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Chiral configurations of spermine-bridged cyclotriphosphazatrienes

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Spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes have been synthesised by two routes. In one route a spermine-bridged cyclophosphazene **2** reacted with monofunctional nucleophiles known to favour *gem* disubstitution in cyclophosphazene rings (*e.g. tert*-butylamine) to give **3b**, or to favour formation of spiro-derivatives with difunctional nucleophiles (*e.g.* 1,3-propanediol) to give **3c**. In the other route a *gem*-disubstituted cyclophosphazene (*i.e.* diphenyl, $N_3P_3Ph_2Cl_4$, compound **4**) reacted with spermine to give **3a**. The >P(N-spiro) group in each cyclophosphazene ring of **3a**–**c** is stereogenic and homotopic, and so it is expected, and confirmed, that the spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes (**3a**–**c**) should be chiral and exist in *meso* and racemic forms. The proton-decoupled ^{31}P NMR spectroscopy of **3a**–**c** gave rise to two sets of signals in a 1 : 1 ratio consistent with formation of *meso* and racemic forms. The *meso* and racemic forms of **3a** (*gem*-diphenyl derivative) were separated by column chromatography and characterised by X-ray crystallography; this enabled the unequivocal assignment of the two sets of ^{31}P NMR signals to the *meso* and racemic forms of **3a**. This is the first time that the existence of chiral configurational isomers has been elucidated in the field of spermine-bridged cyclophosphazene compounds, and only the second time in cyclophosphazene chemistry.

Introduction

The systematic chemistry of the cyclophosphazenes has been extensively reviewed over the years.[1–4] In addition to geminal and non-geminal replacement paths,[1–4] positional and geometric isomers were isolated and characterised,[5] and in a number of cases confirmed by X-ray crystallography.[6–8] Realising that the tetra-coordinated phosphorus atoms in cyclophosphazenes $(NPXY)_n$ are pentavalent and potential stereocentres, the possibility of optical isomerism was first discussed in a review[1] in 1962, *viz.* with two different substituents, X and Y, geminal trisubstituted compounds (type I) and nongeminal *trans* di- and tetra-substituted derivatives (type II) lack all elements of symmetry.

(I) (II)

Until recently, chirality does not seem to have been considered in any of the many papers on cyclophosphazenes. Analysis of the reactions of the *cis*-ansa cyclotriphosphazatriene-macrocyclic compound, 1,3-[oxy(tetraethylenoxy)]-1,3,5,5-tetrachlorocyclotriphosphazatriene, (**1**), with aliphatic diamines $[NH_2–(CH_2)_n–NH_2$, n = 2–6, 8, 10, 12],[9,10] however, opened up a convenient route to investigate the chiral configurational properties of a series of cyclophosphazene compounds because there are multiple stereogenic centres giving rise to diastereoisomers. Although many of the products were stable in non-polar solvents at ambient temperatures, it was found that crystals of the singly-bridged compounds were not sufficiently stable for structure determination by X-ray crystallography. It was suggested that the most likely cause of instability in the derivatives of **1** was the presence of both P–Cl and P–NH groupings, which could react to give polymerisation and/or decomposition products.[11] It was found that compound **1** could undergo a similar series of reactions with the secondary diamine, piperazine, to give analogous singly-bridged (bino) and doubly-bridged (bis-bino) derivatives, whose crystals were stable and suitable for X-ray structure determination.[11] The series of reactions of **1** with piperazine is similar to those with primary diamines,[9,10] except that the reactions with piperazine do not lead to formation of compounds analogous to either the spiro-ansa compound or the ansa-ansa series of compounds.[11]

X-Ray crystallography and ^{31}P NMR with chiral shift reagent, $Eu(tfc)_3$, demonstrated that the macrocyclic-cyclophosphazene derivatives of **1** with a single piperazine bridge exist as a 50 : 50 mixture of *meso* and racemic forms, whereas the doubly-bridged macrocyclic-cyclophosphazene derivatives exist as a 50 : 50 mixture of two different *meso* forms, one with a plane of symmetry and the other with a centre of symmetry.[11] These results were rationalised in terms of the expected inversion of configuration (S_N2 reaction mechanism) for each step of the reaction of a >P(OR)Cl group with amine NH_2R' to form a >P(OR)(NHR′) derivative. The existence of a 50 : 50 mixture of *meso* and racemic forms for macrocyclic-cyclophosphazene derivatives of **1** with a single piperazine bridge explains the observed ^{31}P NMR spectra of two sets of AMX spin systems in a 1 : 1 ratio with a small chemical shift separation, $\Delta\delta$ *ca.* 0.06–0.09 ppm,[11] the similar behaviour observed for lower members of the series of diamine-bridged macrocyclic-cyclophosphazene compounds, $\Delta\delta$ *ca.* 0.02–0.05 ppm,[9] and for two analogous series of singly-bridged cyclotriphosphazatriene-diamine derivatives (denoted as 3*n*3 and 4*n*4 series with n = 6, 7, 8, 9) by Labarre *et al.*[12] Explanation of the above NMR phenomena in terms of chiral configurational properties of the macrocyclic-cyclophosphazene compounds prompted a detailed survey of structures of cyclotriphosphazatrienes in the Cambridge Crystallographic Database.[13] A number of systems were found

