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Isomeric spiro and ansa macrocyclic derivatives of spiro-aminopropanoxy-cyclotriphosphazene

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Abstract

The spiro-aminopropanoxy group enables substituents to be distinguished above and below the plane of the cyclotriphosphazene ring. Spiro and ansa macrocyclic derivatives of cyclophosphazene have been investigated by stepwise reactions of the same two reagents added in different order. In the first route, hexachlorocyclotriphosphazene (**1**) was reacted with 3-amino-1-propanol (**2**) to give 2,2-(3′-amino-1′-propoxy)-4,4,6,6-tetrachloro-cyclotriphosphazene (**4**), which was then reacted with tetraethylene glycol (**3**) to give the mono-spiro (**6**), mono-ansa (**7**) and di-ansa (**8**) derivatives. In the second pathway, cyclophosphazene (**1**) was first reacted with tetraethylene glycol (**3**) to give 4,6-[oxy(tetraethyleneoxy)]-2,2,4,6,-tetrachlorocyclotriphosphazene (**5**), which was then reacted with 3-amino-1-propanol (**2**) to give the spiro-ansa compound (**7**) and its geometric isomer (**9**), in contrast to previous work when bis-β-naphthol was introduced as the second substituent. The mono-ansa compound (**7**) has the macrocycle *cis* to the NH group of the aminopropanoxy moiety, whereas the crystal structure of compound (**9**) confirms that it is the first mono-ansa derivative, when formed in a primary reaction, in which the macrocycle is trans to the NH group of the spiro-aminopropanoxy residue.

Keywords: Macrocyclic-cyclophosphazenes; Spiro and ansa compounds; Geometric isomers; ^{31}P NMR spectroscopy; X-ray crystallography

The reaction mechanism of nucleophilic substitution of macrocyclic-cyclophosphazene derivatives with unbranched amines has recently been investigated [1–3]. Reaction of the sodium derivative of tetraethylene glycol with cyclotriphosphazene, $N_3P_3Cl_6$ (**1**), leads predominantly to the *cis*-ansa derivative (**5**) [4]. No *trans*-ansa structures with this reagent have been reported in such primary reactions, although other spiro and ansa compounds were also characterised as minor products of the reaction [4]. Nevertheless, when compound (**5**) was allowed to react with nucleophiles, the first substitution of one of the two P–Cl(Om) (m = macrocycle) groups of the *cis*-ansa moiety gave rise to a *trans*-ansa structure proving inversion of configuration [2]. Further substitution again gave rise to a *cis*-ansa-structure, which suggested another inversion reaction in the second step, but did not prove it, because the remaining $>PCl_2$ group had the same type of bond (P–Cl) above and below the plane of the ring [2,3]. In order to prove inversion of configuration for the second step of the reaction, a marker was needed to distinguish substituent groups above and below the plane of the cyclophosphazene ring and this was achieved by introducing a spiro-aminopropanoxy group to form the *cis*-ansa macrocyclic-cyclophosphazene compound (**7**). We have recently reported an investigation of nucleophilic substitution reactions of compound (**7**) with a wide range of mono- and di-functional reagents, in which di-substitution resulted in compounds with a *cis*-ansa ring on the opposite side of the cyclophosphazene ring to that of the starting material, proving inversion of configuration and the S_N2 type mechanism for the second step of the reaction [5].

