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Structural and stereogenic properties of spiro- and ansa-substituted 1,3-propanedioxy derivatives of a spermine-bridged cyclotriphosphazene[†]

Simon J. Coles[a], David B. Davies[b]*, Robert J. Eaton[b], Adem Kılıç[c], Robert A. Shaw[b] and Gönül Yenilmez Çiftçi[c]

[a] Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BG, UK.

[b] School of Biological and Chemical Sciences, Birkbeck College (University of London), Malet Street, London WC1E 7HX, UK;

[c] Department of Chemistry, Gebze Institute of Technology, Gebze, Turkey;

* Corresponding Author:

Professor D. B. Davies, School of Biological and Chemical Sciences, Birkbeck College (University of London), Malet Street, London WC1E 7HX, UK.

Fax : 020-7631-6246 Tel : 020-7079-0791 e-mail: davidbry@ndavies.co.uk

[†] Dedicated to Mike Hursthouse on his retirement and in appreciation of our scientific collaboration over the years.

Abstract

Reaction of 1,3-propanediol with the achiral spermine-bridged cyclophosphazene **1** at various molar ratios in THF gives a number of spiro-and ansa-derivatives that exhibit different stereogenic properties, *viz*. racemic, meso or achiral forms. As expected, spiro forms are preferred (giving mono-, di-, tri- and tetra-substitution), although significant amounts of mono- and di-substituted ansa derivatives also occur. A number of new structures have been characterized by NMR spectroscopy and X-ray crystallography in this work; mono-spiro **2**, di-mono-ansa **6** and di-spiro/mono-ansa **8.** The mono-ansa compound **3** was observed in solution by NMR spectroscopy but no evidence was found for the monospiro/monoansa **5**, a necessary precursor of compound **8**. The tri-spiro derivative **7** has been isolated and characterized by ^{31}P NMR spectroscopy, whereas the structures of the di-monospiro **4** (meso) and tetra-spiro **9** have been characterized previously. The stereogenic properties of many of the products have been confirmed by X-ray crystallography and/or by ^{31}P NMR spectroscopy on addition of the chiral solvating agent, (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Although the starting compound **1** is achiral, it is found that unsymmetrically-substituted derivatives with 1,3-propanediol give racemic mixtures for the mono-spiro **2** and tri-spiro **7** derivatives, whereas symmetrically-substituted derivatives such as di-mono-ansa **6** and di-spiro/mono-ansa **8** are meso. It is found that care must taken in interpreting the 'splitting' of ^{31}P NMR signals on addition of CSA in terms of 'chirality' of molecules, because some meso compounds give false positive results due to changes from A_2X-like to A_2B or ABX spin systems.

1. Introduction

Tetra-coordinated phosphorus atoms in cyclophosphazenes are pentavalent and potential stereocentres. Although the possibility of optical isomerism in cyclophosphazene derivatives, [(NPXY)$_n$ n=3,4] was first discussed many years ago [1], chiral properties of molecules have only recently been elucidated [2-5] and used to investigate reaction mechanisms [6, 7]. The spermine-bridged cyclophosphazene compound **1** has been prepared previously [8] by reaction of cyclotriphosphazene with the tetrafunctional amine, spermine. Compound **1** is achiral because the substitution pattern of each cyclophosphazene ring is the same and each cyclophosphazene ring has a plane of symmetry. However, singly-bridged analogues with *gem* disubstituted cyclophosphazene rings (e.g. **4**) exhibit stereoisomerism [3], because the three phosphorus atoms of each cyclophosphazene ring have different substitution patterns and those that are part of the bridge, >P(N-spiro), are stereogenic, *i.e.* there are *R* and *S* forms. It was shown that spermine-bridged compounds such as **4** are diastereoisomeric and exist in 1:1 mixtures of meso (*RS/SR*) and racemic (*RR/SS*) forms [3]. Compound **4** was synthesised by the reaction at room temperature of 1,3-propanediol with **1** and, although a second compound was reported as the tri-spiro derivative, it was not characterized [3]; this compound is expected to be chiral and to exist as a racemic mixture.

Reaction of 1,3-propanediol with compound **1** could, in principle, give rise to a number of different derivatives; if only one functional group of the diol is used, this would give open chain forms, whilst utilisation of both functional groups of the diol can give rise to spiro, ansa and bridged derivatives. Reaction of $N_3P_3Cl_6$ with ethane-, 1,3-propane- and 1,4-butane-diols (in the presence of pyridine to neutralise the hydrochloride formed) predominantly gave spiro derivatives for all three diols, whereas ansa derivatives were rare products obtained only in small yields [9]. A bridged derivative was observed as a minor product with butanediol,

indicating that chain length was a contributing factor in determining derivative-type [9]. It was also found that ansa-derivatives may be formed using sodium salts of diols as reagents in polar solvents such as THF [10]. The spiro- and ansa-derivatives of **1** should exhibit a range of stereogenic properties (achiral, meso, racemic, diastereoisomeric). The purpose of the present work is to investigate the reaction of the sodium derivative of 1,3-propanediol with compound **1** in THF under different reaction conditions, to characterize the structures and stereogenic properties of the products and to show how widespread the question of chirality should be considered in cyclophosphazene chemistry.

2. Experimental

2.1. Materials

Hexachlorocyclotriphosphazene (Otsuka Chemical Co., Ltd) was purified prior to use by fractional crystallisation from hexane. The following chemicals were obtained from Merck; spermine (≥ 97.0%), diethyl ether, dichloromethane, benzene, *n*-hexane, 1,3-propanediol (≥ 99.0%), silica gel 60, sodium hydride (60% oil suspension), tetrahydrofuran, ethyl acetate, chloroform and *n*-heptane. The deuterated solvents for NMR spectroscopy were obtained from Apollo Scientific (toluene-d_8, CDCl$_3$) and the chiral solvating agent, (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, was obtained from Aldrich Chemical Co.

2.2. Measurements

Elemental analyses were obtained using a Carlo Erba 1106 Instrument. Mass spectrometric measurements were recorded on a VG Zab Spec GC-MS spectrometer using the fast atom bombardment (FAB) method (35 kV) with MNBA as the matrix; ^{35}Cl values were used for calculated masses. 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 60, 230-400 mesh; for 3g. crude mixture,

100g. silica gel was used in a column of 3 cm in diameter and 60 cm in length). ^{1}H and ^{31}P NMR spectra were recorded in CDCl$_3$ or toluene-d_8 solutions on a Bruker DRX 500 MHz spectrometer using TMS as an internal reference for ^{1}H and 85% H$_3$PO$_4$ as an external reference for ^{31}P. For all new compounds both proton-coupled and proton-decoupled ^{31}P NMR spectra were recorded. Experiments involving the chiral solvating agent (CSA) were performed by addition of small aliquots of a dilute solution of CSA in the solvent used for NMR spectroscopy and the ^{31}P NMR spectrum recorded at each addition.

2.3. Synthesis

Reaction of the sodium derivative of 1,3-propanediol with compound **1** in THF at different molar ratios gave a number of spiro and ansa derivatives as summarized in Scheme 1.

