

Phosphorus–nitrogen compounds: Part 26. Syntheses, spectroscopic and structural investigations, biological and cytotoxic activities, and DNA interactions of mono and bisferrocenylspirocyclotriphosphazenes



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ABSTRACT

The condensation reactions of the tetrachloro mono (**1** and **2**) and bisferrocenylspirocyclotriphosphazenes (**3–5**) with 1,4-dioxo-8-azaspiro[4,5]decane (DASD) resulted in the formation of the partly and fully DASD-substituted phosphazenes. The reactions of equal amounts of **1–5** and DASD produced the mono-DASD-substituted ferrocenylphosphazenes (**1a–5a**), as the major product. When the reactions were carried out with 1 equiv of **1–5** and 2 equiv of DASD, corresponding geminal-phosphazenes (**1b–5b**) were isolated. Moreover, the reactions of 1 equiv of **1–5** and 3 equiv of DASD gave the tri- (**1c–4c**) and tetra-substituted (**1d–5d**) phosphazenes. When the excess DASD was used, the fully-substituted phosphazenes (**1d–5d**) were obtained. The chirality of **3a** was evaluated using chiral HPLC column. The structures of all the phosphazenes were verified by FTIR, MS, ¹H, ¹³C and ³¹P NMR, and HSQC spectral data. The crystal structures of **4a**, **2b**, **5b**, and **1d** were determined by X-ray diffraction techniques. The 10 phosphazene derivatives were screened for antimicrobial activity. Meanwhile, interactions between the compounds and pBR322 plasmid DNA were presented by agarose gel electrophoresis. The compounds **2b**, **1d**, **2d**, and **4d** were tested against HeLa cancer cell lines. Among these compounds, **4d** had cytotoxic effect on HeLa cell after 24 h treatment.

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1. Introduction

Hexachlorocyclotriphosphazene (trimer), N₃P₃Cl₆, has been a useful molecule for the preparation of the substituted phosphazene frameworks with mono-, di-, tri-, and tetra- functional reagents [1–11]. The monodentate substituents may be replaced with all the Cl atoms, gradually, in different solvents [12]. When the 2 equiv of primary amines exchange with two Cl atoms, cis/trans and/or geminal cyclotriphosphazene derivatives can form via the pathways of SN¹(P), SN²(P) and/or proton abstraction–chloride elimination reaction mechanisms depending on the solvent polarities, base strength and nucleophiles [13–15]. The reactions of N₃P₃Cl₆ with primary amines are much more complex than the secondary amines [15]. The Cl replacement reactions of N₃P₃Cl₆ with the secondary amines afford mainly non-geminal phosphazenes with usually trans products predominating. Aziridine is only one exception

to this trend in the literature [15,16]. It reacts to produce both the geminal and the non-geminal isomers in approximately equal amounts [17]. In contrast to the reactions of trimer with secondary amines, only the geminal products could have been isolated from the reactions of tetrachloro bulky-crypta [18,19] and bulky-monof-ferrocenyl spirocyclotriphosphazenes [20,21] with pyrrolidine, morpholine, and 1-aza-12-crown-4, not depending on the bulkiness of these amines. Besides, there are some papers in the literature comparing the reactivity of trimer and octachlorocyclo-tetraphosphazene (tetramer) [22,23]. On the other hand, cyclotriphosphazene derivatives with pendant mono and bisferrocenyl groups have aroused a considerable amount of interest recently, not only from their synthetic, mechanistic, and electrochemical point of view but also with respect to their stereogenic properties and unusual structural characteristics [24–27].

We report herein: (i) the synthesis of mono- (**1a–5a**), gem- (**1b–5b**), tri- (**1c–4c**), and tetra-DASD-substituted (**1d–5d**) mono and bisferrocenylphosphazenes obtained from the gradually Cl replacement reactions of the tetrachlorocyclotriphosphazenes containing

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mono and bisferrocenyl pendant arms (**1–5**) with DASD (Scheme 1); (ii) the structure determinations of the compounds by elemental analyses, mass spectrometry, Fourier transform (FTIR), one-dimensional (1D) ^1H , ^{13}C , and ^{31}P NMR, and two-dimensional (2D) heteronuclear single quantum coherence (HSQC) techniques; (iii) the solid-state and molecular structures of **4a**, **2b**, **5b** and **1d**; (iv) as an example, the stereogenic properties of **3a** is found out by chiral high pressure liquid chromatography (HPLC) column; (v) the investigations of antibacterial and antifungal activity of 10 phosphazene derivatives; (vi) interactions between the compounds **3a–5a**, **2b**, **4b**, **3c**, **4c** and **1d–5d** and pBR322 plasmid DNA, and (vii) the evaluations of the compounds **2b**, **1d**, **2d** and **4d** for cytotoxic activity against HeLa cancer cell lines.

2. Experimental

2.1. Reagents

Hexachlorocyclotriphosphazatriene (Aldrich), ferrocenecarboxaldehyde (Aldrich), aliphatic amines (Fluka) and 1,4-dioxo-8-aza-spiro[4,5]decane (DASD) (Merck) were purchased and used without further purification. All reactions were monitored using thin-layer chromatography in different solvents and chromatographed using silica gel. All experiments were carried out in an argon atmosphere.

