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Stereogenic properties of spiranes combined with one or two equivalent conventional centres of chirality

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Abstract

Derivatives of the tri-spirane pentaerythritoxy-cyclophosphazene compound **1** have been used to investigate the stereogenic properties of spiranes combined with either one or two conventional centres of chirality. In compound **1**, the two inner rings are carbocyclic and symmetrical and the two outer rings are cyclotriphosphazenes substituted in different positions to provide the conventional centres of chirality. Reaction of **1** in a 1:1 molar ratio with the unsymmetrical dinucleophilic reagent, 1,3-aminopropanol, gave the mono-spiro substituted derivative **2**, which was shown to exist as a racemate by X-ray crystallography and ^{31}P NMR spectroscopy on addition of a chiral solvating agent (CSA). Reaction of **1** with 1,3-aminopropanol in a 1:2 molar ratio gave three diastereoisomeric di-mono-spiro products **3a**–**3c**, which were all shown to be racemates using a combination of X-ray crystallography (**3a**, **3c**) and ^{31}P NMR spectroscopy on addition of a CSA (**3b**), thus proving the case of the stereogenic properties of spirane molecules combined with two equivalent conventional centres of chirality. It is also shown by quantitative ^{31}P NMR spectroscopy of the reaction mixture and by isolation of reaction products that the proportions of the diastereoisomers **3a**:**3b**:**3c** are in approximate ratios of 1:2:1, respectively, and these results have been rationalised by analysis of the stereogenic properties of the series of reactions **1** → **2** → **3**.

Keywords: Trispiranes; Cyclotriphosphazene derivatives; X-ray crystallography; ^{31}P NMR spectroscopy; Chiral solvating agent

1. Introduction

The stereogenic properties of carbocyclic spiranes with two interlocking rings have been established for a number of years [1] and have been categorised in terms of those molecules with axial chirality and those with centres of chirality [2]. The stereogenic properties of linear tri-spiranes[1] (in which the two inner rings are carbocyclic and symmetrical and the two outer rings are substituted cyclotriphosphazenes) have recently been reported [3,4]. All these tri-spiranes are derivatives of the spirane-bridged cyclophosphazene compound $N_3P_3Cl_4(OCH_2)_2C(CH_2O)_2N_3P_3Cl_4$ (**1**), whose structure (Scheme 1) consists of four six-membered rings, each joined at a tetrahedral atom (phosphorus or carbon) to the next ring, with each carbocyclic ring being orthogonal to its neighbours [5]. The stereogenic properties of the derivatives of **1** are based not only on the chirality of the spirane system, but also on the fact that tetra-coordinated phosphorus (V) atoms in cyclophosphazene derivatives may be centres of chirality [6]. The structure of the tri-spirane, compound **1**, is also represented in Scheme 1 in the form of a mono-spirane stick diagram, in which the inner organophosphate rings have been omitted for clarity and the outer cyclophosphazene rings, which

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[1] In our original work on the stereochemistry of spiranes (Ref. [3]), derivatives of compound **1** were incorrectly referred to as tetra-spiranes rather than the correct designation as tri-spiranes.

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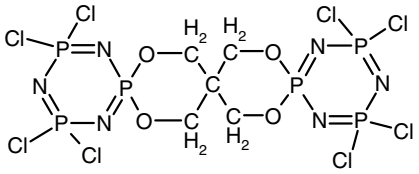

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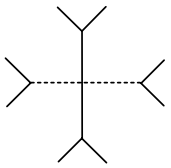


1

Scheme 1.

are orthogonal to each other, are shown with the ring to the back in dotted type. In this representation it can be readily seen that the spirocyclic compound **1** has at least one plane of symmetry and is achiral.

Examination of molecular models indicates that derivatives of compound **1** should exhibit a wide range of configurational isomers, whose stereogenic properties are analogous to those for mono-spirane derivatives. For example, it has recently been shown for bis di-substituted cyclophosphazene derivatives of **1** that racemates were observed for bis geminal derivatives as well as for non-geminally di-substituted *cis* and *trans* (the latter has two diastereoisomers) derivatives [3]. Further cases of the stereochemistry of bis di-substituted cyclophosphazene derivatives of **1** resulted from its reaction with the symmetrical difunctional nucleophilic reagent, 1,3-propanediol, to give four isomeric products, viz. the di-mono-spiro, di-mono-ansa and two mono-spiro/mono-ansa derivatives [4]. It was shown by ^{31}P NMR spectroscopy on addition of a chiral solvating agent (CSA) that both the di-mono-spiro and di-mono-ansa derivatives are racemates, as expected [4], because they correspond to the cases of bis geminal and *cis* non-geminally di-substituted derivatives discussed previously [3]. On the other hand it was confirmed by X-ray crystallography that the two mono-spiro/mono-ansa spirane derivatives are meso, which represented a new case of diastereoisomerism in tri-spirane derivatives [4].

The aim of the present work is to elucidate systematically the stereochemistry of spirane compounds combined with conventional centres of chirality. It is known that reactions of cyclotriphosphazenes with the unsymmetrical dinucleophilic reagent, 1,3-aminopropanol, predominantly give spiro derivatives [7], in contrast to the spiro and ansa derivatives (di-mono-spiro, di-mono-ansa and two mono-spiro/mono-ansa compounds) observed for the reaction of **1** with the analogous symmetrical dinucleophilic reagent, 1,3-propanediol [4]. The phosphorus atoms of each spiro P[NH(CH$_2$)$_3$O] group are potential centres of chirality and so reaction of **1** with 1,3-aminopropanol may be used to investigate the stereogenic properties of spiranes with different numbers of conventional centres of chirality. In this work reaction of **1** with 1,3-aminopropanol in a 1:1 molar ratio gave the mono-spiro substituted compound **2** and reaction of **1** with 1,3-aminopropanol in a 1:2 molar ratio gave a series of three different di-mono-spiro substituted compounds, **3a**–**c**. The stereogenic properties of compounds **2** and **3a**–**c** were investigated by X-ray crystallography and/or ^{31}P NMR spectroscopy on addition of a chiral solvating agent (CSA). As expected, it is found that the mono-spiro substituted compound **2** exists as a racemate. It is also found that the three di-mono-spiro derivatives, **3a**–**c**, are all racemates, thus confirming the classical work on the stereochemistry of spiranes with two equivalent conventional centres of chirality [8]. A quantitative analysis of the reaction products **3a**–**c** has been made by ^{31}P NMR spectroscopy of the reaction mixture and by isolation of each diastereoisomer and the results have been rationalised in terms of the stereogenic properties of their formation reactions.