Scheme 1 about here

2.3.1. **4:1 mole ratio**. 1,3-Propanediol (0.4g, 5.3mmol) and previously prepared [8] compound **1** (1g, 1.33mmol) were dissolved in 50mL of dry THF in a 250mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (60% oil suspension, 0.42g, 10.6mmol) in 50mL of dry THF was added under an argon atmosphere. The reaction mixture was stirred for 21 h at room temperature and the reaction followed to completion by TLC on silica gel plates using CHCl$_3$:ethyl acetate (3:1) as the solvent system. The reaction mixture was filtered to remove the sodium chloride formed, the THF was removed under reduced pressure and the resulting white solid subjected to column chromatography using CHCl$_3$:ethyl acetate(3:1) as eluent. Two fractions were obtained and isolated as white powders and recrystallised from chloroform:hexane (1:1). The first fraction is the dispiro-monoansa compound, **8**, (yield: 0.29 g, 25%, mpt. 147-149°C; isolated as a chloroform adduct) Found: C, 27.02; H, 4.20; N, 15.12 (M+H)$^+$, 761. C$_{20}$H$_{41}$Cl$_5$N$_{10}$P$_6$O$_6$ requires: C, 27.27; H, 4.69; N, 15.90 (M$^+$, 761.34). The second fraction is the tetraspiro-derivative, **9**, whose NMR spectral data [11] and X-ray structure [12] have been characterized

previously (yield: 0.33 g. 32%, mpt. >250°C) Found: C, 34.35; H, 6.2; N, 17.68. $(M+H)^+$, 764. $C_{22}H_{46}N_{10}O_8P_6$ requires: C, 34.56; H, 6.06; N, 18.32 M^+, 764.52.

2.3.2. **3:1 mole ratio**.   1,3-Propanediol (0.9g, 11.95mmol) and previously prepared [8] compound **1** (3g, 3.98mmol) were dissolved in 200mL of dry THF in a 500mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (60% oil suspension, 0.95g, 23.9mmol) in 50mL of dry THF was added under an argon atmosphere. The reaction mixture was stirred for 24 h at room temperature and was followed by TLC on silica gel plates using THF:CH_2Cl_2 (5:2). The reaction mixture was filtered to remove the sodium chloride formed, the THF was removed under reduced pressure and the resulting white solid subjected to column chromatography using THF:CH_2Cl_2 (5:2) as eluent. Two fractions were obtained; the first fraction was isolated as a white powder (yield 0.22 g, 7.3%), (mpt. 84-90 °C) and characterized as the tri-spiro compound, **7**. Found: C, 30.48; H, 5.14; N, 17.95%; $(M+H)^+$, 761. $C_{19}H_{40}Cl_2N_{10}O_6P_6$ requires: C, 30.00; H, 5.30; N, 18.40 % ; M^+, 760. ^1H NMR, $CDCl_3$, 298K: OCH_2 signals at 4.52m, 2H and 4.4m, 10H; 3.23m, 4H, NCH_2; 3.1m, 4H, NCH_2; 2.8m 4H, $NHCH_2$; 2.5, broad triplet, 2H, NH; O-spiro, N-spiro and bridge CCH_2 signals at 2.1m, 4H; 1.9m, 4H; 1.7, 8H. The second fraction was isolated as a white powder (yield: 0.5g, 16.5%) (mpt. 147-149°C), re-crystallized from CH_2Cl_2:THF:Hexane(1:2:1) and characterized as the dispiro-monoansa compound, **8**. Found: C, 29.30; H, 5.90; N, 17.68. $(M+H)^+$, 760.8. $C_{19}H_{40}Cl_2N_{10}O_6P_6$ requires: C, 29.97; H, 5.30; N, 18.40 M^+, 760.

2.3.3. **2:1 mole ratio**.   1,3-Propanediol (1.06 g, 13.2 mmol) and previously prepared [8] compound **1** (5g, 6.6 mmol) were dissolved in 140 mL of dry THF in a 500 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (60% oil suspension, 1.056 g, 26.4 mmol) in 100 mL of dry THF was quickly added under an argon atmosphere. The reaction was stirred for 23 h at room temperature and was followed by TLC

on silica gel plates using CH_2Cl_2:ethyl acetate (6:1). The reaction mixture was filtered to remove NaCl formed, the THF was removed under reduced pressure and the resulting white solid subjected to column chromatography using CH_2Cl_2:ethyl acetate (6:1). Two fractions were obtained. The first fraction has been characterized previously as the di-monospiro derivative **4** (isomer mixture, mpt. 210-216°C) [3] and the meso form characterized by X-ray crystallography [11]. The second major fraction was isolated as a white powder, re-crystallized from dichloromethane:hexane (1:1) and characterized as the di-monoansa derivative **6** (yield: 0.4 g, 8%) (mpt. >250°C decomposition). Found: C, 25.91; H, 4.08; N, 17.88. $(M+H)^+$, 757 $C_{16}H_{34}Cl_4N_{10}O_4P_6$ requires: C, 25.35; H, 4.52; N, 18.47 M^+, 756. ^{1}H NMR, CDCl$_3$, 298K: 4.48m, 4H, OCH$_2$ signals; 4.21m, 4H, OCH$_2$ signals; 3.23m, 4H, NCH$_2$; 3.13m, 4H, NCH$_2$; 2.92m 4H, NHCH$_2$; ansa CCH$_2$ signals at 2.2m, 2H and 1.9m, 2H; spiro and bridge CCH$_2$ signals at 1.75m, 4H and 1.68m, 4H.

2.3.4. **0.75:1 mole ratio**: 1,3-Propanediol (0.25 g, 3.2 mmol) and previously prepared [8] compound **1** (3.3 g, 4.3 mmol) were dissolved in 150 mL of dry THF in a 500 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (60% oil suspension, 0.26g, 6.4 mmol) in 50 mL of dry THF was quickly added under an argon atmosphere. The reaction was stirred for 24 h at room temperature and was followed by TLC on silica gel plates using CH_2Cl_2-ethyl acetate (1:2) as eluent. The reaction mixture was filtered to remove the sodium chloride, the THF was removed under reduced pressure and the resulting white solid subjected to column chromatography using CH_2Cl_2:ethyl acetate (1:2). Two fractions were obtained, the first is the starting compound **1** [8], isolated as a white powder (recovery of starting material: 0.16 g, 5%) whose ^{1}H NMR has not been previously reported in detail. ^{1}H NMR, CDCl$_3$, 298K: 3.24m, 4H, NCH$_2$; 3.14m, 4H, NCH$_2$; 2.84m 4H, NHCH$_2$; 2.67 broad quartet, 2H, NH; spiro and bridge CCH$_2$ signals at 1.82m, 4H and 1.56m, 4H. The second fraction was also isolated as a white powder (yield: 0.45 g, 14 %), (mpt. 150-

151°C), recrystallised from CH_2Cl_2 :hexane:ethyl acetate (2:1:1) and characterized as the mono-spiro compound **2**. Found: C, 19.90; H, 3.50; N, 18.40 $(M+H)^+$, 754.9. $C_{13}H_{28}Cl_6N_{10}O_2P_6$ requires: C, 20.68; H, 3.74; N, 18.55 M^+, 754. ^{1}H NMR, $CDCl_3$, 298K: 4.53m 2H, OCH_2 signals; 4.37m 2H, OCH_2 signals; 3.1 − 3.3m, 8H, NCH_2; 2.8-2.9m, 4H, $NHCH_2$; 2.64, broad quartet, 1H, NH; 2.52, broad triplet, 1H, NH; CCH_2 signals at 2.14m, 1H; 1.75-1.9m, 5H; 1.6m, 4H. ^{1}H NMR, toluene-d_8, 298K: 4.53m 2H, OCH_2 signals; 4.37m 2H, OCH_2 signals; 3.25m 4H, NCH_2; 3.1 − 3.3m 8H, NCH_2; 3.15m 4H, NCH_2; 2.85m 4H, $NHCH_2$; 2.64, broad quartet, 1H, NH; 2.52, broad triplet, 1H, NH; CCH_2 signals at 2.14m, 1H; 1.75-1.9m, 5H; 1.6m, 4H.

