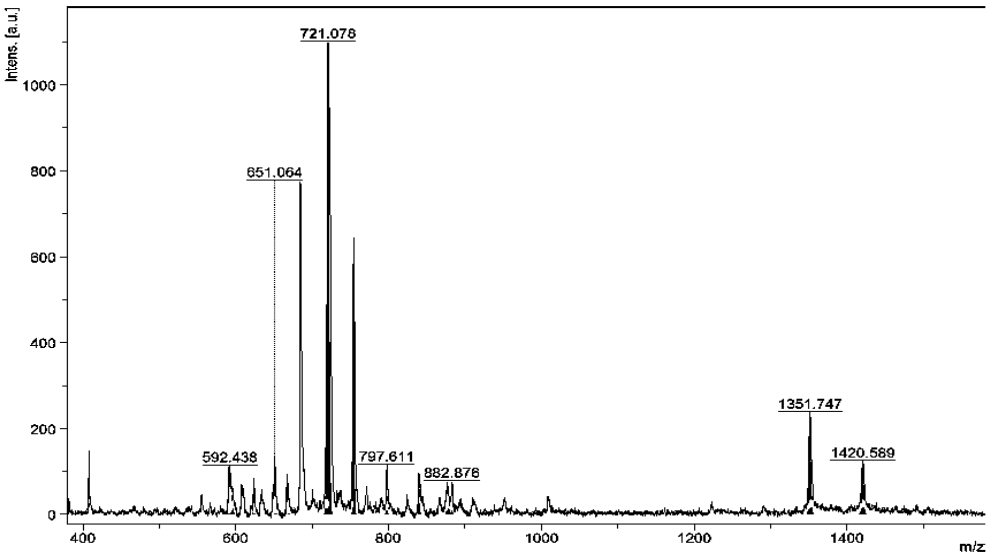


Figure 1. The MALDI-TOF mass spectrum of compound **3**

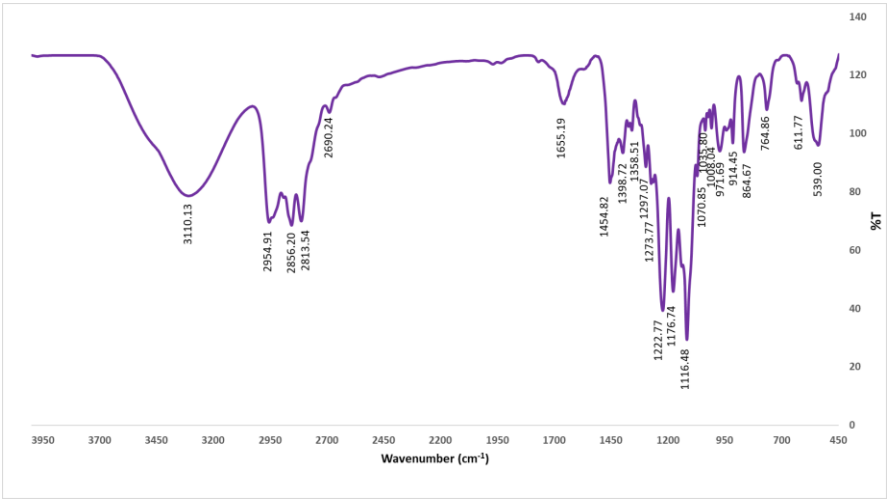


Figure 2. FT-IR spectrum of compound **3**

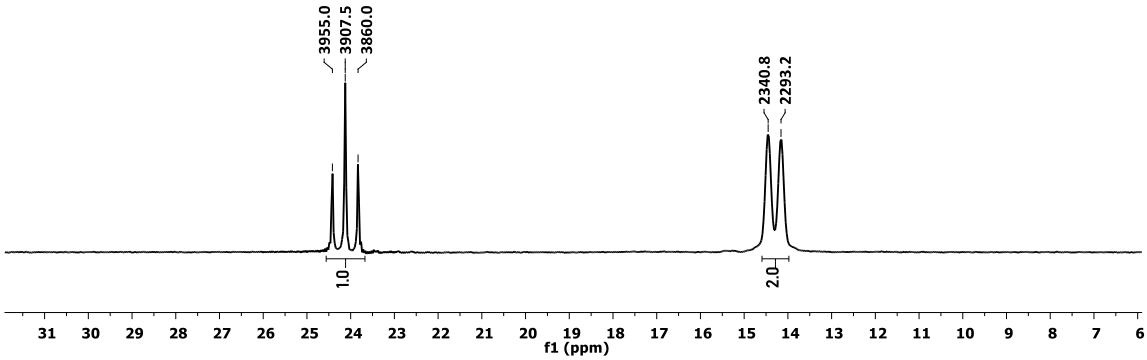


Figure 3. The ^{31}P NMR (^{1}H decoupled) spectrum of compound **3**

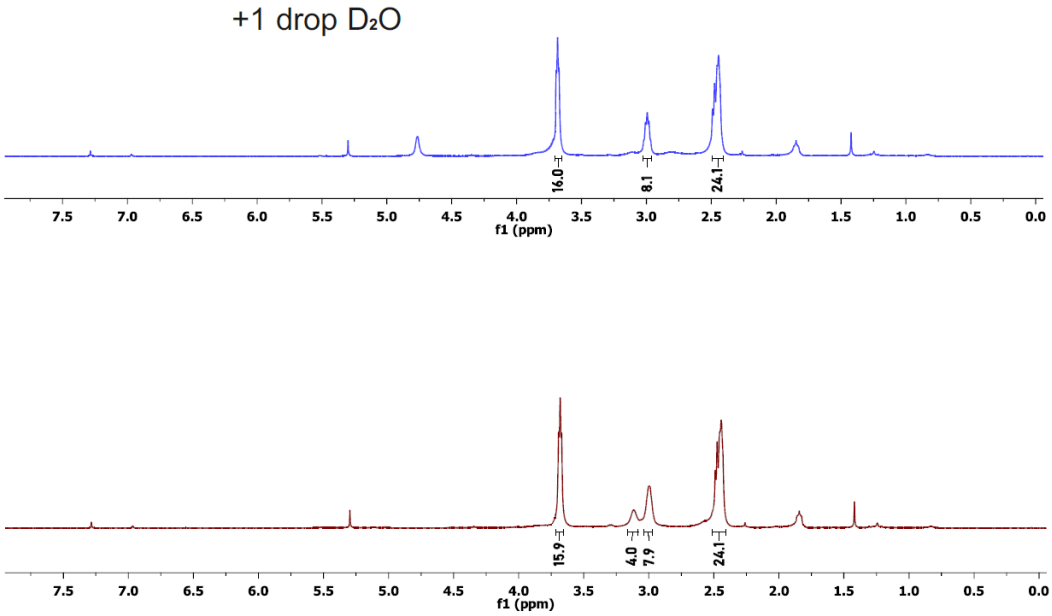


Figure 4. The ^{1}H NMR spectrum of compound **3** in $CDCl_3$

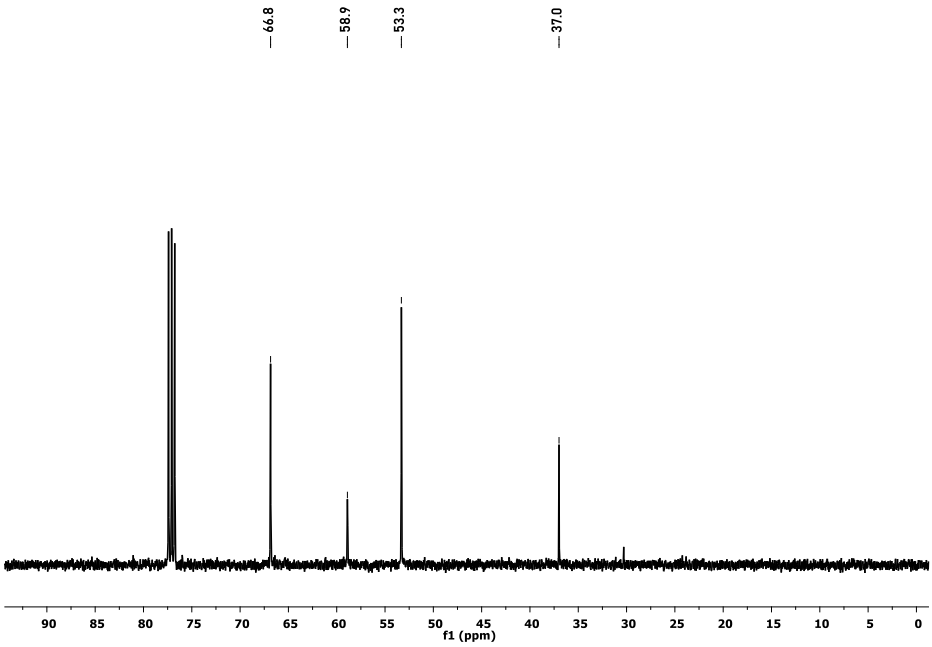


Figure 5. The ^{13}C NMR spectrum of compound **3**

The location of the NH- protons was also confirmed by D_2O exchange in ^1H NMR (Fig 4). As expected, four different carbon signals (66.8, 58.9, 53.3, 37.0) were seen in the ^{13}C NMR spectrum (Fig. 5). All NMR spectra of the final compound (**3**) was consistent with molecular structure.

3.2. Chlorine replacement pattern

The nucleophilic displacement reactions of cyclotriphosphazene derivatives result in the formation of geminal and non-geminal *cis*- or *trans*- isomers due to kinetic, thermodynamic and steric effects [4, 18-24]. Previous works have shown that the non-geminal *trans*-product is formed as the predominant product and the *cis*-isomer was a minor product at the di-substitution stage of the reaction of hexachlorocyclotriphosphazene with morpholine, a secondary amine [23]. In the current work, outcomes from ^{31}P NMR and MALDI-TOF mass data of the cyclotriphosphazene derivative including 4-(2-aminoethyl) morpholine units pointed to the formation of geminal product (**3**). Similar product formations with primary amines such as aniline, cyclopropanemethlyamine and *t*-butylamine are available in the literature [4, 25, 31]. It can be said that S_N1 and proton abstraction-chloride elimination mechanism go together for the formation of the compound **3**. In this reaction pathway, triethylamine used as the base abstracted a proton from the PCl(NHR) center in the cyclotriphosphazene ring, resulting in loss of chloride ion and a three-coordinate phosphoranimine intermediate is formed. With the attack of another amine group on this phosphoranimine, a geminal substitution product is formed.

4 CONCLUSIONS

In this work, the synthesis of 4-(2-aminoethyl) morpholine substituted cyclotriphosphazene derivative was described. The final compound was isolated in moderate yield by simple column chromatography. The molecular structure of the compound (**3**) was confirmed by mass spectrometry, FT-IR, ^{31}P, ^1H and ^{13}C NMR spectroscopies. The formation of the geminal product was explained by the combined action of S_N1 and proton abstraction-chloride elimination mechanisms. The new compound may be useful as antimicrobial or antifungal agents owing to containing its morpholine moieties.

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Conflict of interest
The authors declare no competing financial interest.

Ethical Approval
Ethics Approval is not required for this study.

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