2. Experimental

2.1. Materials

Hexachlorocyclotriphosphazene (Shin Nisso Kako Co Ltd.) was purified by fractional crystallisation from hexane. The following chemicals were obtained from Merck: pentaerythritol (>98%), triethylamine (>99.0%), silica gel 60, tetrahydrofuran (⩾99.0%), dichloromethane (⩾99.0%), ethyl acetate (⩾99.0%), *n*-hexane (>96%), from Fluka: 3-amino-1-propanol (⩾98%), light petroleum (b.p. 40–70 °C). The deuterated solvent ($CDCl_3$) for NMR spectroscopy was obtained from Apollo Scientific and the chiral solvating agent (CSA), (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol, from Aldrich Chem. Co.

2.2. Methods

Elemental analyses were obtained using a Carlo Erba 1106 Instrument. Mass spectra 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. Differential Scanning Calorimetry (DSC) of each compound was performed on a Mettler Toledo DSC 822 instrument from 25 °C to 340 °C at a heating rate of 15 °C/min, except for compound **3b**, which was heated to 200 °C. 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, 230–400 mesh; for 3 g. crude mixture, 100 g. silica gel was used in a column of 3 cm in diameter and 60 cm in length). ^{31}P NMR spectra were recorded in $CDCl_3$ solutions on a Bruker DRX 500 MHz spectrometer using 85% H_3PO_4 as an external reference for ^{31}P. In order to assign the signals of some compounds both proton-coupled and proton-decoupled ^{31}P NMR spectra were recorded. Quantitative ^{31}P NMR spectra were performed with suppression of the NOE and under pulsing conditions ($\pi/3$ pulse, overall repetition time of 3.6 s) that allowed for relaxation times of the ^{31}P nuclei

of up to 6 s in spiro- and ansa-substituted cyclophosphazene derivatives [9]. Experiments involving the chiral solvating agent (CSA) were performed by addition of small aliquots of a concentrated solution of CSA in the solvent used for NMR spectroscopy and the proton-decoupled ^{31}P NMR spectra recorded at each addition.

2.3. Synthesis

Compound **1** was synthesized as in the literature (m.p. 255 °C) [5].

2.3.1. Reaction of compound *1* with 1,3-aminopropanol to give compound *2* (Scheme 2)

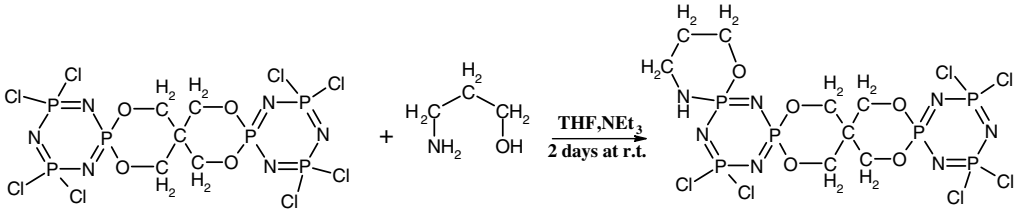
3-Amino-1-propanol (0.044 g, 0.584 mmol) in 20 ml dry THF was added first to a stirred solution of compound **1** (0.4 g, 0.584 mmol) dissolved in 40 ml dry THF at −15 °C under an argon atmosphere and then triethylamine (0.12 g, 1.168 mmol) in 20 ml of dry THF was added drop-wise. The reaction mixture was stirred for two days at room temperature and the reaction followed by TLC. Triethylamine hydrochloride was then removed by filtration and the solvent removed under reduced pressure. One product was isolated by column chromatography using dichloromethane:ethyl acetate (3:2). Compound **2**; 0.1 g, 25%, m.p. 253 °C (DSC on 0.1 mg), (found: C, 13.88; H, 2.17; N, 14.14%); $[M+1]^+$, 686.1; $C_8H_{15}Cl_6N_7O_5P_6$ requires C, 13.97; H, 2.20; N, 14.25, M, 685.

2.3.2. Reaction of compound *1* with 1,3-aminopropanol to give compounds *3a–c* (Scheme 3)

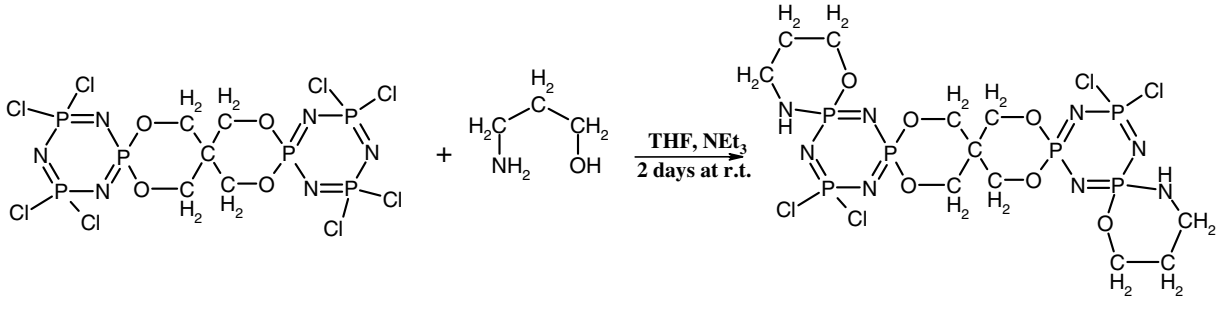
3-Amino-1-propanol (0.44 g, 5.84 mmol) in 40 ml dry THF was added first to a stirred solution of compound **1** (2 g, 2.919 mmol) dissolved in 80 ml dry THF at −15 °C under an argon atmosphere and then triethylamine (1.2 g, 11.68 mmol) in 20 ml of dry THF was added drop-wise. The reaction mixture was stirred for two days at room temperature and was followed by TLC indicating the formation of three products and no starting material remaining. Triethylamine hydrochloride was then removed by filtration and the solvent removed under reduced pressure. Three products were isolated by column chromatography using dichloromethane:light petroleum (3:2). The order of elution was **3a**; 0.5 g, 25%, decomp. 316 °C (DSC on 0.53 mg) (found: C, 19.12; H, 3.19; N, 16.14%); $[M+1]^+$, 689.0; **3b**; 0.8 g, 40%, m.p. 164 °C (DSC on 2.12 mg) (found: C, 19.11; H, 3.18; N, 16.16%); $[M+1]^+$, 688.5; and **3c**; 0.3 g, 15%, decomp. 187 °C (DSC on 1.49 mg) (found: C, 19.14; H, 3.20; N, 16.18%); $[M+1]^+$, 688.9; $C_{11}H_{22}Cl_4N_8O_6P_6$ requires C, 19.15; H, 3.21; N, 16.24, M, 688.