2.4. X-ray crystallography.

Intensity data were recorded at low temperature (120 K) on a Nonius KappaCCD diffractometer situated at the window of an FR591 rotating anode generator, driven by COLLECT [13] and DENZO [14] software. Details of data collection and refinement are given in Table 1. All structures were determined using the direct methods procedure in SHELXS-97 [15] and refined by full-matrix least squares on F^2 using SHELXL-97 [16]. The structure of **8** exhibits a solvent of crystallisation ($CHCl_3$) and some disorder in the central chain (atom C8 / C8'), which is modelled at 55:45 %. Full details of data collection and structure determination have been deposited with the Cambridge Crystallographic Data Centre (CCDC).

Table 1 about here

3. Results and discussion

Formation of spiro- and ansa-substituted spermine-bridged cyclotriphosphazenes

Reaction of the sodium derivative of 1,3-propanediol with the spermine-bridged cyclophosphazene **1** in different mole ratios (4:1, 3:1, 2:1, 0.75:1) in THF gave a number of

spiro- and ansa-substituted derivatives as shown in Scheme 1. In order to investigate all major reaction products, the crude reaction mixtures were routinely characterized by proton-decoupled ^{31}P NMR, as well as all major fractions isolated. Reaction of 1,3-propanediol with **1** in a 4:1 mole ratio for 21 h at room temperature gave the fully substituted dispiro-monoansa **8** and tetra-spiro **9** derivatives, whereas reaction at a 3:1 mole ratio under the same solution conditions gave the tri-spiro derivative **7** and the isomeric compound **8**. Reaction of 1,3-propanediol with **1** in a 2:1 mole ratio for 23h at room temperature gave the di-monospiro **4** and di-monoansa **6** derivatives and reaction at a 0.75:1 mole ratio for 24 h at room temperature gave the mono-spiro **2** and mono-ansa **3** derivative. It is obvious from Scheme 1 that the mono-spiro derivative **2** is the precursor of the spiro-substituted compounds **4** (di), **7** (tri), and **9** (tetra), and the mono-ansa derivative **3** is a precursor of **6** (di-mono-ansa) and **8** (di-spiro/mono-ansa). The mono-spiro/mono-ansa derivative **5** could be formed from either the mono-spiro **2** or the mono-ansa compound **3** and the dispiro/mono-ansa derivative **8** should have compound **5** as precursor. Attempts were made to prepare the mono-spiro/mono-ansa compound **5,** but amounts in the reaction mixtures were too small to isolate and characterize independently. Each of the new compounds **2**, **6** and **8** was characterised by X-ray crystallography and by elemental analysis, MS and ^{31}P NMR using both proton-decoupled and proton-coupled spectra. Although crystals suitable for X-ray crystallography could not be obtained for **3** and **7**, these compounds were characterized by ^{31}P NMR spectroscopy. The ^{31}P NMR results for all of the compounds are summarised in Table 2.

Table 2 about here

X-ray crystal structures of the spiro- and ansa-derivatives (2, 6, 8) of the spermine-bridged compound, 1

The molecular structures of compounds **2, 6** and **8** are shown in Figures 1-3, respectively. The crystal structures of the meso form of the di-mono-spiro compound **4** [11] and the tetra-spiro compound **9** [12] have been published previously.

Figures 1-3, about here

Compound **2**. The molecular structure of the mono-spiro compound **2** in Figure 1 depicts an asymmetrically-bridged molecule, in which one of the cyclophosphazene moieties is unsubstituted and the other exhibits a mono-spiro substituted phosphorus site. Both N_3P_3 rings of compound **2** are nearly planar, with the maximum deviations from the mean ring plane being 0.092Å (atom P2) and 0.104Å (atom N8) for rings 1 (spiro derivative) and 2 (un-substituted), respectively. Ring 2 exhibits slight ring compression with a shortened non-bonded separation between ring phosphorus atoms of 2.699Å (P4…P5), whereas the expected distance surveyed from the Cambridge Structural Database [17] is about 2.78Å. The spermine bridge introduces chirality to the molecule at the phosphorus sites linking it to the unsymmetrically-substituted cyclophosphazene ring and is found to be *S* for atom P3. The molecule is chiral and exists as a racemate. The relative conformation of the two cyclophosphazene rings around the tetra-methylene bridge is neither pure syn nor anti, but is approximately 2/3 of the way towards the latter, forming an angle of 59.5° between the two ring planes. Hydrogen-bonding occurs at the N_3P_3 moiety containing the spiro-propanedioxy group and gives rise to discreet dimers through an N-H…N interaction (N4-H4N…N2 D…A distance = 3.282Å). Eight-membered hydrogen-bonded rings are formed, in which the two heavy atom distances are equal at 3.282Å and result in a twist-boat conformation. At distances >3.4Å a more complex hydrogen-bonded motif links the molecules into an infinite layer structure.

Compound **6.** The molecular structure of the di-monoansa compound **6** in Figure 2 is that of a symmetrically-bridged spermine derivative, where the cyclophosphazene substituents both

possess a propanedioxy ansa-bridged moiety, giving rise to a centrosymmetric structure with the centre of inversion about the central C-C bond of the spermine bridge. The cyclophosphazene ring is heavily distorted, as observed in similar ansa-bridged examples [18], with a maximum deviation from the mean ring plane of 0.328Å for the nitrogen atom (N1) bridged by the ansa group. This give rise to compression of the cyclophosphazene ring, where the non bonded P…P separation between atoms P1 and P2 is 2.615Å. The ansa bridge introduces chirality into the molecule such that P1 = R and P2 = S, with the symmetry generated partners having the opposite chirality due to the inversion centre resulting in **6** being a meso compound. As a result of the centrosymmetric nature of the structure, the two cyclophosphazene rings are disposed exactly syn to each other with respect to the spermine bridge. The supramolecular structure is that of a hydrogen bonded dimer, where an NH of the spermine group interacts with a cyclophosphazene ring nitrogen in a head to tail fashion (N4-H4N…N2 D…A distance = 3.154Å). Longer range interactions arrange these dimers into an infinite sheet structure. This arrangement is similar to that of the hydrogen bonded structure of **2,** apart from the conformation of the eight-membered hydrogen-bonded ring, which forms a slightly twisted chair in the crystal structure of **6**.

Compound **8.** The molecular structure of the dispiro-monoansa compound **8** in Figure 3 is that of a spermine moiety bridging two asymmetrically-substituted cyclophosphazene rings, one with an ansa propanedioxy substituent and the other with two spiro groups. As in the structure of **6** the cyclophosphazene ring of the ansa-bridged moiety is highly distorted, with the ansa-bridged cyclophosphazene ring nitrogen (N1) positioned out of the mean ring plane by 0.31Å and with the compressed non bonded P…P separation between atoms P1 and P2 being 2.627Å. On the other hand, the di spiro substituted cyclophosphazene ring is nearly planar with a maximum deviation from the mean ring plane of 0.117Å for atom P6. Although the ansa bridge introduces chirality into the molecule such that P1 = S and P2 = R, overall the

molecule is meso. The relative conformation of the two cyclophosphazene rings around the tetra-methylene bridge is in an approximate syn conformation with an angle of 26.7° between the two ring planes. As observed in structures **2** and **6** the hydrogen bonded structure of **8** is that of a dimer, formed between the NH hydrogen of the spermine group and a cyclophosphazene ring nitrogen, with the separation between donor and acceptor atoms being 3.039 and 3.140Å. These unequal distances result in a saddle-shape hydrogen-bond ring conformation. The hydrogen-bonded motifs occur at both ends of these molecules, thus forming an infinite chain.

