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Research paper

Phosphorus-nitrogen compounds. Part 40. The syntheses of (4-fluorobenzyl) pendant armed cyclotetraphosphazene derivatives: Spectroscopic, crystallographic and stereogenic properties, DNA interactions and antimicrobial activities

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ABSTRACT

The Cl substitution reaction of octachlorocyclotetraphosphazene, $N_4P_4Cl_8$ (**1**), with 1.2 equimolar amounts of sodium salt of N/O donor-type bidentate ligand (**2**) gave four different new (4-fluorobenzyl) pendant armed cyclotetraphosphazene derivatives; namely, mono-(4-fluorobenzyl)-spiro- (spiro; **3**), mono-(4-fluorobenzyl)-2-*cis*-4-dichloro-ansa- (2,4-ansa; **4**), bis-(4-fluorobenzyl)-2-*trans*-6-dispiro (**5**) and bis-(4-fluorobenzyl)-2-*trans*-4-dispiro (**6**) cyclotetraphosphazenes of which **3** was the major product (yield 55%). Compound **3** was treated with mono and difunctional reagents to prepare the fully substituted products (**3a-3j**) due to its very high yield. However, tetrapyrrolidino-2-*cis*-4-dichloro-ansa- product (**4a**) was obtained from the reaction of 2,4-ansa (**4**) with excess pyrrolidine. The new cyclotetraphosphazenes were characterized by elemental analyses, mass spectrometry (ESI-MS), Fourier transform infrared (FTIR), ^1H, ^{13}C, and ^{31}P NMR techniques. The structures of **3** and **3g** were determined by X-ray crystallography. 2,4-Ansa compounds (**4** and **4a**) have two stereogenic P atoms. The stereogenic property of **4** was identified by ^{31}P NMR spectra in the addition of the chiral solvating agent, (R)-(+)-2,2,2-trifluoro-1-(9′-anthryl)-ethanol (CSA). The tetraspiro compounds (**3i** and **3j**) look similar to a propeller, and they may have P and M atropisomers. The antimicrobial activities of the compounds were screened against some G(−)/G(+) bacteria and yeast strains. The interactions of the compounds with supercoiled plasmid pBR322 DNA and their inhibited DNA restriction were examined.

1. Introduction

Octachlorocyclotetraphosphazene [tetramer, $N_4P_4Cl_8$ (**1**)] is a highly reactive inorganic heterocyclic ring system which is a starting material used in the syntheses of new substituted cyclotetraphosphazene derivatives [1,2]. The investigations of the substituent exchange reaction patterns of Cl atoms in tetramer with monodentate ligands, such as amines and alkoxides, are substantially examined in the literature [3–5]. However, the reactions of $N_4P_4Cl_8$ with the bifunctional (diamines, dialkoxides and aminoalkoxides) and polyfunctional (polyamines, polyaminoalkoxides and polyalkoxides) reagents are quite limited [6–10]. The partly and fully substituted products, e.g. spiro, ansa, bino, dispiro, spiroansa, spirobino, trispiro, tetraspiro, spiroansa-spiro and ansa-spiroansa, were produced as the result of these condensation reactions depending upon the substituents and reaction conditions [8,10,11,12]. Furthermore, as a result of the reactions, the geometrical (geminal and *non*-geminal *cis*/*trans*) and optical isomers ought to be obtained. The chiralities of the cyclotetraphosphazenes have also been the exciting topic in recent years [8,13–15]. But, the separations, purifications and characterizations of the geometrical and optical isomers of these products are very difficult in some cases [14]. In the literature, there are a pretty small number of papers investigating the stereogenic properties of the tetrameric phosphazenes using ^{31}P NMR spectroscopy in the addition of (*R*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)-ethanol (CSA) and by the chiral HPLC techniques [8,15].

Besides, some of the organocyclophosphazenes have attracted much interest in their diverse chemical, technological and biological applications, eg. the utilization as ligands and strong bases in

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coordination and organometallic chemistry [16], preparation of the phosphazenes polymers because of a great deal of the flexibility of phosphazene ring [17], dendrimers [18], liquid crystalline materials [19], ionic liquids [20], flame retardant additives [21], fluorescence chemosensors [22], photosensitizers [23], Langmuir–Blodgett thin films [24], and antibacterial, antifungal, anti-cancer and antituberculosis agents [8,15,25,26].

On the other hand, the N/O donor-type bidentate ligand, sodium 3-(4-fluorobenzylamino)-1-propanoxide (**2**), used as the starting material in the present study treated with hexachlorocyclotriphosphazene (trimer, $N_3P_3Cl_6$) to obtain only the spirocyclotriphosphazenes, regioselectively [27]. But, it was observed in this study that $N_4P_4Cl_8$ and **2** gave four kinds of compounds; namely, mono-(4-fluorobenzyl)-spiro- (**3**), mono-(4-fluorobenzyl)-2-*cis*-4-dichloro-ansa-(**4**), bis-(4-fluorobenzyl)-2-*trans*-6-dispiro (**5**) and bis-(4-fluorobenzyl)-2-*trans*-4-dispiro (**6**) cyclotetraphosphazenes.

Eventually, the present work essentially focuses on the Cl replacement reactions of $N_4P_4Cl_8$ with 1.2 equimolar amounts of **2** (Scheme 1) for assessment of the spectroscopic, crystallographic and stereogenic properties, antimicrobial activities and the pBR322 DNA interactions of the cyclotetraphosphazenes.