2.4. X-ray crystallography

X-ray crystallographic data for structures **3a** and **3c** were collected by means of combined phi and omega scans on a Bruker-Nonius KappaCCD area detector situated at



Scheme 2.



Scheme 3.

the window of a rotating anode (λMo K$\alpha = 0.71073$ Å). Data collection on compound **2** using the same laboratory-based facilities as for compounds **3a** and **3c** resulted in a very weak dataset that produced a structure with unsatisfactory statistics and molecular geometry and so X-ray crystallographic data for compound of **2** were collected at the Daresbury Synchrotron Radiation Source [10] (Station 16.2SMX). Although some of the statistics for the structure of compound **2** arising from the synchrotron dataset are a little high, the molecular geometry and thermal parameters are reasonable and hence of an adequate standard for inclusion in this study on spirane chirality.

All data were collected at 120 K. The structures were solved by direct methods, SHELXS-97 and refined using SHELXL-97 [11] and the data were corrected for absorption effects using SADABS [12]. The NH hydrogen atoms were determined experimentally and the other hydrogen atoms were included in the refinement, but thermal parameters and geometry were constrained to ride on the atom to which they are bonded.

3. Results and discussion

Previous work has shown that reaction of **1** with the symmetrical dinucleophilic reagent, 1,3-propanediol, gave four isomeric products, viz. the di-mono-spiro, di-mono-ansa and two mono-spiro/mono-ansa derivatives, though the di-mono-spiro compound predominated [4]. If an analogous reaction is effected with the unsymmetrical dinucleophilic reagent, 1,3-aminopropanol, then the phosphorus atoms to which the reagent is attached (spiro or ansa) become centres of chirality, enabling the investigation of the stereogenic properties of spirane compounds combined with the same conventional equivalent centres of chirality. In this work it is found that reaction of **1** with the unsymmetrical dinucleophilic reagent, 1,3-aminopropanol, predominantly gave spiro-derivatives, in agreement with previous work on cyclophosphazenes [7].

3.1. Spirane compounds combined with one conventional centre of chirality

The spirane-bridged compound **1** was allowed to react with 1,3-aminopropanol in a 1:1 molar ratio to give compound **2** (Scheme 2). The proton-decoupled ^{31}P NMR spectrum of compound **2** is observed in Fig. 1a as the superposition of an ABX spin system for the unsubstituted cyclophosphazene moiety and an AMX spin system for the cyclophosphazene substituted with the spiro $NH(CH_2)_3O$ group. The two sets of signals were differentiated by detailed analysis of the magnitudes of the coupling constants and assignment of signals of **2** was assisted by the proton-coupled ^{31}P NMR spectrum shown in Fig. 1b. The signals at ca. 25 ppm correspond to the $\geq PCl_2$ groups (no coupling), the signal at ca. 13 ppm corresponds to the $\geq P[NH(CH_2)_3O]$ group and the signals at ca. 5 and 11 ppm correspond to the $\geq$P(bridge) groups by comparison with previous results on the spiro and ansa 1,3-propanedioxy derivatives of **1** [4]. The ^{31}P NMR chemical shifts and ^2J(PP) coupling constants for compound **2** are summarised in Table 1(i).

The structure of compound **2** was investigated by X-ray crystallography. The small crystals of compound **2** resulted in a very weak dataset and so X-ray crystallographic data were collected using a synchrotron radiation source. Although some of the statistics for the structure of compound **2** arising from the synchrotron dataset are a little high, the molecular structure (Fig. 2) is of sufficient quality to confirm that compound **2** is the mono-substituted derivative of compound **1** and that **2** exists as a racemate; the *R* form of compound **2** is depicted in Fig. 2. It can be seen that compound **2** contains five rings, two phosphazene units bridged by a pentaerythritoxy moiety in a spirane arrangement, and a spiro-$O(CH_2)_3NH$ unit in one of the cyclophosphazene rings. The cyclophosphazene rings are essentially planar, with the maximum deviation from the plane being 0.098 Å (for P4, the bridging P atom of the unsubstituted ring) and 0.123Å (for N1, one of the N atoms adjacent to the spiro-$O(CH_2)_3NH$) substituent.

The stereogenic properties of compound **2** were also investigated by ^{31}P NMR spectroscopy on addition of the chiral solvating agent (CSA), (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol. Addition of CSA causes shifts in ^{31}P NMR signals indicating complexation with compound **2** and eventually, as shown in Fig. 1c, signals of compound **2** split into two lines in a 1:1 ratio indicating that compound **2** exists as a racemate. The changes in chemical shifts and separation of ^{31}P NMR signals on addition of CSA at ca. 20:1 mole ratio are summarised in Table 1(ii) and (iii), respectively. Reaction of 1,3-aminopropanol with the trispirane compound **1** in a 1:1 ratio to give the *R* and *S* enantiomers of compound **2** is shown diagrammatically in Scheme 4 in terms of the mono-spirane stick diagram representation.

3.2. Spirane compounds combined with two equivalent conventional centres of chirality

1,3-Aminopropanol was allowed to react with the spirane-bridged compound **1** in a 2:1 mole ratio to give three compounds, **3a**–**c**, (Scheme 3), which were separated by column chromatography in the order **3a**, **3b** and **3c**. Characterization by elemental analysis and mass spectrometry give the same results for the three products, as expected for isomers. The proton-decoupled ^{31}P NMR spectra of two of the isomers (**3a** and **3c**) are observed as ABX spin systems resulting from the two phosphazene rings in each compound having the same substitution pattern. Assignment of signals of **3a** and **3c** was assisted by proton-coupled ^{31}P NMR spectra, which show that the signals at ca. 25 ppm correspond to $\geq PCl_2$ groups (no coupling), the signals at ca. 13 ppm correspond to the $\geq P[O(CH_2)_3NH]$ groups and the signals at ca. 10 ppm corresponds to the