Characterization of the chiral configurational properties of compounds 2 and 7 by ^{31}P NMR on addition of a chiral solvating agent, (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol

It is found that one set of proton-decoupled ^{31}P NMR signals are observed for compounds **2, 3, 6-9** whereas two sets of closely-spaced signals are observed for the di-monospiro compound **4**. The latter two sets of signals correspond to the meso and racemic forms of compound **4** as shown previously for analogous spermine-bridged compounds [3]. On addition of chiral solvating agent [19], (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, CSA, in CDCl$_3$ or toluene-d_8 solution some of the ^{31}P NMR signals for compounds **2** and **7** separate into two signals of equal intensity characteristic of racemic mixtures. X-ray crystallography has shown that compound **2** is chiral and exists as a racemate, whereas crystals of compound **7** suitable for X-ray analysis could not be obtained. As an example, the stereogenic properties of the tri-spiro compound **7** are demonstrated by NMR spectroscopy in Figure 4. The proton-decoupled ^{31}P NMR spectrum of compound **7** in toluene-d_8 shown in Fig.4(a) consists of five multiplets corresponding to an AMX spin system for the mono-spiro substituted cyclophosphazene ring [signals expanded in Fig.4(b)] and an A$_2$X spin system for the di-spiro-substituted ring. Assignment of the ^{31}P NMR signals of the AMX part of compound **7**

to >PCl$_2$, >P(N-spiro) and >P(O-spiro) groups was made by comparison of proton-coupled (not shown) and proton-decoupled spectra, whereas assignment of the A$_2$X spin system to >P(N-spiro) and >P(O-spiro) follows simply from the triplet and doublet signals, respectively. Addition of CSA to the solution of compound **7** causes changes in chemical shifts of all signals indicating complexation and, as shown in Fig.4(c), it also causes splitting of all peaks for the AMX part of the spectrum, which is consistent with compound **7** being chiral and existing as a racemate.

Figure 4 about here

The effect of addition of CSA on chemical shifts of all the spiro and ansa derivatives in either CDCl$_3$ or toluene-d_8, as appropriate, is summarised in Table 3 at a molar ratio of CSA:compound of 10:1. It is found that changes in chemical shifts occur for all compounds indicating complexation with CSA, whether the compounds are racemic, meso or achiral. Normally there is a differential effect on signals probably reflecting the mode of complexation of CSA with the compound and the proximity of the CSA to each of the groups in the complex. For example, it is found that the effect of CSA on the P(N-spiro) group of all compounds is negative (signals move to low frequency), whereas the effect on the PCl$_2$ and P(O-spiro) groups is smaller and can be either positive or negative. It is likely that the NH moiety of the P(N-spiro) group of all compounds is a major site of complexation of CSA, in line with previous work on many different compounds containing NH and OH groups [19]. It is also found that the effect of CSA on chemical shifts of compound **2** is greater for solutions in toluene-d_8 compared with CDCl$_3$ (Table 3), which prompted the choice of toluene-d_8 for NMR investigation of the stereogenic properties of compound **7** in solution.

Table 3 about here

It is found that care must be taken in interpreting the stereogenic properties of compounds by NMR spectroscopy on addition of CSA (or CSR) to the solution, because there are many

cases of false positive results. It has already been shown [11] that the ^{31}P NMR signals of meso forms of spermine-bridged compounds such as compound **4** may exhibit doubling of peaks on addition of CSA. Another 'false positive effect' may be observed for ^{31}P NMR signals of meso compounds because the changes in chemical shifts on addition of CSA cause the spectra to change from A_2X-like to an A_2B spin system; this was observed for the 'doublet' signals of the >P(OR)Cl group of meso compound **6,** in which each resonance split into two signals of unequal and small separation (*e.g.* 1.8 and 2.4 Hz at an 18:1 mole ratio) that may be due to an A_2B (or even ABX) spin system rather than as a result of a stereogenic effect (Table 3). An analogous, but larger, effect has also been observed for compound **8** in this work (Table 3). On addition of CSA the 'doublet' signals of the >P(OR)Cl groups of meso compound **8** split into two signals of unequal and small separation (*e.g.* 3.1 and 3.8 Hz at a 17:1 mole ratio) that could be fitted as an ABX spin system, but not an A_2B spin system, which probably indicates another example of the 'anomalous meso effect' (as in ref. [11])

4. Conclusions

The chiral configurational isomers of spiro- and ansa-substituted spermine-bridged cyclophosphazene compounds have been investigated by X-ray crystallography and ^{31}P NMR spectroscopy. The symmetry of spermine-bridged cyclophosphazene compound **1** indicates that it is achiral, though it contains two potential homotopic stereogenic centres [>P(N-spiro) moiety of the two N_3P_3 units], which could lead to chiral compounds if substitution of the cyclophosphazene rings leads to asymmetry in the molecule. Substitution with 1,3-propanediol gives a series of spiro- and ansa-substituted spermine-bridged cyclo-phosphazene compounds; unsymmetrically-substituted bridged compounds are found to be chiral and exist as racemic mixtures of *R* and *S* forms, *viz.* mono-spiro **2** and tri-spiro **7**, whereas symmetrically-substituted bridged compounds may be meso, such as the di-mono-ansa **6** and di-spiro-mono-ansa **8** derivatives, or achiral, such as the tetra-spiro derivative **9**. Using X-ray

crystallography and ^{31}P NMR spectroscopy with addition of a chiral solvating agent, (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, it has been shown previously that the di-mono-spiro derivative **4** exists as a 1:1 mixture of meso and racemic forms [11]. In this work, X-ray crystallographic studies have provided definitive proof of the stereogenic properties of compounds **2, 6** and **8**, which have been confirmed using ^{31}P NMR spectroscopy and addition of a chiral solvating agent. In addition, the stereogenic properties of chiral compounds **2** and **7** have been elucidated using ^{31}P NMR spectroscopy and addition of CSA. The work demonstrates that derivatives of bridged cyclophosphazene compounds exhibit a range of stereogenic properties and that the question of chirality is an important consideration in cyclophosphazene chemistry.

Supplementary data are available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK on request, quoting deposition numbers CCDC 27630 – 276732 for compounds **2**, **6** and **8**, respectively.

References

[1] R.A. Shaw, B.W. Fitzsimmons and B.C. Smith, *Chem. Rev*., 62, (1962), 247.

[2] D.B. Davies, T.A. Clayton, R.J. Eaton, R.A. Shaw, A Egan, M. B. Hursthouse, G. Sykara, I. Porwolik-Czomperlik, M. Siwy and K. Brandt, *J. Amer. Chem Soc.,* 122, (2000), 12447.

[3] S.J. Coles, D.B. Davies, R.J. Eaton, M.B. Hursthouse, A. Kılıç, T.A. Mayer, R.A. Shaw and G. Yenilmez, *J. Chem. Soc. Dalton,* (2001), 365.

[4] I. Porwolik-Czomperlik, K. Brandt, T.A. Clayton, D.B. Davies, R.J. Eaton and R.A Shaw, *Inorg. Chem.,* 41, (2002), 4944.

[5] I.Dez, J. Levalois-Mitjaville, H. Grützmacher, V. Gramlich and R. De Jaeger, *Eur. J. Inorg. Chem.,* (1999), 1673.