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in which the relative distribution of the X,Y substituents leads to pairs of chiral centres [in *R,S* (*meso*) or *R,R*/*S,S* (homotopic) relationships], even though chirality was neither discussed nor the implications of chirality considered. Examples of both types I and II have been examined crystallographically, *e.g.* geminal $N_3P_3Cl_3(NMe_2)_3$,[6] *trans*-$N_3P_3Cl_4(NMe_2)_2$,[14] and *trans*-$N_3P_3(NH_2)_2(OPr^n)_4$.[15] Additional complications occur when a chiral molecule crystallises from a racemic mixture through spontaneous resolution as a chiral crystal; an example from our own work is 2,2-(1′,3′-propanedioxy)-*trans*-4,6-dichloro-4,6-bis(pyrrolidinyl)cyclotriphosphazatriene,[16] which crystallizes in space group $P2_12_12_1$. In one other case, an optically active trimer derivative has been reported,[17] but this was based on cyclization of an optically active acyclic precursor.

The spermine-bridged cyclophosphazene compound **2** has been prepared previously[18] by reaction of cyclotriphosphazatriene with the tetrafunctional amine, spermine, as shown in Scheme 1. Compound **2** is not chiral because the substitution pattern of each cyclophosphazene ring is the same and each cyclophosphazene ring has a plane of symmetry. Singly-bridged analogues with *gem*-disubstituted cyclophosphazene rings (**3**, X ≠ Cl) are expected to exhibit stereoisomerism, 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. Following the previous analysis of singly-bridged cyclophosphazene-macrocyclic compounds,[11] the spermine-bridged compounds (**3**, X ≠ Cl) are expected to exist in 1 : 1 mixtures of *meso* (*RS*/*SR*) and racemic (*RR*/*SS*) forms. This paper deals with the synthesis and characterisation of the chiral configurational isomers (*meso* and racemate) of spermine-bridged cyclophosphazene compounds **3** (X ≠ Cl).

Results and discussion

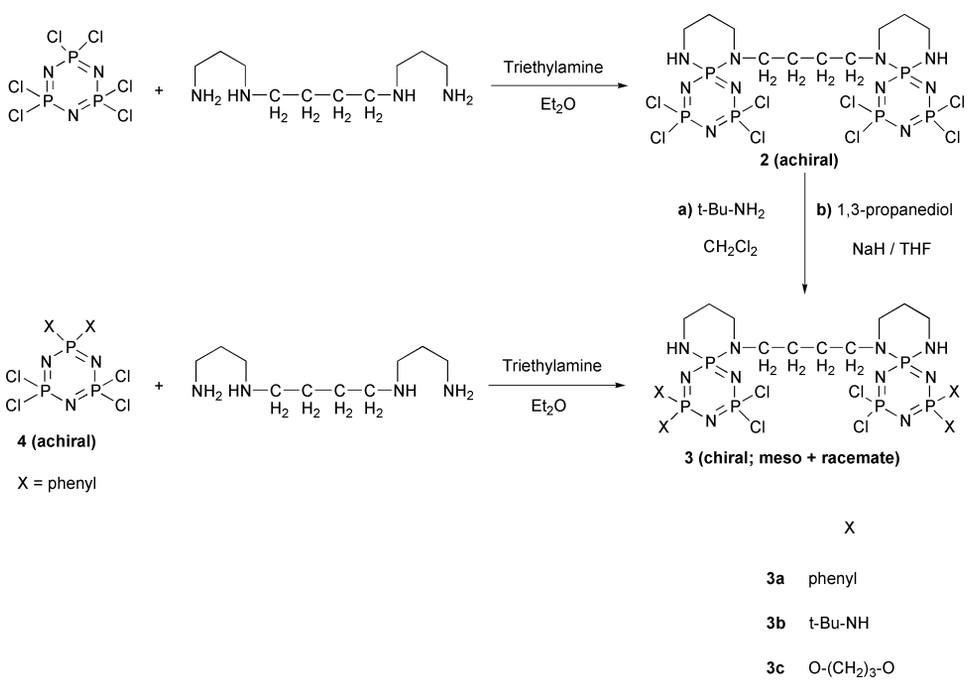
Formation of spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes (3)

Two routes were used to synthesise spermine-bridged *gem*-disubstituted cyclophosphazenes as shown in Scheme 1. One route used the reaction of spermine with a previously prepared *gem*-disubstituted cyclophosphazene, **4**, (X = Ph,[19]) to give **3a**, whereas the other route allowed the previously prepared spermine-bridged cyclophosphazene **2**[18] to react with nucleophiles known to favour *gem* disubstitution in cyclophosphazene rings (*e.g. tert*-butylamine,[20]) to give **3b** or to favour formation of spiro-derivatives (*e.g.* 1,3-propanediol,[21]) to give **3c**. In some cases, separation of the *meso* and racemic forms by column chromatography was achieved (*e.g.* **3a**, X = Ph) and in other cases one form was more readily separated (*e.g.* **3b**, X = NHBu^t) leading to some confusion in the analysis of *meso* and racemic forms. In order to overcome this problem, we routinely characterised the crude reaction mixture by proton-decoupled ^{31}P NMR, as well as all major fractions isolated. As a result of the separation and crystallisation of the *meso* and racemic forms of the *gem*-diphenyl cyclophosphazene derivative (**3a**), both forms have been completely characterised by X-ray crystallography and ^{31}P NMR spectroscopy.