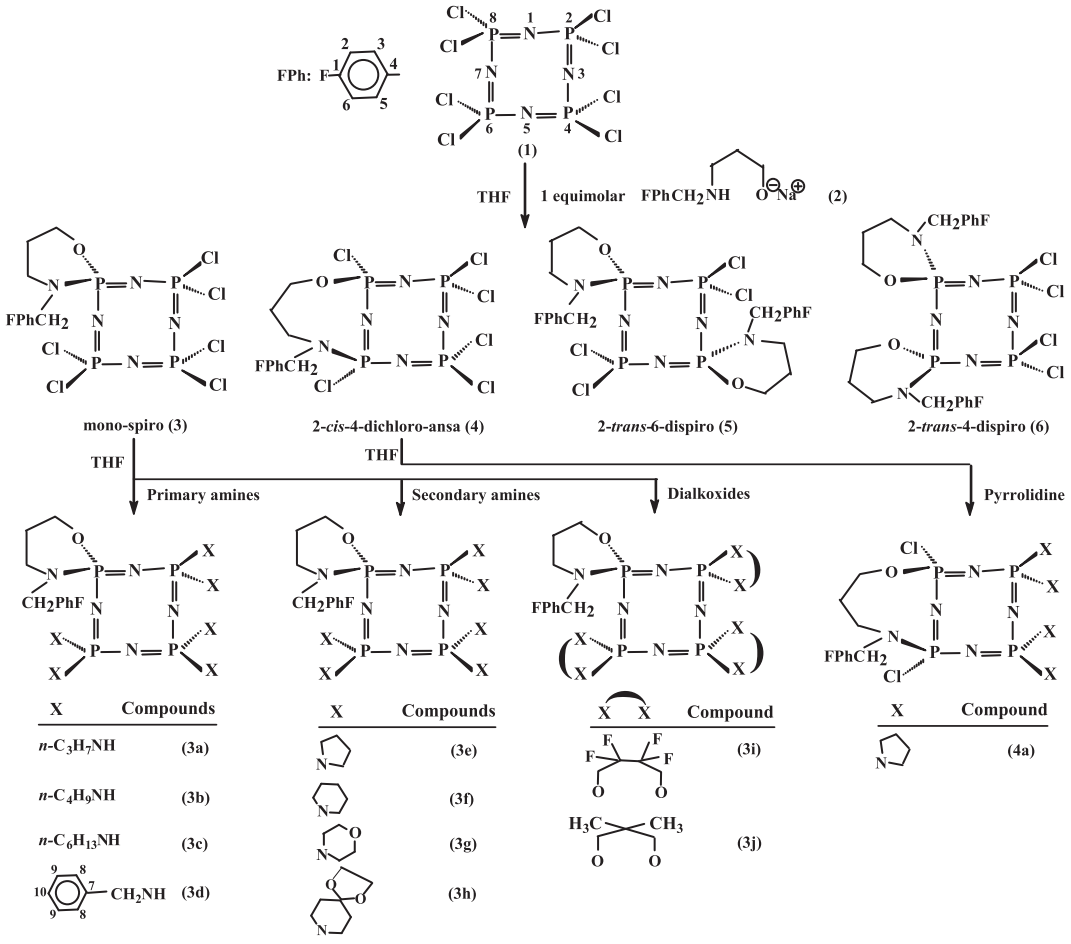
2. Experimental part

2.1. Materials and method

The condensation reactions were pursued by thin-layer chromatography on Merck DC Alufolien Kiesegel 60 B_{254} sheets in suitable solvents. The column chromatography was realised on the Merck Kiesegel 60 (230–400 mesh ATSM) silica gel. The melting points of the obtained compounds were determined with a Gallenkamp apparatus using a capillary tube. The elemental analyses were carried out using the Leco CHNS-932 instrument. ESI mass spectra of the products were enrolled with a Waters 2695 Alliance Micromass ZQ spectrometer. The FTIR spectra were recorded on a Jasco FT/IR-430 spectrometer in KBr discs. ^{1}H and ^{13}C {^{1}H} NMR spectra of all the cyclotetraphosphazenes were monitored on a Varian Mercury FT-NMR (400 MHz) spectrometer using $SiMe_4$ as an internal standard operating at 400.13 MHz and 100.62 MHz, respectively. ^{31}P {^{1}H} NMR spectra were saved on a Bruker Avance III HD (600 MHz) spectrometer using H_3PO_4 (85%) as an external standard operating at 242.94 MHz. Experiments involving the CSA were done by the addition of small aliquots of a concentrated solution of the CSA in the solvent used in NMR spectroscopy, and the ^{31}P {^{1}H} NMR spectra were recorded for each addition. The spectrometers were fitted with the 5 mm PABBO BB inverse-gradient probe, and the standard Bruker pulse programs [28] were employed. The microanalyses were designated by the microanalytical service of Ankara University (FTIR, ESI-MS, ^{1}H and ^{13}C {^{1}H} NMR) and İnönü University (^{31}P {^{1}H} NMR).

2.2. Materials used in the syntheses

The Cl replacement reactions were performed under Ar atmosphere. The organic solvents were dried and purified using the standard methods. $N_4P_4Cl_8$ (Otsuka and recrystallized from hot



Scheme 1. Phosphazene derivatives obtained from the reactions of $N_4P_4Cl_8$ (**1**) with **2**, and amino and/or dialkoxy derivatives of the compounds (**3** and **4**).