[6] S. Beşli, S.J. Coles, D.B. Davies, R.J. Eaton, M.B. Hursthouse, A. Kılıç and R.A. Shaw, *Eur. J. Inorg. Chem.,* (2005), 959.

[7] S. Beşli, S.J. Coles, D.B. Davies, M.B. Hursthouse, H. İbişoğlu, A. Kılıç and R.A. Shaw, *Chem. Eur. J.,* 11 (2004), 4915.

[8] (a) J-F. Labarre, G. Guerch, F. Sournies, R. Lahana, R. Enjalbert and J. Galy, *J. Mol. Struct.,* 116, (1984), 75; (b) J-F. Labarre, *Topics Curr. Chem.,* 129, (1985), 173. (c) A. Kılıç, Z. Kılıç and R.A. Shaw, *Phosphorus, Sulfur, and Silicon,* 57, (1991), 111.

[9] A. H. Alkubaisi, H. G. Parkes and R.A Shaw. *Heterocycles,* 28, (1989), 347.

[10] K. Brandt, T. Kupka, J. Drozd, J.C. van de Grampel, A. Meetsma and A.P. Jekel, *Inorg. Chim. Acta,* 228, (1995), 187

[11] S. Beşli, S.J. Coles, D.B. Davies, R.J. Eaton, M.B. Hursthouse, A. Kılıç, R.A. Shaw, G. Yenilmez Çiftçi and S. Yeşilot. *J. Amer. Chem. Soc.,* 125, (2003), 4943.

[12] S.J. Coles, D.B. Davies, M.B. Hursthouse, A. Kılıç, T.A. Mayer, R.A. Shaw and G. Yenilmez Çiftçi, *Acta Cryst.* B60, (2004), 739.

[13] R. Hooft, *Collect: Data Collection Software, Nonius B.V.,* 1998.

[14] Z. Otwinowski and W. Minor, *Methods in Enzymology,* 276, (1997), 307.

[15] G.M. Sheldrick, SHELXS-97, Program for crystal structure solution; University of Göttingen, Germany, 1997.

[16] G.M. Sheldrick, SHELXL-97, Program for crystal structure refinement; University of Göttingen, Germany, 1997.

[17] F. H. Allen, *Acta Crystallogr.*, B58, (2002), 380.

[18] S.R. Contractor, M.B. Hursthouse, H.G. Parkes, L.S. Shaw, R.A. Shaw and H. Yılmaz, *J.Chem.Soc..Chem Commun.,* (1984), 675.

[19] (a) W. Pirkle and J.D. Hoover, *Topics in Stereochemistry,* 13, (1982), 263.; (b) G.R. Weissman, in *Asymmetric Synthesis,* 1, (1983), 153. Ed. Morrison, J. D. Academic Press, New York… (c) G.R. Sullivan, *Topics in Stereochemistry,* 10, (1978), 287.; (d) R.R. Fraser, in *Asymmetric Synthesis,* 1, (1983)**,** 173. Ed. Morrison, J. D. Academic Press, New York.; (e) P.L Rinaldi, *Progr. in NMR Spectr.,* 16, (1982)**,** 291. and references therein

Table 1 X-ray crystallographic data

	2	**6**	**8**[a]
Empirical formula	$C_{13}H_{28}Cl_6N_{10}O_2P_6$	$C_{16}H_{34}Cl_4N_{10}O_4P_6$	$C_{20}H_{41}Cl_5N_{10}O_6P_6$
Formula weight	754.97	758.15	880.70
Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_1/c$	$P\text{-}1$	$Pna2_1$
a (Å)	9.5842(2)	8.5849(17)	15.229(3)
b (Å)	12.5090(2)	9.5425(19)	26.120(5)
c (Å)	25.3979(5)	15.6271(19)	9.2683(19)
α (°)	90	84.46(3)	90
β (°)	101.1840(10)	84.63(3)	90
γ (°)	90	75.67(3)	90
Volume (Å^3)	2987.10(10)	758.6(3)	3686.7(13)
Z	4	1	4
Density (calc) (Mg/m^3)	1.679	1.660	1.587
Absorption coefficient (mm^{-1})	0.931	0.752	0.705
F(000)	1536	390	1816
Crystal size (mm)	0.55 × 0.42 × 0.10	0.28 × 0.2 × 0.05	0.45 x 0.14 x 0.12
θ_{max} (°)	27.50	27.42	27.48
Reflections collected	34810	11470	24873
Independent reflections ($I>2\sigma I$)	6836	3392	7818
R(int)	0.0779	0.0724	0.0723
Final R indices $F^2>2\sigma F^2$	R1 = 0.0607 wR2 = 0.1463	R1 = 0.0396 wR2 = 0.1013	R1 = 0.0432 wR2 = 0.0973
Δρ max / min (eÅ^{-3})	1.103 / −0.814	0.407 / −0.702	0.584 / −0.389

[a] Isolated as a 1:1 adduct with chloroform

Table 2. ^{31}P NMR parameters of spiro- and ansa-forms of 1,3-propanedioxy-substituted spermine-bridged cyclophosphazenes[a]

Compound: ring config.[b]		Chemical shifts / ppm				[2]J(PP) / Hz			
		>PCl$_2$	>P(Nspiro)	>P(Ospiro)	>P(OR)Cl	1,2	1,3	2,3	2,4
		1	2	3	4				
1[c]		22.1	10.4			40.5			
2		22.1	10.2			40.4			
	sp	25.0	15.5	9.0		41.1	68.0	63.6	
2[d]		21.5	11.2			40.3			
	sp	23.5	16.8	9.4		38.0	65.5	68.2	
3		22.0	10.2			40.4			
	an		16.8		30.8				46.5
4[e,f] r	sp	25.01	15.45	9.01		40.5	68.7	63.4	
m	sp	25.0	15.42	8.99		40.5	68.7	63.4	
6	an		16.4		30.4				46.3
7	sp	25.1	15.5	9.1		40.2	68.8	63.1	
	di-sp		19.8	14.6				57.9	
7[d]	sp	23.5	16.9	9.5		36.6	66.8.	68.0	
	di-sp		20.8	14.9				59.9	
8	an		16.4		30.3				46.3
	di-sp		19.4	14.1				58.2	
9[e]	di-sp		19.8	14.6				58.0	

[a] 202.45 MHz ^{31}P NMR measurements in CDCl$_3$ solutions at 298K. Chemical shifts referenced to external 85% H$_3$PO$_4$

[b] Abbreviations: sp = spiro, an = ansa; r = racemate, m = meso

[c] Data taken from ref.[3]

[d] Data on toluene-d_8 at 298K. It is noted that, in comparison of the ^{31}P NMR spectra of the mono-spiro substituted ring of both compounds 2 and 7 in toluene-d_8 and CDCl$_3$ solutions, changes occur not only in chemical shifts (as expected) but also in [2]J(PP) values.

[e] Data taken from ref.[11]

[f] Unequivocal assignment of meso (m) and racemic (r) forms resulted from characterization of the meso form of the diastereoisomer by X-ray crystallography [11].

