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Ansa versus spiro selectivity in substitution reactions of a mono ansa fluorodioxycyclotriphosphazene derivative with diols

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ABSTRACT

In this study, regio-selectivity in the nucleophilic substitution reactions of a mono ansa fluorodioxycyclotriphosphazene derivative with diols has been investigated. The cyclotriphosphazene derivative, $N_3P_3Cl_4[OCH_2(CF_2)_3CH_2O]$ (**1**), was reacted with the disodium salts of 1,3-propanediol and tetraethyleneglycol in THF solution at a 1:1 M ratio and eight new products (**2**–**6**, **7a**, **7b** and **8**) were formed. These products were separated and characterized by elemental analysis, mass spectrometry, ^1H and ^{31}P NMR spectroscopy. The crystal structures of **2**, **3**, **5**, **6** and **7a** have been characterized by X-ray crystallography. The spiro derivatives (**3**, **6**) were formed as the major product in the reactions of compound **1** with both diols.

1. Introduction

The determination of substitution patterns is very important for cyclophosphazene chemistry due to the fact that the multiple available pathways in these nucleophilic substitution reactions lead to a large number of cyclophosphazene derivatives [1–20]. Systematic studies of the substitution patterns will lead to a fundamental understanding of the factors which control these processes. The substitution pattern in classic cyclophosphazene chemistry is usually governed by steric, electronic and mechanistic effects [1–3,14–19,21,22]. When electron-donating substituents are on the N_3P_3 ring, the positive charge at the P-atoms is reduced and therefore non-geminal substitution patterns are observed for alcoholate and phenolate anions [1,20,21,25]. If the nucleophile is a diol, formation of spiro products are favored because of the great thermodynamic stability of the five-, six- or seven-membered spiro rings. [22,23,26,27]. Nevertheless ansa compounds are obtained when long chain aliphatic diols and glycols are used [27–35].

We have previously investigated the reactions of fluorodioxy *cis*-ansa cyclotriphosphazenes, $N_3P_3Cl_4[OCH_2(CF_2)_3CH_2O]$ and $N_3P_3Cl_4[OCH_2(CF_2)_4CH_2O]$, with the sodium salts of methanol and phenol at different molar ratios [24,25]. Important details were obtained about the reaction mechanisms and pathways. In this work, the mono ansa cyclotriphosphazene derivative $N_3P_3Cl_4[OCH_2(CF_2)_3CH_2O]$ (**1**), having the PCl_2 group available for spiro substitution and two fluorodioxy bearing P-atoms for ansa substitution, was used as the precursor compound and the substitution reactions were examined with the sodium salts of 1,3-propandiol and tetraethyleneglycol. While, 1,3-propandiol is a short chain aliphatic diol, tetraethyleneglycol is a larger and flexible aliphatic diol (glycol) and both of them, in principle, can give spiro and ansa products. Furthermore, both diols are important for cyclophosphazane chemistry since their reactions with $N_3P_3Cl_6$ have been studied extensively [29–35].

The reactions of compound **1** with the disodium salts of 1,3-propandiol and tetraethyleneglycol lead to eight new products. The spiro derivatives are formed as the major product in the reactions of both diols. The formation of the spiro product is expected for the propanedioxy nucleophile, but it is unusual for the large and flexible oxy(tetraethyleneoxy) nucleophile. This indicates that the two P-Cl bonds of the PCl_2 group are more reactive than those of the P(OR)Cl moiety in the compound **1**.

2. Experimental

2.1. Materials and physical measurements

Hexachlorocyclotriphosphazene (Aldrich) was purified by fractional crystallization from hexane. 2,2,3,3,4,4-Hexafluoro-1,5-pentanediol (Aldrich) was used as received. Tetraethyleneglycol (Fluka) and 1,3-propanediol (Aldrich) were dried over 4 Å molecular sieves. THF (Merck) was distilled over a sodium/potassium alloy under an atmosphere of dry argon. Sodium hydride, 60% dispersion in mineral oil (Merck) was purified prior to use by washing with