X-Ray crystal structures of the *meso* and racemic forms of the spermine-bridged compound, 3a

The molecular structures of the *meso* (a) and racemic (b) diastereoisomers are shown in Fig. 1. Some positional disorder is present in Cl(3) and Cl(4) of the *meso* structure (50 : 50 and 70 : 30, respectively), which has been omitted from Fig. 1(a) for clarity. The absolute configurations of the two stereocentres in compound **3a** have been designated as *R* and *S* noting that, for each >P(N-spiro) group, the Cahn–Ingold–Prelog (CIP)[22] priority order of groups is N[PCl_2] > N[PPh_2] > N(CH_2)$_2$ > NH(CH_2). As a result of the centrosymmetric nature of the space group, the *meso* form depicted in Fig. 1(a) has two spiro-bridged stereocentres, P(1) = *S* and P(6) = *R*, which will generate P(1) = *R* and P(6) = *S* upon inversion through the centre of symmetry. The second isomer shown in Fig. 1(b) is racemic with its spiro-bridged centres P(3) and P(4) both having *S* configurations, which generate the *RR* isomer through an inversion centre in this centrosymmetric space group.

Apart from chirality, the structural features of the two isomers are essentially the same and may be considered together. The bond lengths and angles of the *meso* and racemic structures (selected values are given in Table 1) are in accordance with expected values, and the non-bonded cross-ring P ··· P separations are typical for this type of ring system.[13] The cyclotriphosphazatriene rings are reasonably planar



Scheme 1

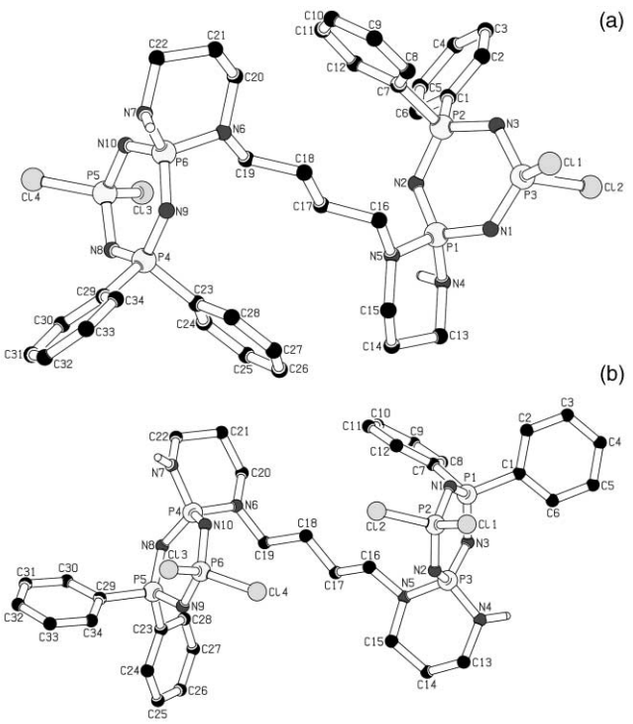


Fig. 1 Crystal structures of the (a) *meso*, and (b) racemic forms of the spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes (**3a**). Amido protons are retained to demonstrate the difference in chiral configurations between the two forms.

(puckering amplitudes = 0.151(4), 0.110(3) and 0.106(2), 0.322(2) Å for the *meso* and racemic structures, respectively). The six-membered *N*-spiro rings exist in chair conformations and are mutually perpendicular to the connected cyclophosphazene rings, forming angles between their mean planes of 86.72, 88.13 and 88.40, 89.44° for the *meso* and racemic forms, respectively.

There are also subtle differences in the supramolecular network of the crystal structures that arise from the stereoisomerism. The *meso* isomer forms a relatively simple zigzag array by interactions of both the amido protons in the spermine bridge (on opposite sides of the molecule) with a cyclophosphazene ring of two different neighbouring molecules [D ··· A: N(4)–H(4)N ··· N(9) = 3.025(5) Å and N(7)–H(7)N ··· N(2) = 3.115(5) Å]. Although the racemic form interacts with its neighbours in the same fashion, the amido donors are now on the same side of the molecule. A further phenyl–cyclophosphazene interaction arises from this, resulting in an infinite three dimensional array [D ··· A: N(4)–H(4)N ··· N(10) = 2.957(4), N(7)–H(7)N ··· N(3) = 3.103(4) and C(30)–H(30) ··· N(9) = 3.211(6) Å].