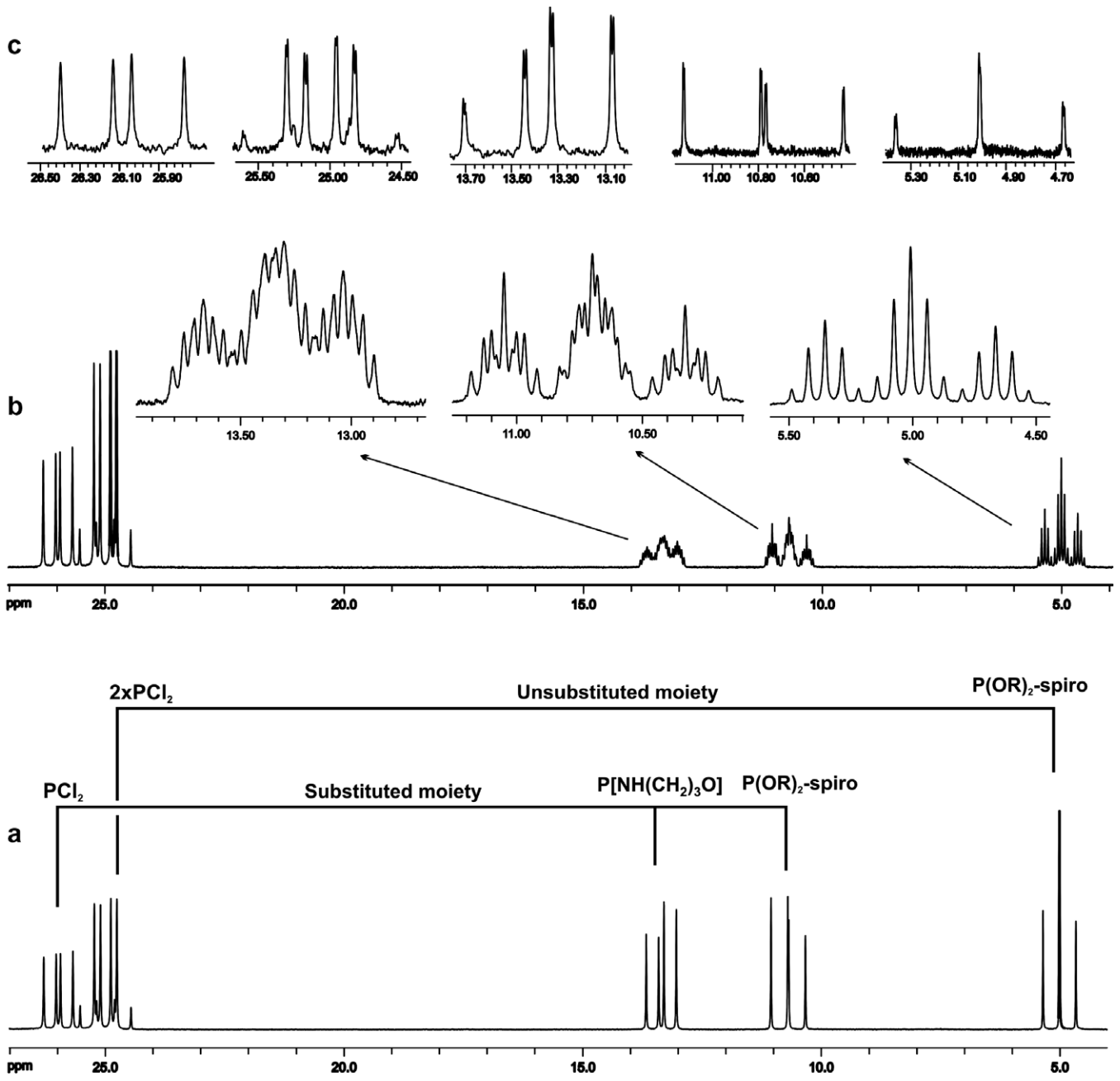


Fig. 1. (a) Proton-decoupled ^{31}P NMR spectrum of compound **2** in $CDCl_3$ solution showing the superposition of the ABX spin system for the unsubstituted cyclophosphazene moiety and the AMX spin system for the cyclophosphazene substituted with the $P[NH(CH_2)_3O]$ group. (b) Proton-coupled ^{31}P NMR spectrum of compound **2** used to assign the signals at ca. 25 ppm to the PCl_2 groups (no coupling), the signal at ca. 13 ppm corresponds to the $P[NH(CH_2)_3O]$ groups and the signals at ca. 5 and 11 ppm correspond to the P(bridge) groups. (c) Proton-decoupled ^{31}P NMR spectrum of compound **2** with added CSA at ca. 20:1 mole ratio shows the doubling of a number of NMR signals in a 1:1 ratio indicating that compound **2** exists as a racemate.

>P(bridge) groups. The ^{31}P NMR data for compounds **3a** and **3c**, which are summarised in Table 1(i), exhibit small differences in chemical shifts and, in particular, some values of $^{2}J(PP)$. The proton-decoupled ^{31}P NMR spectrum of the remaining product **3b** is shown in Fig. 3a. Expansion of the ^{31}P NMR signals of compound **3b** in Fig. 3b confirms that it consists of two ABX spin systems in a 1:1 ratio that are very similar to those for compounds **3a** and **3c**, even to the extent that one ABX spin system has similar chemical shifts and coupling constants to compound **3a** and the other to **3c**, Table 1(i). The similarity in ^{31}P NMR data for compounds **3a**–**c** indicates that they are all di-mono-spiro derivatives of compound **1** having different stereochemical relationships. The stereogenic properties of compounds **3a**–**c** were investigated by ^{31}P NMR spectroscopy in the presence of a chiral solvating agent [CSA, (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol] similar to previous work on other spirane derivatives [3,4]. On titration with CSA it

Table 1
^{31}P NMR parameters of pentaerythritoxy-bridged cyclophosphazene derivatives and the effect of addition of a chiral solvating agent (CSA)[a]

Cpd	Relation of *NH* groups	>P(bridge)	$>PCl_2$	$>PX_2$	X_2	^2J(PP)/Hz
		1	2	3		1,2; 1,3; 2,3
(i) ^{31}P NMR chemical shifts (ppm)						
1[b]		4.5	24.6			69.9
2		5.06	25.19	24.88	Cl	70.5; 69.0; 60.1
		10.81	26.07	13.39	$NH(CH_2)_3O$	71.1; 75.6; 52.4
3a	*anti*	10.28	25.62	12.81	$NH(CH_2)_3O$	71.5; 74.8; 52.6
3b	*anti*	10.31	25.60	12.80	$NH(CH_2)_3O$	71.6; 74.8; 52.6
	syn	10.23	25.40	12.96	$NH(CH_2)_3O$	69.7; 76.1; 52.8
3c	*syn*	10.25	25.41	12.94	$NH(CH_2)_3O$	69.8; 76.0; 52.8
(ii) Change in chemical shifts (ppb) at a mole ratio of CSA:compound of 20:1						
1[b]		−12	18			69.9
2		−27	11	6	Cl	70.4; 68.9; 60.4
		−9	25	−10	$NH(CH_2)_3O$	71.0; 75.3; 52.2
3a	*anti*	−36	36	−5	$NH(CH_2)_3O$	71.3; 74.5; 52.4
3b	*anti*	−33	30	−2	$NH(CH_2)_3O$	71.6; 74.6; 52.3
	syn	−32	36	−10	$NH(CH_2)_3O$	69.7; 75.8; 52.6
3c	*syn*	−31	30	−8	$NH(CH_2)_3O$	69.8; 75.7; 52.7
(iii) Separation of signals of enantiomers (ppb) at a mole ratio of CSA:compound of 20:1						
2		5	11	17	Cl	
		5	[c]	10	$NH(CH_2)_3O$	
3a	*anti*	9	22	23	$NH(CH_2)_3O$	
3b	*anti*	9	23	[c]	$NH(CH_2)_3O$	
	syn	[c]	28	21	$NH(CH_2)_3O$	
3c	*syn*	15	32	4	$NH(CH_2)_3O$	