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dry hexane (Merck) followed by decantation. All reactions were performed under a dry argon atmosphere. $CDCl_3$ for NMR spectroscopy was obtained from Merck. Analytical Thin Layer Chromatography (TLC) was performed on Merck silica gel plates (Merck, Kieselgel 60, 0.25 mm thickness) with F_{254} indicator. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 70–230 mesh; for 3 g crude mixture, 100 g silica gel was used). Elemental analyses were obtained using an Elementar Vario MICRO Cube. Mass analyses were recorded on a Bruker MALDI–TOF (Matrix-Assisted Laser Desorption/Ionization–Time-Of-Flight) spectrometer using 2,5-dihydroxybenzoic acid as a matrix. ^1H and ^{31}P NMR spectra were recorded for all compounds in $CDCl_3$ on a Varian INOVA 500 MHz spectrometer using TMS as an internal reference for ^1H and 85% H_3PO_4 as an external reference for ^{31}P NMR measurements.

2.2. X-ray crystallography

Intensity data were recorded on a Bruker APEX II QUAZAR diffractometer using mono-chromatized Mo Kα radiation (λ = 0.71073 Å). Absorption corrections were performed by the multi-scan method implemented in SADABS [36] and space groups were determined using XPREP implemented in APEX2 [37]. The structures were determined using the direct methods procedure in SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97 [38]. All non-hydrogen atoms were refined with anisotropic displacement factors and C–H hydrogen atoms were placed in calculated positions and allowed to ride on their parent atom. The compounds **2** and **6** exhibited positional disorder in the fluorodioxy and oxy(tetraethyleneoxy) rings, respectively. The components of the disordered groups were modelled by assigning refined fractional occupancy. The unusual high peaks of compound **6** showed that the disorder continues slightly along the oxy(tetraethyleneoxy) ring, but we preferred to limit the disordered fragment at only high values. In the unit cell of **5**, there existed dichloromethane as a solvent molecule which was not modelled because of the high disorder. Therefore, the SQUEEZE command of PLATON [39] was used for removing the solvent molecule then the rest of the molecule was refined without solvent. There was one cavity with 106.4 Å^3 volume and 46.2 void electron count. The final geometrical calculations were carried out with PLATON [39] and MERCURY [40] programs and the molecular drawings were done with the DIAMOND [41] program.

2.3. Synthesis

Compound **1** was prepared as in the literature [26].

2.3.1. Synthesis of compounds *2*–*5*

Ansa-[$N_3P_3Cl_4(OCH_2(CF_2)_3CH_2O)$] (**1**) (0.487 g, 1 mmol) and 1,3-propanediol (0.076 g, 1 mmol) were dissolved in 50 mL of dry THF in a 100 mL three-necked round-bottomed flask. NaH (0.08 g, 2 mmol) in 10 mL of dry THF was quickly added to the stirred solution under an argon atmosphere. The reaction was stirred for a further 24 h at room temperature and examined by TLC on silica gel plates using hexane–tetrahydrofuran (3:2) as the mobile phase. Three products were observed. The reaction mixture was filtered to remove the sodium chloride and any other insoluble material. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using hexane–tetrahydrofuran (3:2) as the eluent. The first product was compound **2** {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]ansa-[$O(CH_2)_3O$]}, the second product was compound **3** {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]spiro-[$O(CH_2)_3O$]} and the third product was compound **5** {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]spiro-[$O(CH_2)_3O$]ansa-[$O(CH_2)_3O$]}. The separated products **2**–**5** were in the powder form and these were used for chemical and spectroscopic analyses, while single crystals for X-ray work were obtained by recrystallization from hexane–dichloromethane (3:1). The recrystallized sample of compound **5** contained dichloromethane as a solvent molecule.

Anal. Calc. for **2** and **3**, $C_8H_{10}Cl_2F_6N_3O_4P_3$: C, 19.61; H, 2.06; N, 8.58%, M, 490.0. *Anal.* Calc. for **5**, $C_{11}H_{16}F_6N_3O_6P_3$: C, 26.79; H, 3.27; N, 8.52%, M, 493.2

2: (0.02 g, 4%, m.p. 123 °C). Found: C, 19.32; H, 1.81; N, 8.45%, M$^+$, 489.7. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.72, 4.56, 4.42, 4.18 (m, 8H, –OCH_2CH$_2$– and –OCH_2CF$_2$–), 2.56, 2.26 (m, 2H, –CH$_2$CH_2CH$_2$–).