^{31}P NMR signal assignment of *meso* and racemic forms of compounds, 3a–c

The proton-decoupled ^{31}P NMR spectra of the reaction mixtures of **3a**–**c** in $CDCl_3$ solution are observed as pairs of ABX spin systems in a 1 : 1 ratio, consistent with the existence of *meso* and racemic forms with small chemical shift differences between NMR signals of the diastereoisomers. Unequivocal assignment of *meso* and racemic forms of **3a** was aided by their chromatographic separation and complete structural characterisation by X-ray crystallography; the first isomer eluted being the *meso* form and the second the racemic form. The ^{1}H NMR spectrum of the spermine moiety is very complex, consisting of one C–CH_2–CH_2–NH and two C–CH_2–CH_2–N coupling paths, made more complicated by being the superposition of spectra of the *meso* and racemic forms. Hence, the ^{1}H NMR spectra have not been analysed nor used for structural analysis. On the other hand, the ^{31}P (and ^{13}C) NMR signals of each of the pure isomers of **3a** (and of an intermediate fraction with *meso* : racemate in the ratio 1 : 3) in $CDCl_3$ solution enabled the complete assignment of the spectra of the *meso* and racemic forms. It is found that the ^{31}P NMR signals of the *meso* and racemic forms of compound **3a** are more widely separated in toluene-d_8 than in $CDCl_3$ solution and so, for demonstration purposes, the expanded signals of the 200 MHz ^{31}P NMR spectrum of a cleaned up sample of compound **3a** are shown in Fig. 2(a).

Assignment of the ^{31}P NMR signals of **3a** to >PCl_2, >PPh_2 and >P(N-spiro) groups was made by comparison of proton-coupled (not shown) and proton-decoupled spectra. The proton-decoupled ^{31}P NMR signals of the *meso* and racemic forms of **3a** are shown in Figs 2(b) and 2(c), respectively. Each consists of an ABX spin system that mirrors one component of the two sets of ABX signals of the spectrum in Fig. 2(a) and so have been used for unequivocal assignment of the *meso* and racemic isomers. It is found that the set of ^{31}P NMR signals of the racemate are to high frequency of those for the *meso* form. It should also be noticed in Fig. 2(a) that the ^{31}P NMR signals of the racemic and *meso* forms exist in *ca.* 60 : 40 ratio; this is consistent with the observation that, in the chromatographic separation of diastereoisomers of **3a**, the *meso* form elutes before the racemate, which must also occur to a small extent in the initial clean up of the reaction mixture. Observation of a 60 : 40 ratio of racemic and *meso* isomers greatly assists the unequivocal assignment of ^{31}P NMR signals of **3a** in other solvents such as $CDCl_3$ (Table 2). The results show that the racemic form of **3a** in $CDCl_3$ is also the set of signals to high frequency of the *meso* form, with the effect on >PCl_2 [$\Delta\delta$ ($r-m$) 0.06 ppm] being slightly greater than for the >PPh_2 (*ca.* 0.04 ppm) and >P(N-spiro) *ca.* 0.03 ppm. In addition to signals reflecting the 60 : 40 ratio of racemic : *meso* isomers, the

Table 1 Selected bond lengths (Å) and angles (°) for the *meso* and racemic forms of **3a**