[a] 202.45 MHz ^{31}P NMR measurements in $CDCl_3$ solutions at 298 K. CSA is the chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol.
[b] Data taken from Ref. [3]; for comparison purposes the CSA results are given at a 20:1 molar ratio, whereas they were quoted for 100:1 molar ratio in Ref. [3].
[c] Magnitude too small to measure at 202.45 MHz.

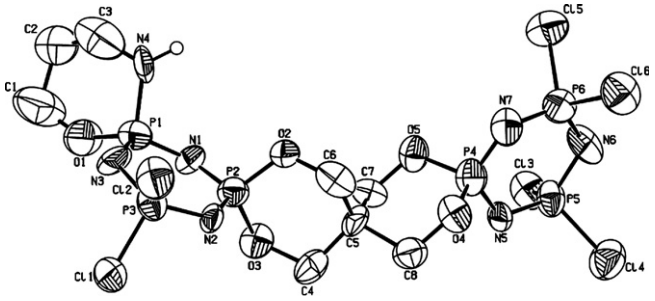
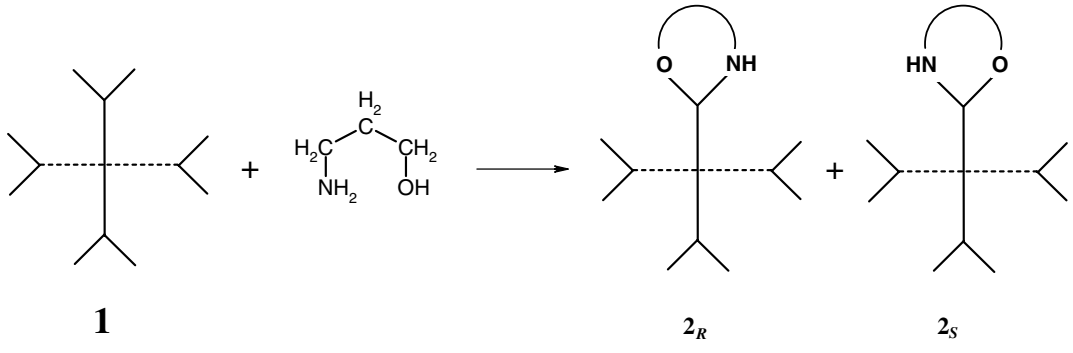


Fig. 2. Molecular structure of the *R* enantiomer of compound **2**.

was found that the ^{31}P NMR signals of compounds **3a–c** exhibit chemical shift changes indicating complexation with the CSA, and that most signals separate into two lines of equal intensity consistent with all three compounds existing as racemates. An example is shown in Fig. 3c for the ^{31}P NMR spectrum of compound **3b**, with added CSA at ca. 28:1 mole ratio, which exhibits doubling of a number of NMR signals in a 1:1 ratio indicating that compound **3b** exists as a racemate. The changes in ^{31}P NMR chemical shifts and separation of signals of compounds **3a–c** at a 20:1 mole ratio of CSA:**2** are summarised Table 1(ii) and (iii), respectively.



Scheme 4. Formation of tri-spiranes with one conventional centre of chirality giving a racemate.