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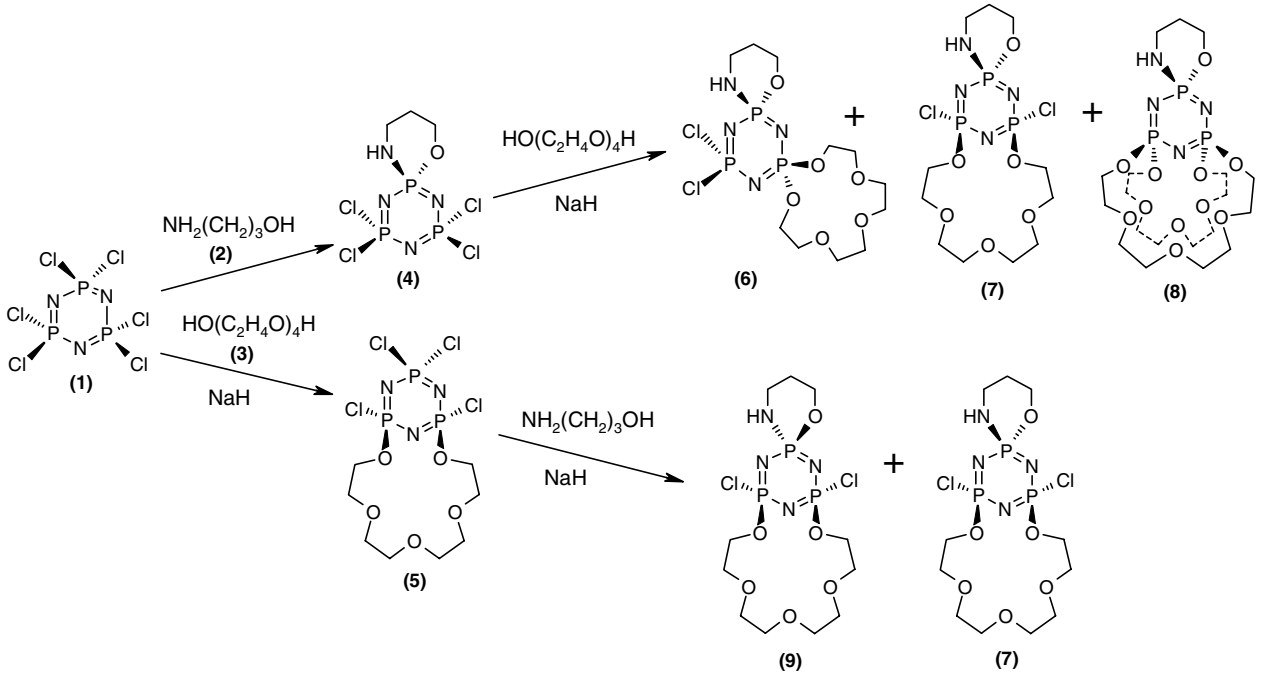
A study has been reported [6] in which the sodium derivatives of tetraethylene glycol and bis-β-naphthol were introduced in a different order into the cyclophosphazene molecule, (**1**). Initial reaction of bis-β-naphthol with (**1**) gives a spiro-binaphthoxy derivative and further reaction with tetraethylene glycol gives the expected spiro-ansa derivative, which is analogous to that of compound (**7**). In the reverse order of the introduction of these two groupings, reaction of tetraethylene glycol with (**1**) gives the *cis*-ansa derivative (**5**) and then addition of bis-β-naphthol leads to one or both of the oxygen atoms of the binaphthol group reacting with the P–Cl(Om) groups giving rise to geminal and non-geminal ansa-ansa isomers, instead of formation of the thermodynamically favoured spiro-isomer [6]. A supramolecular chemistry effect, resulting from sodium cation-assisted regiospecific reaction [7], was postulated to explain the formation of the ansa compounds [6]. Supramolecular effects have also been suggested for the rapid reaction of compound (**5**) with aliphatic primary amines [1,2], which proceed regioselectively at the macrocycle-bearing P-atoms, as a result of supramolecular assistance [8] based on hydrogen-bonding interactions between host, compound (**5**), and guest (diamine). In particular, with unbranched primary diamines, H_2- $N(CH_2)_nNH_2$, $n = 2$–12, reaction at the P–Cl(Om) groups was observed, giving rise to either geminal ansa-ansa derivatives or singly- and doubly bridged dimers [1,2]. The crystal structure of the ansa-ansa derivative with ethylene diamine, $H_2N(CH_2)_2NH_2$, has been reported and shown to be rather strained [1]. With longer chain lengths of the spacer $(CH_2)_n$ group, bridged compounds predominated [1,2]. These results are in contrast to those for reactions of short chain diamines with non-macrocyclic cyclophosphazenes, which for thermodynamic reasons usually yield spirocyclic structures [9], except for reactions with "blocked precursors" having no sites available for spiro-cyclosubstitution [10]. In fact, with propylene diamine, $H_2N(CH_2)_3NH_2$, a spiro-ansa derivative analogous to compound (**7**) was also isolated, in addition to the bridged and ansa derivatives presumed to have arisen by supramolecular chemistry effects [1]. This appeared to be the only case ($n = 3$) of a diamine of the series ($n = 2$–12) where a compound was isolated that resulted from nucleophilic attack at the PCl_2 group, as well as to the P–Cl(Om) groups [1].

In the present work (Scheme 1), the reactions of cyclophosphazene (**1**) with the sodium derivatives of two reagents, 3-amino-1-propanol (**2**) and tetraethylene glycol (**3**), added in different order, analogous to previous work using bis-β-naphthol and (**3**) have been investigated [6]. When propanolamine (**2**) was added first to (**1**), the known [11] spiro-aminopropanoxy compound (**4**) was isolated, which was then reacted further with (**3**) to give the spiro-spiro (**6**), spiro-ansa (**7**) and spiro-bis-ansa (**8**) compounds, analogous to those formed when (**3**) was reacted with (**1**) directly [4]. The spiro-ansa compound (**7**) has been characterised previously by ^{31}P NMR spectroscopy and X-ray crystallography [5], whereas the new compounds, spiro-spiro (**6**) and spiro-bis-ansa (**8**), have been characterised by elemental anal-



Scheme 1.