meso form		Racemate	
N(1)–P(3)	1.565(4)	N(1)–P(2)	1.563(3)
N(1)–P(1)	1.602(4)	N(1)–P(1)	1.624(3)
N(2)–P(1)	1.599(4)	N(2)–P(2)	1.557(3)
N(2)–P(2)	1.607(4)	N(2)–P(3)	1.615(3)
N(3)–P(3)	1.573(4)	N(3)–P(3)	1.580(3)
N(3)–P(2)	1.599(4)	N(3)–P(1)	1.606(3)
N(4)–P(1)	1.640(5)	N(4)–P(3)	1.618(3)
N(5)–P(1)	1.642(4)	N(5)–P(3)	1.676(3)
N(6)–P(6)	1.655(4)	N(6)–P(4)	1.644(3)
N(7)–P(6)	1.643(4)	N(7)–P(4)	1.638(3)
N(8)–P(5)	1.559(4)	N(8)–P(5)	1.582(3)
N(8)–P(4)	1.612(4)	N(8)–P(4)	1.593(3)
N(9)–P(4)	1.592(4)	N(9)–P(5)	1.616(3)
N(9)–P(6)	1.593(4)	N(9)–P(6)	1.561(3)
N(10)–P(5)	1.561(4)	N(10)–P(4)	1.620(3)
N(10)–P(6)	1.618(4)	N(10)–P(6)	1.573(3)
P(1) ··· P(2)	2.824(5)	P(1) ··· P(2)	2.766(4)
P(2) ··· P(3)	2.757(5)	P(2) ··· P(3)	2.774(4)
P(1) ··· P(3)	2.766(5)	P(1) ··· P(3)	2.816(3)
P(4) ··· P(5)	2.750(6)	P(4) ··· P(5)	2.813(4)
P(5) ··· P(6)	2.765(5)	P(5) ··· P(6)	2.730(4)
P(4) ··· P(6)	2.821(5)	P(4) ··· P(6)	2.778(4)
N(1)–P(1)–N(2)	115.6(2)	N(2)–P(3)–N(3)	115.19(15)
N(4)–P(1)–N(5)	105.0(2)	N(4)–P(3)–N(5)	105.85(15)
N(2)–P(2)–N(3)	116.4(2)	N(1)–P(1)–N(3)	116.06(15)
C(1)–P(2)–C(7)	103.8(3)	C(1)–P(1)–C(7)	106.77(17)
N(1)–P(3)–N(3)	120.1(2)	N(1)–P(2)–N(2)	121.03(16)
Cl(1)–P(3)–Cl(2)	99.32(12)	Cl(1)–P(2)–Cl(2)	98.46(6)
N(8)–P(4)–N(9)	116.3(2)	N(8)–P(5)–N(9)	114.78(17)
C(23)–P(4)–C(29)	105.4(3)	C(23)–P(5)–C(29)	107.10(18)
N(8)–P(5)–N(10)	121.7(2)	N(9)–P(6)–N(10)	119.70(17)
Cl(3)–P(5)–Cl(4)	99.2(8)	Cl(3)–P(6)–Cl(4)	99.41(7)
N(9)–P(6)–N(10)	114.8(2)	N(8)–P(4)–N(10)	113.41(17)
N(6)–P(6)–N(7)	104.7(2)	N(6)–P(4)–N(7)	104.01(17)

Table 2 ^{31}P NMR parameters of *meso* (*m*) and racemic (*r*) forms of spermine-bridged cyclophosphazenes[a]

Compound		Chemical shifts/ppm >PCl_2 1	>P(N-spiro) 2	>PX_2 3	^2J(PP)/Hz X	1, 2	1, 3	2, 3
2		22.09	10.36	—	—	40.0		
3a[b]	*r*	20.45	13.39	20.06	phenyl	18.1	20.2	20.6
	m	20.39	13.36	20.02	phenyl	17.2	20.2	21.1
	$\Delta\delta$ (*r*−*m*)	0.06	0.03	0.04				
3b[c]		22.48	14.30	6.88	$NHBu^t$	40.3	50.0	42.0
		22.46	14.21	6.86	$NHBu^t$	40.4	50.0	42.1
	$\lvert\Delta\delta\rvert$	0.02	0.09	0.02				
3c[c]		25.01	15.45	9.01	$O(CH_2)_3O$	40.5	68.7	63.4
		25.00	15.42	8.99	$O(CH_2)_3O$	40.5	68.7	63.4
	$\lvert\Delta\delta\rvert$	0.01	0.03	0.02				

[a] 200 MHz ^{31}P NMR measurements in $CDCl_3$ solutions at 298 K. [b] The *meso* and racemic forms have been unequivocally assigned as a result of independent determination of structures by X-ray crystallography. [c] Unequivocal assignment not made so only modulus of $\Delta\delta$ given.

assignment of the ^{13}C NMR spectrum of **3a** was also assisted by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC. The results summarized in Table 3 show that the signals of the racemic form of **3a** are to high frequency of the *meso* form for the aromatic ring carbons, whereas signals of the racemic form are to low frequency of the *meso* form for the carbon atoms of the spermine moiety, except for the C–*C*H_2–C group of the *N*-spiro ring.

Although separate signals for *meso* and racemic forms were not observed in 125 MHz ^{13}C NMR spectra of **3b**,**c** (Table 3), the 200 MHz ^{31}P NMR spectra of compounds **3b**,**c** did exhibit two sets of signals, which should correspond to *meso* and racemic forms. In cases where the diastereoisomers have not been separated and characterised by X-ray crystallography (such as **3b**,**c**), it is expected that assignment of NMR signals to the *meso* and racemic forms can be made using a chiral shift reagent (CSR),[23] in a similar way to the previous use of Eu(tfc)$_3$ with singly-bridged cyclophosphazene-macrocyclic compounds.[11] As unexplained complications arose with the use of CSRs [and the chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol],[23] which are currently under investigation, it means that unequivocal assignment of the ^{31}P NMR signals to *meso* and racemic forms of compounds **3b**,**c** has not been made at the present time, as indicated in the summary of their chemical shifts in Table 2.