2.2. Instruments

The ^1H , ^{13}C , and ^{31}P NMR spectra were recorded on a Bruker DPX FT-NMR spectrometer (SiMe_4 as an internal standard and 85% H_3PO_4 as an external standard), operating at 499.94, 125.72, and 202.38 MHz. The spectrometer was equipped with a 5 mm

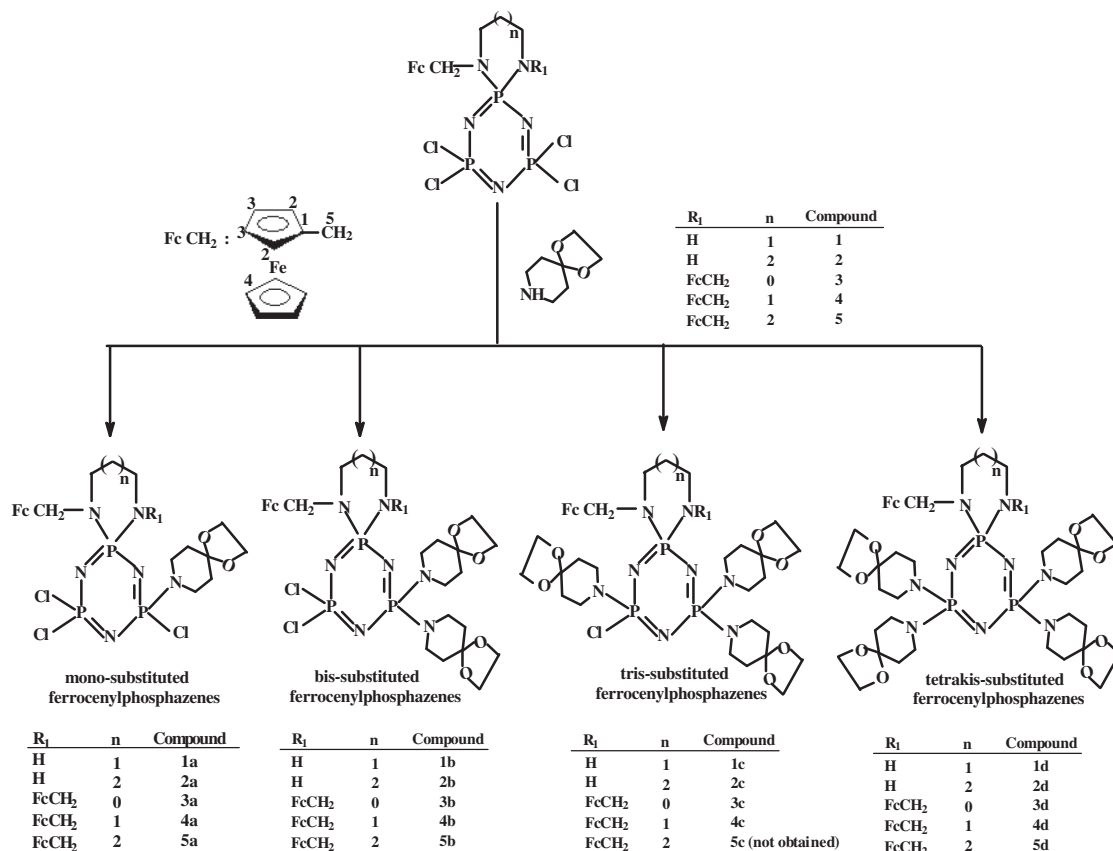
PABBO BB inverse-gradient probe. Standard Bruker pulse programs [28] were used. The IR spectra were recorded on Jasco FT/IR-430 spectrometer in KBr disks and were reported in cm^{-1} units. APIES mass spectrometric analyses were performed on an AGILENT 1100 MSD spectrometer. The melting points were measured on a Gallenkamp apparatus using a capillary tube.

2.3. X-ray crystallography

The suitable crystals of compounds **4a**, **2b**, **5b**, and **1d** were crystallized from acetonitrile at room temperature. Crystallographic data were recorded on a Bruker Kappa APEXII CCD area-detector diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) at $T = 100(2) \text{ K}$. Absorption corrections by multi-scan [29] were applied. Structures were solved by direct methods and refined by full-matrix least squares against F^2 using all data [30]. All non-H atoms were refined anisotropically. H atom positions were calculated geometrically at distances of 0.95 Å (CH) and 0.99 Å (CH_2) Å from the parent C atoms; a riding model was used during the refinement process and the $U_{\text{iso}}(\text{H})$ values were constrained to 1.2 $U_{\text{eq}}(\text{carrier atom})$ for CH and CH_2 groups. In compounds **1d** and **2b**, H atoms of NH groups were located in difference Fourier maps and were freely refined. In compound **4a**, the two Cl atoms of the phosphazene ring attached at P2 were disordered over two orientations. During the refinement process, the disordered Cl2, Cl2', Cl3 and Cl3' atoms were refined with occupancies of 0.62, 0.38, 0.74 and 0.26, respectively.

2.4. Preparation of compounds

The tetrachloro mono and bisferrocenylphosphazenes (**1–5**) were obtained from the reactions of mono and bisferrocenylamines



Scheme 1. The formulae of DASD-substituted mono and bisferrocenylphosphazenes.

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