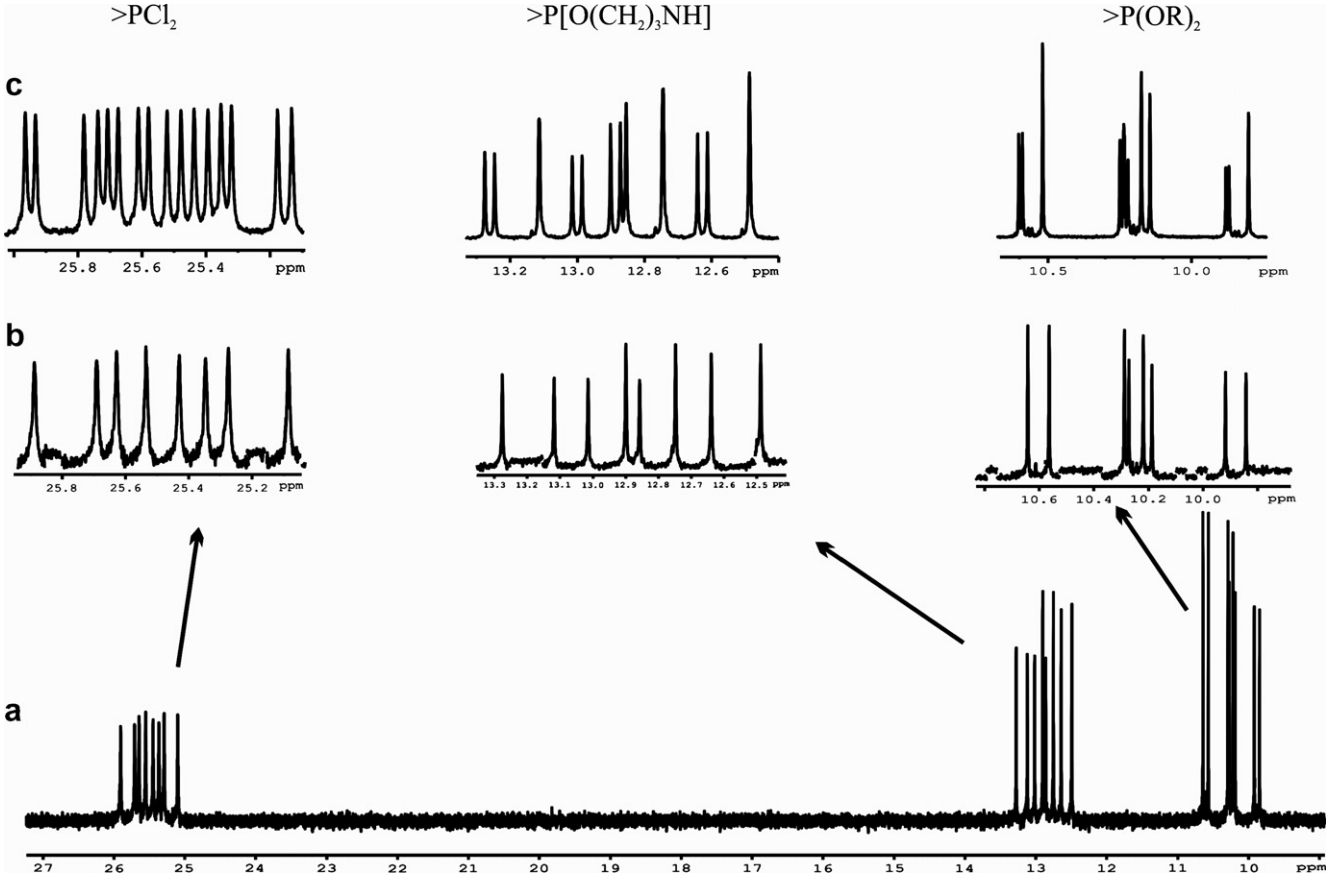


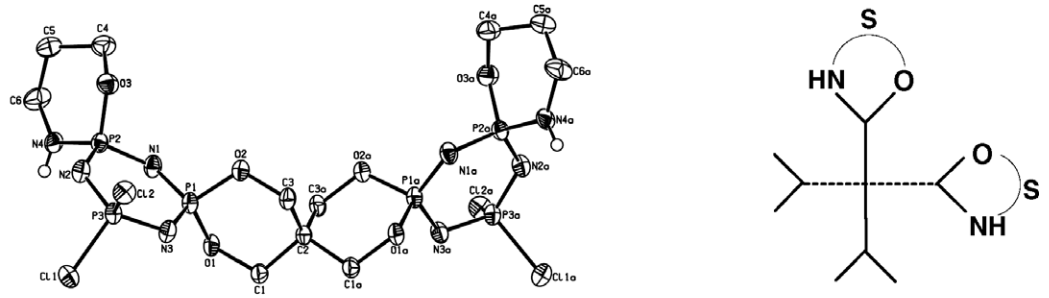
Fig. 3. (a) Proton-decoupled ^{31}P NMR spectrum of compound **3b** in $CDCl_3$ solution. (b) Expansion of the ^{31}P NMR spectrum of compound **3b** shows two ABX spin systems as the superposition of those for **3a** and **3c**, because the stereochemistry of the spiro group in one cyclophosphazene ring of **3b** resembles that of **3a** and the other ring resembles that of **3c**. (c) ^{31}P NMR spectrum of compound **3b** with added CSA at ca. 28:1 mole ratio shows the doubling of a number of NMR signals in a 1:1 ratio indicating that compound **3b** exists as a racemate.

Table 2
X-ray data for compounds **2**, **3a** and **3c**

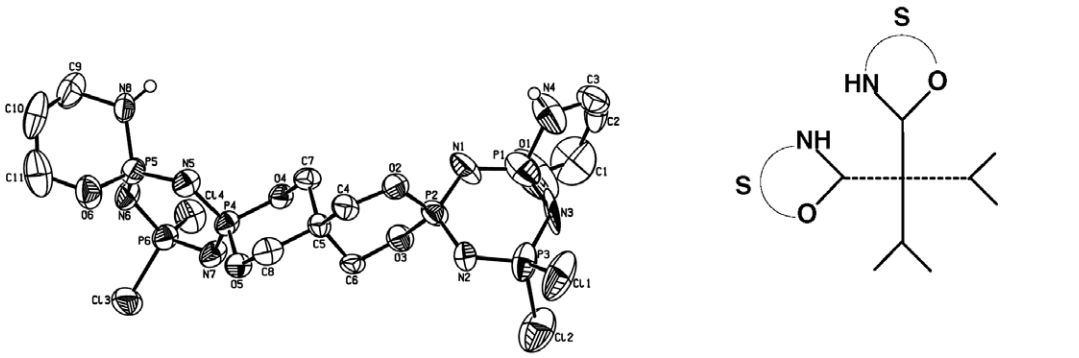
	2	**3a**	**3c**
Empirical formula	$C_8H_{15}Cl_6N_7O_5P_6$	$C_{11}H_{22}Cl_4N_8O_6P_6$	$C_{11}H_{22}Cl_4N_8O_6P_6$
Formula weight	687.79	689.99	689.99
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	11.925(15)	28.605(3)	11.7919(9)
b (Å)	14.250(18)	8.4274(7)	15.0734(15)
c (Å)	14.929(19)	11.8629(11)	15.2160 (12)
α (°)	90	90	90
β (°)	101.104(13)	108.196(6)	99.611(4)
γ (°)	90	90	90
Volume (Å^3)	2489(5)	2716,7(5)	2666.6(4)
Z	4	4	4
D_{calc} (Mg/m^3)	1.835	1.687	1.719
Absorption coefficient (mm^{-1})	1.113	0.834	0.850
$F(000)$	1376	1400	1400
Crystal size (mm)	$0.04 \times 0.005 \times 0.005$	$0.15 \times 0.01 \times 0.01$	$0.08 \times 0.02 \times 0.01$
θ_{max} (°)	27.5	27.48	24.22
Reflections collected	10189	15491	26667
Independent reflections	2282	2946	4263
Final R indices $F^2 > 2\sigma F^2$	$R_1 = 0.1830$, $wR_2 = 0.4670$	$R_1 = 0.0604$, $wR_2 = 0.1268$	$R_1 = 0.1066$, $wR_2 = 0.2056$
$\Delta\rho$ max/min (e Å^{-3})	1.179/−0.782	0.466/−0.482	1.025/−0.749

Although NMR spectroscopy has been used to show that compounds **3a–c** are different di-mono-spiro derivatives of compound **1**, such methods cannot be used to assign their absolute structures. Suitable crystals for X-ray crystallographic studies were obtained for **3a** and **3c**, though not for **3b**. The X-ray data are summarised in Table 2 and the crystal structures of **3a** and **3c** are shown in Fig. 4. It can be seen that both molecules contain six rings, two phosphazene units bridged by a pentaerythritoxy moiety in a spirane arrangement, and a spiro-$O(CH_2)_3NH$ unit in both cyclophosphazene rings. In the structures of both **3a** and **3c** the cyclophosphazene ring is essentially planar, with the maximum deviation from the plane for **3a** being 0.091 Å (N1, the ring N atom flanked by the two P(spiro) moieties), and for the two different units in compound **3c** being 0.084 Å (P2, the bridging P atom) and 0.094 Å (P5, the P atom of the P(spiro) moiety). The crystal structures show that both **3a** and **3c** exist as racemates and the *S*/*S* enantiomers are depicted for both diastereoisomers in Fig. 4. The chiral structures of compounds **3a** and **3c** both have twofold symmetry and the difference in the stereochemistry of the two structures is in the relationship of the two spiro-aminopropanoxy units, as shown diagrammatically in Fig. 4. Using the relationship of the NH atoms of the spiro-$O(CH_2)_3NH$ unit as a reference, it can be seen that the two spiro groups have an *anti* arrangement in **3a** and a *syn* arrangement in **3c**. These relationships may be used to explain the ^{31}P NMR spectrum of isomer **3b** as the superposition of those for **3a** and **3c**, because the stereochemistry of the spiro group in one cyclophosphazene ring resembles that of **3a** and the other ring resembles that of **3c** which leads to small differences in chemical shifts and coupling constants for the analogous ^{31}P NMR signals (Table 1).