Table 3. Effect of addition of CSA on ^{31}P NMR chemical shifts of spiro- and ansa-forms of 1,3-propanedioxy-substituted spermine-bridged cyclophosphazenes

Compound			Change in chemical shifts/ppb[b]				Separation of signals/ppb		
No.	Type[a]								
(i)	CSA with symmetrically substituted spermine-bridged compounds at 10:1 mole ratio								
			X or X$_2$	>PX$_2$	>P(bridge)	>PCl$_2$	>PX$_2$	>P(bridge)	>PCl$_2$
1[c]	ach		Cl		-21	37		-	-
4[d]	s-s	r	O(CH$_2$)$_3$O	16	-140	26	13	53	25
	s-s	m	O(CH$_2$)$_3$O	14	-145	28	15	56	27
9[c]	ss-ss	ach.	O(CH$_2$)$_3$O	-48	-164			-	
6	a-a	m	Cl/{O(CH$_2$)$_3$O]0.5	11	-158		e	-	
(ii)	CSA with unsymmetrically substituted spermine-bridged compounds at a 10:1 mole ratio								
			X or X$_2$	>PX$_2$	>P(bridge)	>PCl$_2$	>PX$_2$	>P(bridge)	>PCl$_2$
2			Cl		-5	11	f		0 [g]
	s	r	O(CH$_2$)$_3$O	-9	-25	4			5 [h]
2[i]			Cl		-70	70	0		
	s	r	O(CH$_2$)$_3$O	105	-470	110	40		70
7[i]	ss		O(CH$_2$)$_3$O	-223	-1020		f	f	
	s	r	O(CH$_2$)$_3$O	74	-325	65	47	80	10
8	ss	m	O(CH$_2$)$_3$O	-100	-320				
	a		Cl/[O(CH$_2$)$_3$O]0.5	20	-184		j	-	

[a] s = spiro, a = ansa; ach = achiral, m = meso, r = racemate

[b] $\Delta\delta = (\delta_{CSA}-\delta_{orig.})$; $\Delta\delta$ positive for high frequency shifts on addition of CSA in CDCl$_3$ unless otherwise noted.

[c] Data from ref. [11]

[d] Although compound **4** was known to exhibit meso and racemic forms in ref. [3], the effect of CSA (or CSR) was not reported. The effect of CSA on the meso form was reported in ref. [11]

[e] On addition of CSA the 'doublet' signals of the >P(OR)Cl group of meso compound **6** split into two signals of unequal and small separation (*e.g.* 1.8 and 2.4 Hz at an 18:1 mole ratio) due to the A$_2$B spin system rather than as a result of a stereogenic effect; cf. ref. [11].

[f] signals are broad and mask any effect of CSA

[g] signals are sharp but no effect is observed up to 84:1 mole ratio.

[h] Approximate value derived by extrapolation of effect from higher mole ratios (between 46:1 to 84:1)

[i] In toluene-d_8 solution

[j] On addition of CSA the 'doublet' signals of the >P(OR)Cl group of meso compound **8** split into two signals of unequal and small separation (*e.g.* 3.1 and 3.8 Hz at a 17:1 mole ratio) that could be fitted as an ABX spin system rather than an A_2B spin system, which probably indicates another type of example of the 'anomalous meso effect' (cf. ref. [11])
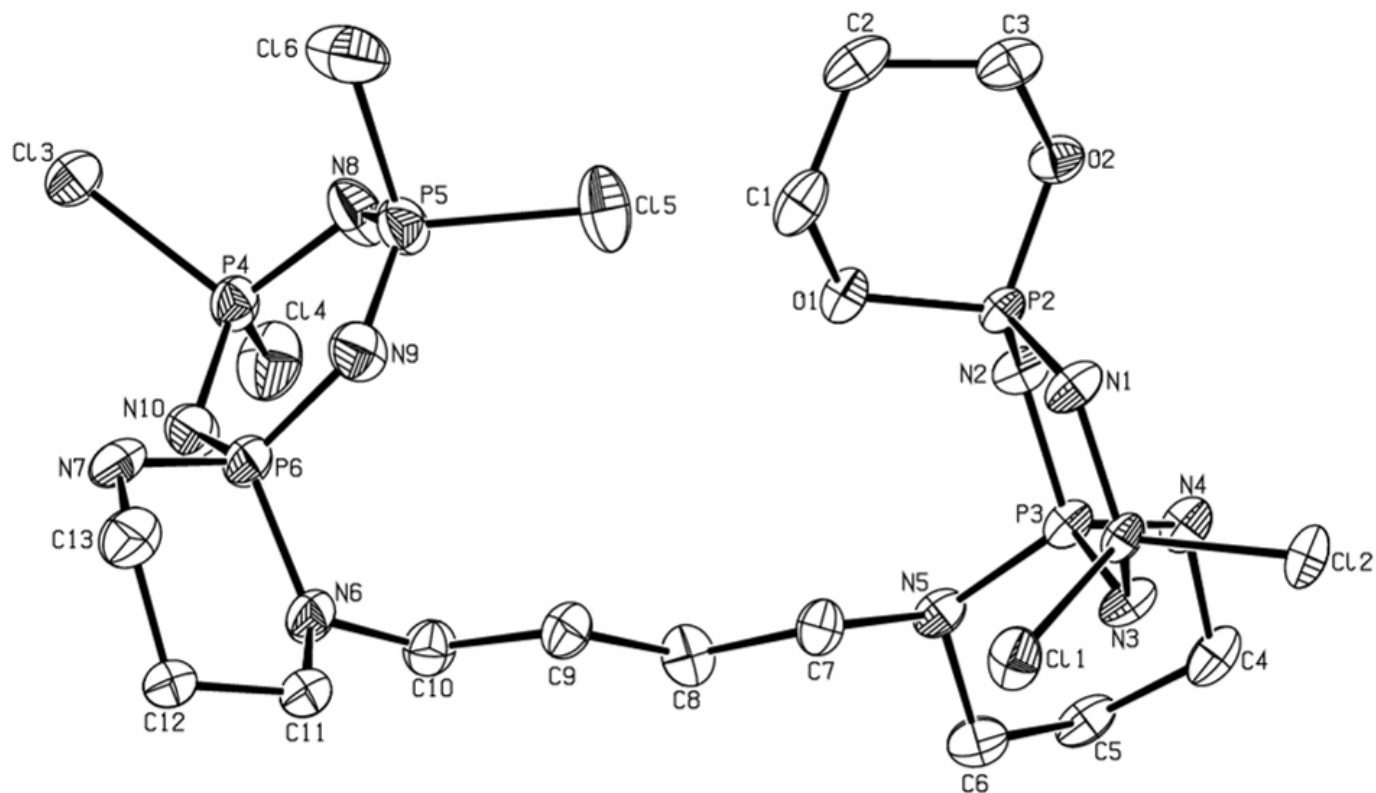
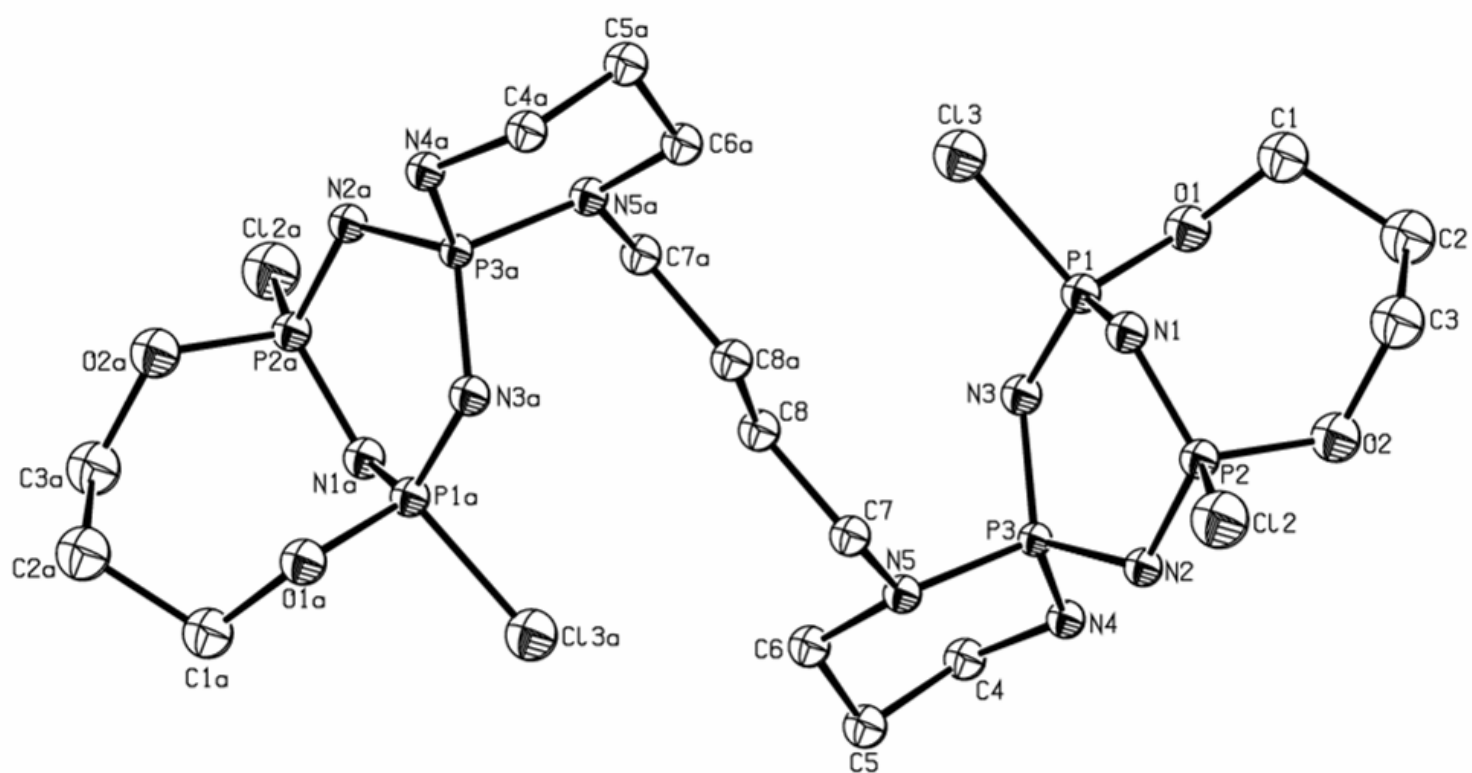Figure 1.   Crystal structure of the mono-spiro compound **2**.