3: (0.30 g, 61%, m.p. 194 °C). Found: C, 19.54; H, 1.77; N, 8.53%, [M + H]$^+$, 490.9. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.83 (m, 2H, –OCH_2CF$_2$–), 4.46–4.39 (m, 6H, –OCH_2CH$_2$– and –OCH_2CF$_2$–), 1.98 (q, 2H, –CH$_2$CH_2CH$_2$–).

5: (0.005 g, 1%, m.p. 201 °C). Found: C, 28.06; H, 3.15; N, 8.10%, M$^+$, 493.7. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.74, 4.54, 4.36, 4.18 (m, 12H; –OCH_2CH$_2$– and –OCH_2CF$_2$–), 2.55, 2.22 (m, 2H, ansa–CH$_2$CH_2CH$_2$–), 2.06 (q, 2H, spiro-CH$_2$CH_2CH$_2$–).

2.3.2. Synthesis of compounds *6*–*8*

Ansa-[$N_3P_3Cl_4(OCH_2(CF_2)_3CH_2O)$] (**1**) (0.487 g, 1 mmol) and tetraethylene glycol (0.194 g, 1 mmol) were dissolved in 60 mL of dry THF in a 100 mL three-necked round-bottomed flask. NaH (60%, 0.08 g, 2 mmol) in 15 mL of dry THF was quickly added to the stirred solution under an argon atmosphere. The reaction was stirred for a further 24 h at room temperature and followed by TLC on silica gel plates using hexane–tetrahydrofuran (3:2) as the mobile phase. Three products were observed. The reaction mixture was filtered to remove the sodium chloride and any other insoluble material. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using hexane–THF (3:2) as the eluent. The products were eluted from the column in the order {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]spiro-[$O(CH_2CH_2O)_3CH_2CH_2O$]} (**6**), {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]-*trans* ansa-[$O(CH_2CH_2O)_3CH_2CH_2O$]} (**7a**) and then an isomer of compound **7a**, {$N_3P_3Cl_2$ansa-[$OCH_2(CF_2)_3CH_2O$]*cis* ansa-[$O(CH_2CH_2O)_3CH_2CH_2O$]} **7b**. The compounds **6** and **7a** were crystallized from *n*-hexane–dichloromethane (3:1) and obtained as colorless crystals. *Anal.* Calc. for **6**, **7a** and **7b**, $C_{13}H_{20}Cl_2F_6N_3O_7P_3$: C, 25.68; H, 3.31; N, 6.91%, M, 608.1.

6: (0.15 g, 24%, m.p. 150 °C). Found: C, 25.19; H, 2.99; N, 6.84%, M$^+$, 608.0. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.94, 4.43 (m, 4H, –OCH_2CF$_2$–), 4.21 (m, 4H, –POCH_2CH$_2$O–), 3.82, 3.78, 3.68 (m, 12H, –POCH$_2$CH_2O– and –OCH_2CH_2O–).

7a: (0.06 g, 10%, m.p. 121 °C). Found: C, 26.26; H, 3.22; N, 6.62%, M$^+$, 608.2. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.90, 4.72 (m, 4H, –OCH_2CF$_2$–), 4.51–4.37 (m, 4H, –POCH_2CH$_2$O–), 3.81–3.67 (m, 12H, –POCH$_2$CH_2O– and –OCH_2CH_2O–).

7b: (0.07 g, 12%, m.p. 93 °C). Found: C, 26.09; H, 3.17; N, 6.51%, M$^+$, 608.0. ^1H NMR, $CDCl_3$, 298 K, δ (ppm): 4.96, 4.68 (m, 4H, –OCH_2CF$_2$–), 4.44–4.28 (m, 4H, –POCH_2CH$_2$O–), 3.81–3.68 (m, 12H, –POCH$_2$CH_2O– and –OCH_2CH_2O–).

3. Results and discussion

3.1. Synthesis and characterization of the reaction products by ^1H and ^{31}P NMR spectroscopy

Investigations of the reaction pathways in nucleophilic substitution reactions at phosphazene phosphorus atoms are important for the prediction of region and stereo chemical isomer distributions. Compound (**1**), [2,4-(2′,2′,3′,3′,4′,4′-hexafluoro-1′,5′-pentanedioxy)-2,4,6,6-tetrachloro)cyclo-triphosphazene], contains one PCl_2 group and two fluorodioxy bearing P-atoms, PCl(OR), which