Conclusions

The chiral configurational isomers of spermine-bridged cyclophosphazene compounds have been investigated. As spermine gives a symmetrically-bridged derivative, the *gem*-disubstituted spermine-bridged cyclophosphazene compounds **3a**–**c** have two homotopic stereogenic centres [>P(N-spiro) moiety of the two N_3P_3 units], so that the molecules exist as 1 : 1 mixtures of *meso* (*RS* = *SR*) and racemic (*RR* and *SS*) forms. The numbers and

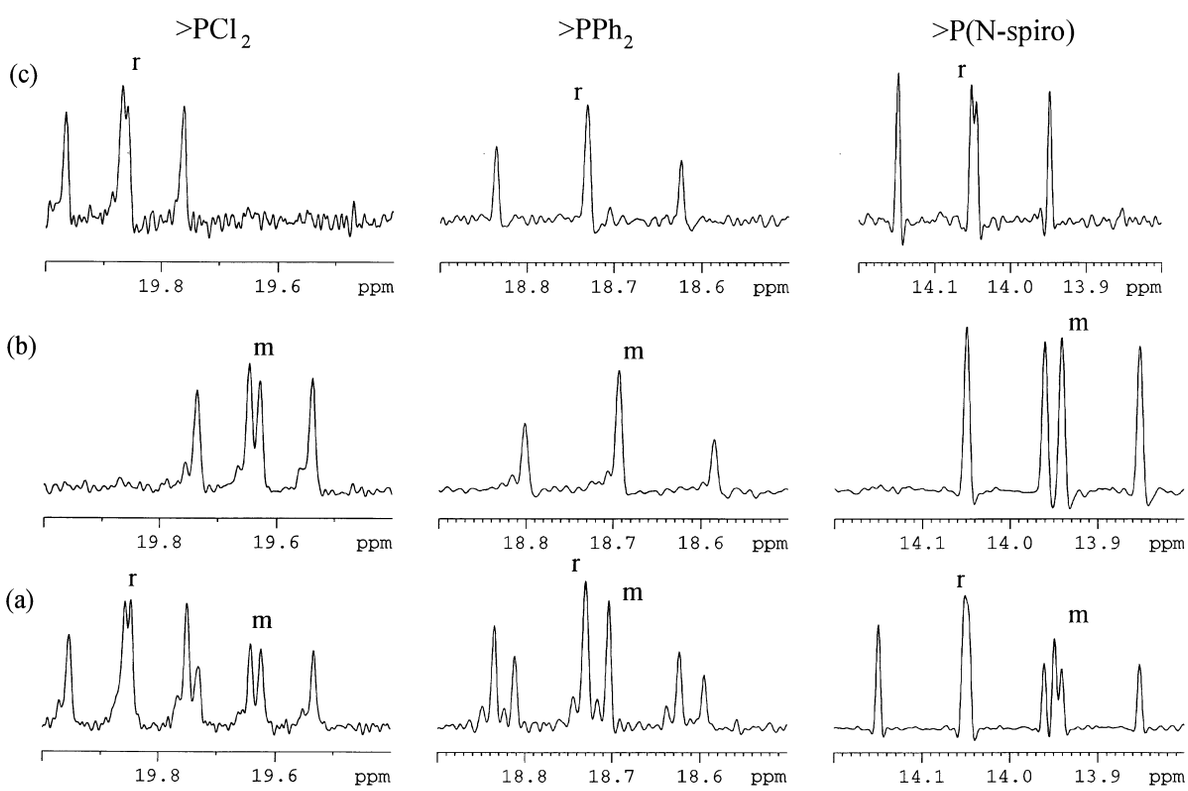


Fig. 2 200 MHz proton-decoupled ^{31}P NMR spectra of compound **3a** in toluene-d_8 solution at 298 K. (a) The two sets of expanded ABX signals correspond to racemic (*r*) and *meso* (*m*) diastereoisomers in the ratio of *ca.* 60 : 40. Unequivocal assignment of signals was made by comparison with those for the (b) *meso* and (c) racemic isomers of **3a**.

Table 3 ^{13}C NMR parameters of spermine-bridged cyclophosphazenes[a]

Compound		Spiro group						Bridge			
		CH_2–NC		CH_2–NH		C–CH_2–C		CH_2–N		C–CH_2–C	
		δ	J	δ	J	δ	J	δ	J	δ	J
2		46.50	<1	40.63	3.4	26.64	3.6	47.36	2.1	24.94	5.4
3a[b]	*r*	46.83	*c*	41.26	3.9	27.11	3.9	47.41	*c*	24.93	6.6
	m	46.86	*c*	41.26	3.9	27.10	3.9	47.42	*c*	25.00	6.6
$\Delta\delta(r-m)$		−0.03		—		0.01		−0.01		−0.07	
3b[d]		46.72	*c*	41.20	4.0	27.41	4.2	47.60[e]	*c*	25.41[f]	6.8
3c[g]		46.54	*c*	40.92	3.4	26.94	4.4	47.19	*c*	25.98	6.9