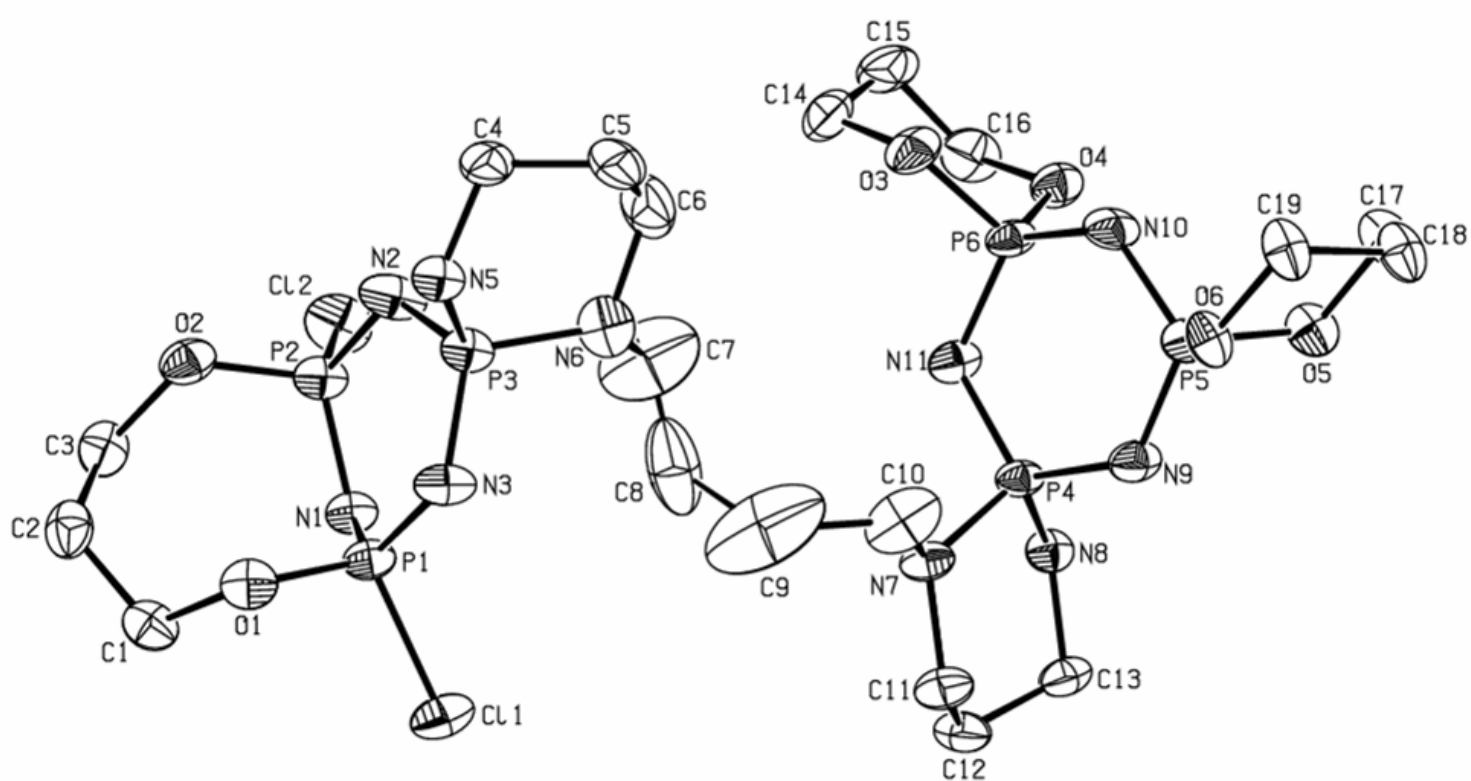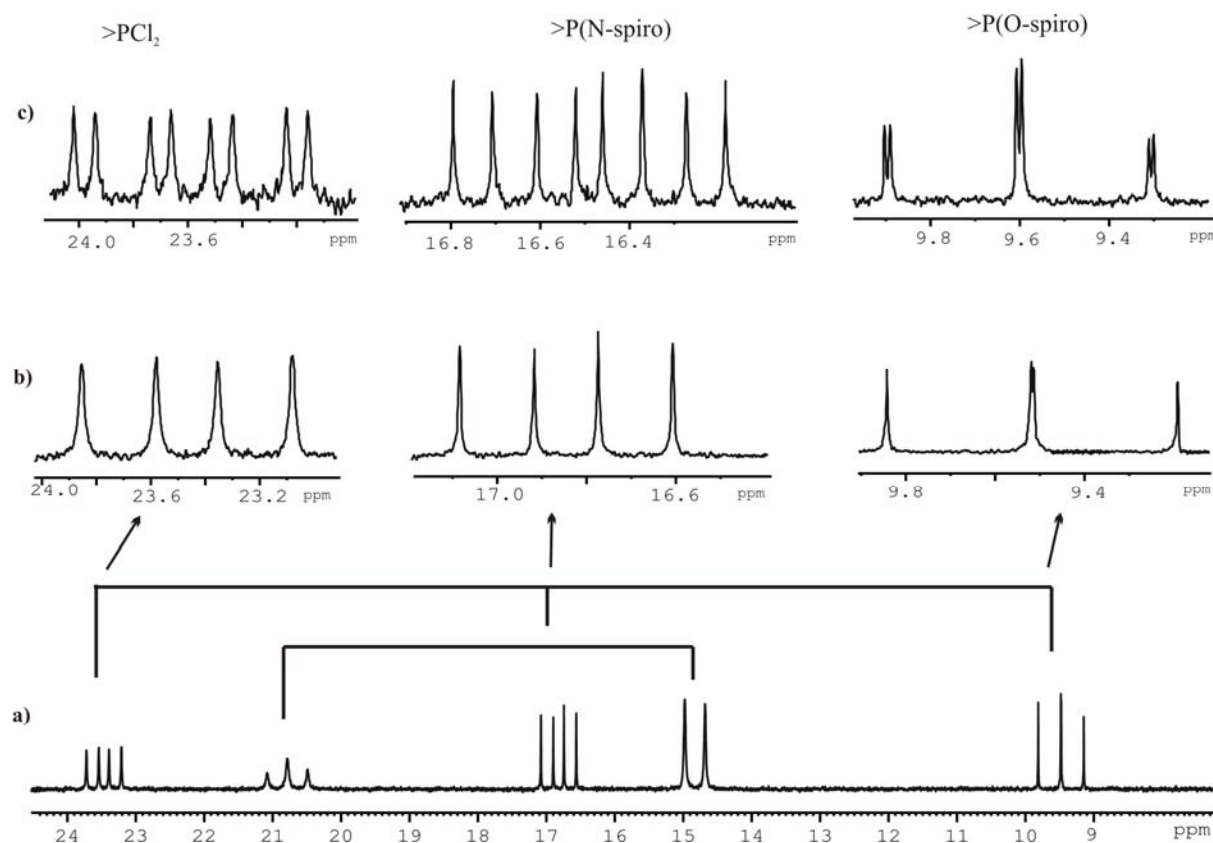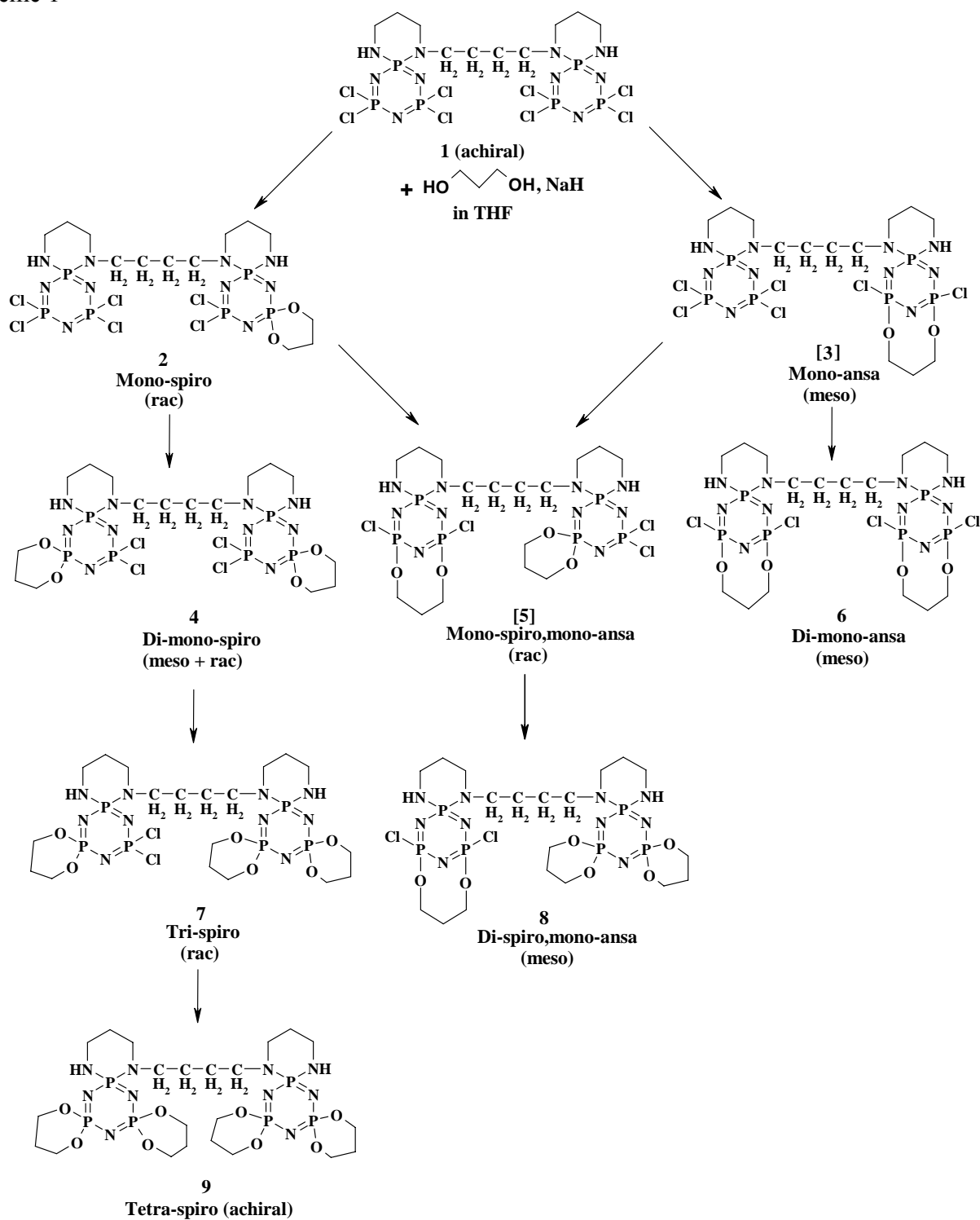Figure 2. Crystal structure of the di-mono-ansa compound **6**