Reaction of 1,3-aminopropanol with the trispirane compound **1** in a 2:1 ratio to give the enantiomers of compound **3a–c** is shown diagrammatically in Scheme 5 for one of the enantiomers of each diastereoisomer using the mono-spirane stick diagram representation. The chiral configurations of the phosphorus atoms containing the spiro-$O(CH_2)_3NH$ moiety are designated *R* and *S* analogous to the notation used in Ref. [1] for the stereogenic properties of spiranes combined with two conventional centres of chirality. There is a direct correspondence between the chiral structure and point group symmetry for each compound **3a–c** in Scheme 5 and the analogous general structures in Fig. 14.31 of Ref. [1], which summarises the knowledge that

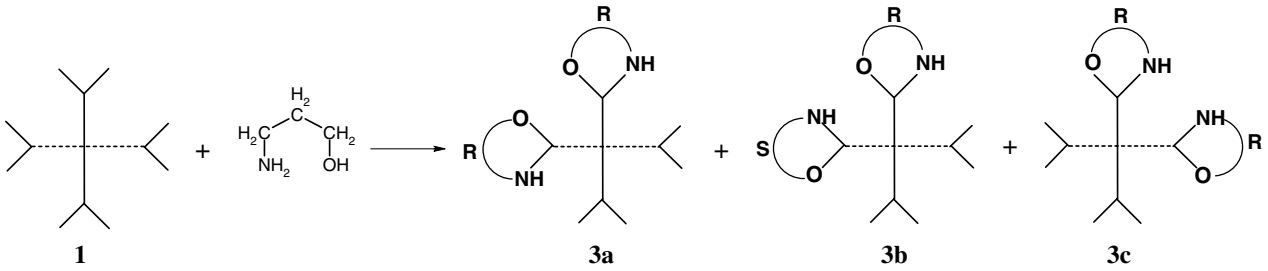


3a *NH-anti*



3c *NH-syn*

Fig. 4. X-ray crystal structures of the two di-mono-spiro derivatives **3a** and **3c** with C_2 point group symmetry. The *S*/*S* enantiomers are depicted for both **3a** and **3c**. The structures are also shown diagrammatically in terms of the mono-spirane representation and designated *anti* (**3a**) and *syn* (**3c**) according to the relationships of the NH groups of the aminopropanoxy spiro moieties.



Scheme 5. Formation of tri-spiranes with two equivalent conventional centres of chirality.

mono-spirane compounds with two equivalent conventional chiral centres exist as three diastereoisomers, all racemates [8]. One enantiomer of each diastereoisomer is represented (compare Fig. 14.31 in Ref. [1]).

When bridged molecules contain two equivalent centres of chirality, one on either side of the bridge, some care has to be taken in interpreting the separation of ^{31}P NMR signals in a 1:1 ratio on addition of CSA. For example, it has been found that for some piperazine-bridged and spermine-bridged cyclophosphazenes the addition of CSA (or a chiral shift reagent, CSR) results in the separation of signals for both the racemic and meso forms of the molecules [13]. The results were explained by consideration of the equilibrium in solution of the independent complexation of a chiral ligand with molecules that have two chiral cyclophosphazenes moieties separated by an achiral spacer group, i.e. the piperazine or spermine bridge [13]. The molecules in the present work have two chiral cyclophosphazene moieties separated by a spirane spacer group, which itself confers chirality on the molecule. On addition of CSA up to a 20:1 molar ratio, each of the tri-spirane derivatives (**3a**–**c**) shows a splitting of the ^{31}P NMR signals in a 1:1 ratio (Table 1(iii)), which is consistent with them existing as racemates, but the conclusion from NMR may not be unequivocal. On the other hand, previous work on spiro and ansa 1,3-propanedioxy derivatives of the tri-spirane, compound **1**, has shown that addition of CSA up to a 20:1 molar ratio causes splitting of signals for the racemic isomers (di-mono-spiro and di-mono-ansa), but no splitting of signals for the two meso isomers (*syn*- and *anti*-spiro-ansa, whose structures have been determined crystallographically) even up to a 50:1 molar ratio of CSA [4]. Within the limitations of these NMR experimental observations, it appears that addition of a chiral ligand to solutions of molecules containing two centres of chirality separated by a spacer group, may be able to differentiate the meso and racemic diastereoisomers as long as the spacer group is also chiral.

*3.3. Quantitative analysis of formation of spiranes combined with two equivalent conventional centres of chirality, compounds **3a–c***

In the reaction of 1,3-aminopropanol with compound **1** in a 2:1 ratio to form compounds **3a**–**c**, it was found that there was an overall yield of about ca. 80% with significant proportions of each separate isomer (**3a**, ca. 25%; **3b**, ca. 40% and **3c**, ca. 15%), i.e. the relative proportions of the three isomers are **3a**, ca. 32%; **3b**, ca. 50% and **3c**, ca. 19% (Table 3). Normally one might consider that these differences in yield of the separate isomers resulted from inadequate separation and purification procedures. However, it was also observed that the proton-decoupled ^{31}P NMR spectrum of the reaction mixture gave separate signals for the $\gtrdot$P(bridge) and $\gtrdot P(O(CH_2)_3NH)$ groups of the three diastereoisomers **3a**–**c**, which were quantified in terms of the relative proportions of the three diastereoisomers; the average values for both sets of results gives the relative proportions of the three isomers for **3a**, ca. 28%; **3b**, ca. 48% and **3c**, ca. 24% (Table 3). Although these results are slightly different to those found by the isolation and purification procedure, the ^{31}P NMR of the reaction mixture is likely to be more representative of the quantitative analysis of the reaction products because the only separation procedure of the reaction mixture was to filter off the triethylamine hydrochloride prior to NMR measurements. NMR quantitative analysis suggests that the three diastereoisomers of compounds **3a**–**c** are formed in the relative proportions of ca. 1:2:1 for **3a**:**3b**:**3c**, respectively.