[a] 125 MHz ^{13}C NMR measurements in $CDCl_3$ solutions at 298 K. [b] Aromatic ring assignment: carbon [δ (*r*), δ (*m*), $\Delta\delta$ (*r*−*m*) ppm; *J*/Hz] C1 [135.7, 135.2, 0.5; 128]: C2 [130.60, 130.56, 0.04; 10.8]: C3 [128.30, 128.29, 0.01; 13.4]: C4 [131.42, 131.40, 0.02; 2.7]. [c] Not observed. [d] Separate signals for *meso* and racemic forms of the spermine moiety are observed for the CH_2–C and CH_2–N of the bridge, and two environments [*cis* and *trans* to the P–NH(spiro)] for the *tert*-butylamino groups are observed; *viz.* (δ ppm/$^3J_{CP}$ Hz) CH_3; 31.72/4.5, 31.46/5.0: quaternary 51.33/51.16 ppm ($^2J_{CP}$ < 2Hz). [e] Signal observed as two lines with separation 9.9 Hz, probably resulting from $^2J_{CP}$ < 2 Hz and $|\Delta\delta\ (r-m)|$ *ca.* 0.08 ppm. [f] Signal observed as a triplet due to coupling *ca.* 6.8 Hz and $|\Delta\delta\ (r-m)|$ *ca.* 0.05 ppm. [g] Separate signals for *meso* and racemic forms of the spermine moiety are not observed, though two environments [*cis* and *trans* to the P–NH(spiro)] for the $O(CH_2)_3O$ groups are observed; *viz.* O–CH_2; 67.13/67.08 ppm, $^3J_{CP}$ *ca.* 6.7 Hz: C–CH_2; 24.99/24.95 ppm, $^2J_{CP}$ *ca.* 5.8 Hz.

types of ^{31}P NMR signals observed for each of the compounds **3a**–**c** are consistent with the chiral configurational analysis. X-Ray crystallographic studies have provided definitive proof of the structures of the *meso* and racemic chiral configurational isomers of the spermine-bridged cyclophosphazene compound **3a**. Characterisation of chiral isomers of spermine-bridged cyclophosphazene compounds is only the second time that chirality has been elucidated in the whole field of phosphazene chemistry,[11] the common feature being singly-bridged cyclotriphosphazatriene derivatives.

Experimental

Materials

Hexachlorocyclotriphosphazatriene (Shin Nisso Kako Co Ltd) was purified by fractional crystallisation from hexane. Except for triethylamine (>98.0%, Fluka) 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, heptane and *tert*-butylamine (≥97.0%). Deuteriated solvents for NMR spectroscopy were obtained from Apollo Scientific ($CDCl_3$) and Goss Scientific (toluene-d_8) and the chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, (**5**), was obtained from Sigma Chemical Co. The chiral shift reagents tris[3-(trifluoromethylhydroxymethylene)-+-camphorato]europium(III), $Eu(tfc)_3$, and tris(+,+-dicampholymethanato)europium(III), $Eu(dcm)_3$ were obtained from Fluka.

Methods

Elemental analyses were obtained using a Carlo Erba 1106 Instrument and FT-IR spectra were recorded on a Bio-Rad FTS 175C Spectrophotometer as KBr pellets. 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. 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 3 g crude mixture, 100 g silica gel was used in a column of 3 cm in diameter and 60 cm in length).

^1H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ solutions on a Bruker DRX 500 MHz spectrometer using TMS as an internal reference for ^1H and ^{13}C, and 85% H_3PO_4 as an external reference for ^{31}P. In most cases both proton-coupled and proton-decoupled ^{31}P NMR spectra were recorded.

X-Ray crystallography

Intensity data were recorded on a Nonius KappaCCD diffractometer driven by COLLECT[24a] and DENZO[24b] software. Details of data collection and refinement are given in Table 4. Measurements on the *meso* and racemic forms of **3a** were recorded at 150 K and those for the *meso* form of **3a** were also recorded at 298 K due to crystal degradation in the cold stream. Structures were determined using the direct methods procedure in SHELXS-97[25] and refined by full-matrix least squares on F^2 using SHELXL-97.[26]

CCDC reference numbers 166075 and 166076.

See http://www.rsc.org/suppdata/dt/b1/b104973a/ for crystallographic data in CIF or other electronic format.

Synthesis

Reaction of 2,2,4,4-tetrachloro-6,6-diphenylcyclotriphosphazatriene (4) with spermine to form compound 3a and isolation of the *meso* and racemic forms. Spermine (2.9 g, 14.3 mmol) in 200 mL of Et_2O was added dropwise over 0.5 h to a stirred solution of NEt_3 (5.78 g, 57.4 mmol) together with previously prepared 2,2,4,4-tetrachloro-6,6-diphenylcyclotriphosphazatriene,[19] **4**, (6.17 g, 14.3 mmol) in 200 mL of Et_2O. The reaction mixture was stirred for 13 days under an atmosphere of argon, and the reaction followed by TLC. Triethylamine hydrochloride was removed by filtration and, after removal of solvent under reduced pressure, the resulting white powder was subjected to column chromatography. The starting material (0.38 g, 4.2%) was eluted using dichloromethane, and the product eluted using dichloromethane–ethyl acetate (1 : 1); mp 70–75 °C, (yield 1.5 g, 11.45%). Found: C, 44.74; H, 4.10; N, 14.74; $(M + H)^+$, 917. $C_{34}H_{42}Cl_4N_{10}P_6$ requires: C, 44.46; H, 4.61; N, 15.25%; M^+, 916.