Figure 3. Crystal structure of the di-spiro/mono-ansa compound **8**, with disorder (about atom C8) and the CHCl$_3$ solvent molecule removed for clarity.

Figure 4. 202.45 MHz proton-decoupled ^{31}P NMR spectra of the tri-spiro substituted compound **7** in toluene-d_8 solution at 298K (a) The AMX spin system corresponds to the mono-spiro substituted ring and the A$_2$X spin system corresponds to the di-spiro substituted ring. (b) Expanded signals of the AMX spin system of the mono-spiro substituted ring. (c) Addition of CSA causes each line of the AMX signals to split into two, corresponding to the two enantiomers.

Scheme 1[†]

1 (achiral)

+ HO ⌒ OH, NaH
in THF

2
Mono-spiro
(rac)

[3]
Mono-ansa
(meso)

4
Di-mono-spiro
(meso + rac)

[5]
Mono-spiro,mono-ansa
(rac)

6
Di-mono-ansa
(meso)

7
Tri-spiro
(rac)

8
Di-spiro,mono-ansa
(meso)

9
Tetra-spiro (achiral)

[†] Stereogenicity confirmed by X-ray (or by NMR + CSA) except for compounds with numbers in brackets

Graphical abstract

Reaction of the achiral spermine-bridged cyclotriphosphazene compound (A-Z =Cl) with 1,3-propanediol at different molar ratios in THF gives various spiro- and ansa-derivatives with different stereogenic properties, *i.e.* racemates for unsymmetrically-substituted derivatives and meso, diastereoisomeric or achiral forms for symmetrical substitution.