Analysis of the stereogenic properties of the reaction of 1,3-aminopropanol in a 1:1 molar ratio with **1** to form compound **2** and then in a 2:1 molar ratio to form compounds **3** is shown diagrammatically in Fig. 5. At each stage of the reaction it is assumed that 1,3-aminopropanol reacts with a PCl_2 group of a cyclophosphazene ring to form, with equal probability, both the *R* and *S* isomers of spiro derivatives. This is shown very clearly in Fig. 5 for the mono-substituted derivative compound **2**, in which the enantiomeric compounds are labelled $\mathbf{2}_R$ and $\mathbf{2}_S$ and, if

Table 3
Estimation of the relative proportions of the diastereoisomers **3a–c**

Cpd	Isolation procedure (%)	Quantitative analysis using ^{31}P NMR signals[a] (%)		
		≻P(bridge) (%)	≻P(O(CH$_2$)$_3$NH) (%)	NMR average (%)
3a	31	31	25	28
3b	50	47	49	48
3c	19	22	26	24

[a] The relative proportions of the isomers could not estimated from the ^{31}P NMR peaks of the PCl_2 groups because of signal overlap.

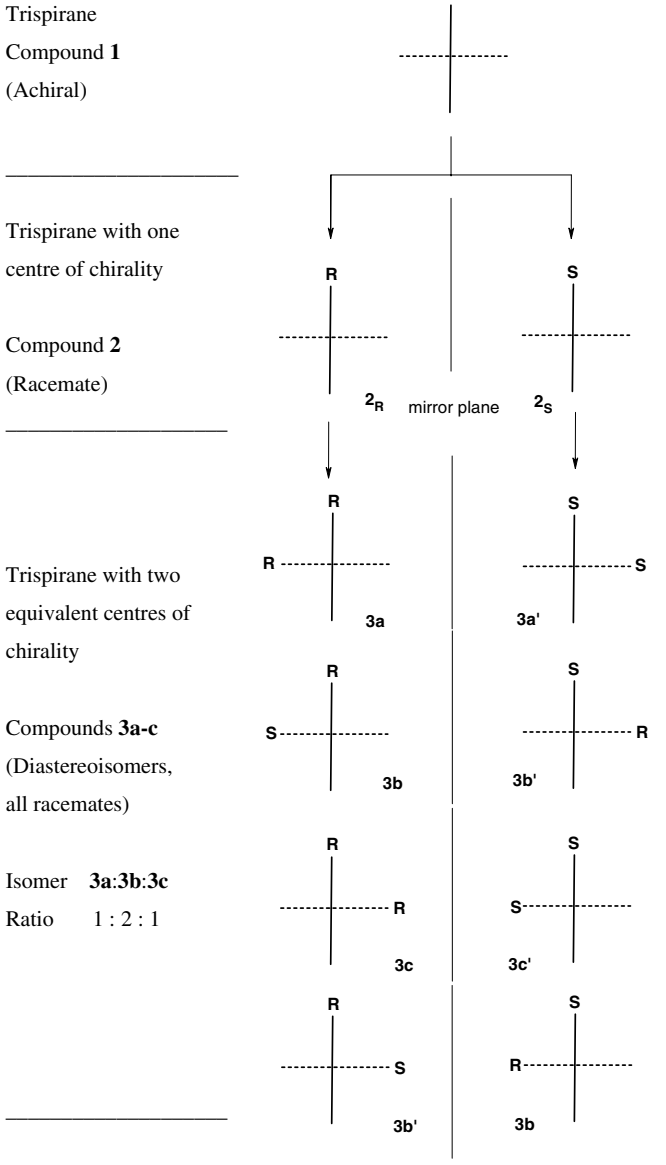


Fig. 5. Diagrammatic representation of the reaction of the achiral compound **1** with 1,3-aminopropanol to give spiranes with one conventional centre of chirality (compound **2** as a racemate) and spiranes with two equivalent conventional centres of chirality as three diastereoisomers **3a**:**3b**:**3c**, all racemates, in the ratios 1:2:1, respectively.

formed with equal probability, compound **2** exists as a racemate, as observed. In the formation of the di-mono-substituted compounds **3a**–**c**, it is assumed that 1,3-aminopropanol reacts with equal probability with either PCl_2 group of the second cyclophosphazene in ring compound **2**, to form both the *R* and *S* isomers of spiro derivatives. The analysis in Fig. 5 shows that isomer $\mathbf{2}_R$ reacts with 1,3-aminopropanol to give isomers labelled **3a**, **3b**, **3c** and **3b′**, whereas $\mathbf{2}_S$ gives the corresponding enantiomers **3a′**, **3b′**, **3c′** and **3b**, respectively. As the tri-spirane compound **3** is substituted with two conventional centres of chirality that are equivalent, it can be seen in Fig. 5 that compound **3b** occurs with twice the probability of its diastereoisomers **3a** and **3c**, which is consistent with the observed quantitative analysis of the reaction mixture by ^{31}P NMR spectroscopy giving the relative ratios of **3a**:**3b**:**3c** as 1:2:1, respectively (Table 3).

The results in this work show that derivatives of compound **1** can be used to elucidate the stereogenic properties of spiranes combined with one or two conventional centres of chirality, and, in principle, may be used to elucidate the cases of combining spiranes with up to three or four conventional centres of chirality.

4. Conclusions

Although compound **1** is a tri-spirane, the stereochemistry of derivatives of **1** may be considered to be analogous to those for mono-spiranes, because each sequential six-membered ring in **1** is orthogonal to its neighbour and so the two outer cyclophosphazene rings are also orthogonal to each other. It is shown in this work that a derivative of compound **1** with one additional conventional centre of chirality exists as a racemate (compound **2**) and that tri-spirane **1** with two equivalent conventional centres of chirality exists as three diastereoisomers, all racemates (compounds **3a**–**c**). It has been known for a long time that mono-spirane compounds with two equivalent chiral centres exist as three diastereoisomers [8] and a general description and stick diagram representation has been provided [1]. In this work, characterisation of compounds **3a** and **3c** by X-ray crystallography and compound **3b** by ^{31}P NMR spectroscopy on addition of the chiral solvating agent confirms that they exist as three diastereoisomers and proves the stereochemistry of each of these three diastereoisomers. It is also found by analysis of the stereogenic properties of the formation of compounds **3a**, **3b** and **3c** that they should occur in the ratios of 1:2:1, respectively, which confirms the relative proportions of the diastereoisomers observed by ^{31}P NMR spectroscopy of the reaction mixture.

5. Supplementary material

CCDC 620367, 266978 and 266979 contain the supplementary crystallographic data for **2**, **3a** and **3c**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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