^{31}P NMR of the product **3a** showed two sets of signals of an ABX spin system corresponding to the expected mixture of diastereoisomers (Fig. 2), which were separated by silica gel column chromatography using dichloromethane–THF (10 : 1). The first isomer (*meso*) to be eluted formed crystals as small blocks (from CH_2Cl_2–hexane), mp 222–227 °C; the second isomer, the racemate, crystallised as thin plates (from $CHCl_3$–heptane), mp 205–206 °C.

Reaction of hexachlorocyclotriphosphazatriene with spermine to form compound 2. Spermine (4.5 g, 21 mmol) in 125 mL Et_2O was added dropwise over 1 h to a stirred mixture of hexachlorocyclotriphosphazatriene (7.5 g, 21 mmol) and NEt_3 (2.5 g, 25 mmol) in 200 mL Et_2O. The reaction mixture was stirred for 7 days under an atmosphere of argon, the reaction followed by TLC. Triethylamine hydrochloride was removed by filtration and the solvent removed under reduced pressure. The

Table 4 Details of crystallographic data collection and structure refinement of **3a**

	Compound **3a** (*meso*)	Compound **3a** (racemic)
Empirical formula	$C_{34}H_{42}Cl_4N_{10}P_6$	$C_{34}H_{42}Cl_4N_{10}P_6$
Formula weight	918.40	918.40
T/K	293(2)	150(2)
Crystal system	Orthorhombic	Orthorhombic
Space group	$Pna2_1$	$Pna2_1$
a/Å	32.910(7)	28.970(6)
b/Å	10.436(2)	13.965(3)
c/Å	13.554(3)	10.247(2)
V/Å^3	4655.1(16)	4145.9(14)
Z	4	4
μ/mm^{-1}	0.497	0.558
Reflections collected	21779	28171
Independent reflections	7869	8200
R(int)	0.0921	0.0759
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0512$; $wR2 = 0.0764$	$R1 = 0.044$; $wR2 = 0.077$

residue was washed three times with 100mL of n-hexane to eliminate unreacted $N_3P_3Cl_6$ ($N_3P_3Cl_6$ is soluble in n-hexane, whereas the reaction product is not). The reaction mixture was separated by column chromatography using dichloromethane–THF (2 : 1) as eluent. Compound **2** was isolated as a white powder and crystallized from Et_2O–dichloromethane (3 : 1) to give colourless crystals (yield 2.7 g, 17%, mp 225–227 °C). Found: C, 16.38; H, 2.85; N, 18.26; $(M + H)^+$, 749. $C_{10}H_{22}N_{10}Cl_8P_6$ requires: C, 15.98; H, 2.95; N, 18.63%; M^+, 748.

Reaction of compound 2 with *tert*-butylamine to form compound 3b. Compound **2** (1 g, 1.33 mmol) was dissolved in 10 mL dichloromethane and added to an excess of *tert*-butylamine (40 g, 550 mmol) in a 250 mL three-necked round-bottomed flask. The reaction was stirred under an argon atmosphere at room temperature for 8 days and then filtered to remove the *tert*-butylammonium chloride. Excess *tert*-butylamine and solvent were removed under reduced pressure and the resulting white solid subjected to column chromatography using dichloromethane–ethyl acetate (1 : 1) as eluent. Compound **3b** was isolated as a white powder (yield: 0.35 g, 29%; mp 206 °C). Found: C, 34.50; H, 6.02; N, 21.38; $(M + H)^+$, 897. $C_{26}H_{62}Cl_4N_{14}P_6$ requires: C, 34.76; H, 6.96; N, 21.82%; M, 896.

Reaction of compound 2 with 1,3-propanediol to form compound 3c. Compound **2** (1 g, 1.33 mmol) and 1,3-propanediol (0.405 g, 5.32 mmol) were dissolved in 50 mL of dry THF in a 250 mL three-necked round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (60% oil suspension, 0.25 g., 10.6 mmol; the oil was removed by washing with dry heptane, followed by decantation) in 50 mL of dry THF was added under an argon atmosphere. The reaction was stirred for 5 h at room temperature and was followed by TLC on silica gel plates using dichloromethane–THF (2 : 1). The reaction mixture was filtered to remove the sodium chloride, the THF removed under reduced pressure and the resulting white solid subjected to column chromatography using dichloromethane–THF (2 : 1) as eluent. Two fractions were obtained and isolated as white powders: the first is the di-monospiro compound, **3c**, (0.3 g, 24.7%, mp 77–83 °C; Found: C, 26.44; H, 4.73; N, 16.43; $(M + H)^+$, 757. $C_{16}H_{34}Cl_4N_{10}O_4P_6$ requires: C, 25.35; H, 4.52; N, 18.47 %; M^+, 756; the second fraction is the trispiro-derivative (yield 0.22 g, 20%, mp 84–90 °C) to be published elsewhere.

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