Chiral Configurations of Cyclophosphazenes

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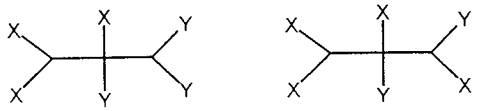
Abstract: Tetracoordinated phosphorus atoms in derivatives of cyclophosphazenes are pentavalent and are potentially chiral. Chirality does not seem to have been investigated nor discussed for any literature examples of crystal structures of those cyclophosphazene compounds which are expected to be chiral. In cyclotriphosphazatriene compounds with ansa-substituted macrocyclic rings the two phosphorus atoms attached to the macrocycle are chiral, although the *cis*-ansa cyclotriphosphazatriene-macrocycle **1** is the meso form. Reaction of **1** with the di-secondary amine, piperazine, provides a convenient way to investigate the chiral configurational properties of cyclophosphazene compounds. It is found by X-ray crystallography that there are two configurational isomers (one meso and one racemate) of the singly bridged di(cyclophosphazene-macrocyclic) piperazine derivative **6i**, and that there are two configurational isomers (both meso) of the doubly bridged di(cyclophosphazene-macrocyclic) piperazine derivative **8i**; in **8i** one meso form has a center of symmetry and the other a plane of symmetry. The chiral configurational properties of each stage of the reaction scheme for formation of **6i** and **8i** from **1** have been confirmed by ^{31}P NMR spectroscopy and the results are consistent with inversion of configuration at phosphorus at each step of the reaction of >P(OR)Cl groups with HNR′R″ to form >P(OR)(NR′R″) derivatives: viz. reaction of **1** with piperazine gives the monosubstituted compound **4i**, which exists as a racemate with the macrocyclic ring in the *trans*-configuration; reaction of compound **4i** with **1** gives the two configurational forms (meso and racemate) of the singly bridged derivative **6i** with the macrocyclic rings in the *trans-trans* configuration; reaction of **6i** with piperazine gives the monosubstituted singly bridged derivative **7i**, which exists as two racemic mixtures with the macrocyclic rings in *cis*−*trans* configurations; and intramolecular condensation of **7i** gives the two configurational forms of the doubly bridged derivative **8i** with each of the macrocyclic rings in the *cis*−*cis* configuration. In this work the configurational properties of derivatives of cyclotriphosphazatriene rings with two (one N_3P_3 unit) or four (two N_3P_3 units) chiral centers have been rationalized. It is found that the chiral structures of cyclotriphosphazatriene derivatives may be represented by 2D molecular diagrams, as long as the Fischer rules for chiral carbon compounds are followed for phosphorus compounds.

Introduction

The systematic chemistry of the cyclophosphazenes commenced about 40 years ago, when the separation and characterization techniques of organic chemistry were applied to this "inorganic" group of compounds. The subject has been extensively reviewed over the years.[1−4] Geminal and nongeminal replacement paths were observed.[1−4] Positional and geometric isomers were isolated and characterized,[5] and in a number of cases confirmed by X-ray crystallography.[6−8] The tetracoordinated phosphorus atoms in cyclophosphazenes $(NPXY)_n$ are pentavalent and are potentially chiral, offering considerable scope for the synthesis and study of configurational variants. The possibility of optical isomerism was first discussed in a review 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.[1]



(I) (II)

A detailed survey of structures of cyclotriphosphazatrienes in the Cambridge Crystallographic Data Base[9] (some 188 at

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(1) Shaw, R. A.; Fitzsimmons, B. W.; Smith, B. C. *Chem. Rev.* **1962**, *62*, 247−281.
(2) Allcock, H. R. *Phosphorus-Nitrogen Compounds*; Academic Press: New York-London, 1972.
(3) Labarre, J.-F. *Top. Curr. Chem.* **1985**, *129*, 173−230.
(4) Allen, Ch. W. *Chem. Rev.* **1991**, *91*, 119−135.
(5) Keat, R.; Shaw, R. A. *J. Chem. Soc.* **1965**, 2215−2223.
(6) Ahmed, F. R.; Pollard, D. R. *Acta Crystallogr.* **1972**, *B28*, 513−519.
(7) Ahmed, F. R.; Pollard, D. R. *Acta Crystallogr.* **1972**, *B28*, 3530−3537.
(8) Ahmed, F. R.; Gabe, E. J. *Acta Crystallogr.* **1975**, *B31*, 1028−1037.
(9) Allen, F. H.; Kennard, O.; Galloy, J. J.; Johnson, O.; Watson, D. G. *Chem. Struct. 2, Proc. 2nd Int. Conf. 1990*; Warr, W. A., Ed.; Springer: Berlin, Germany, 1993; pp 343−358.

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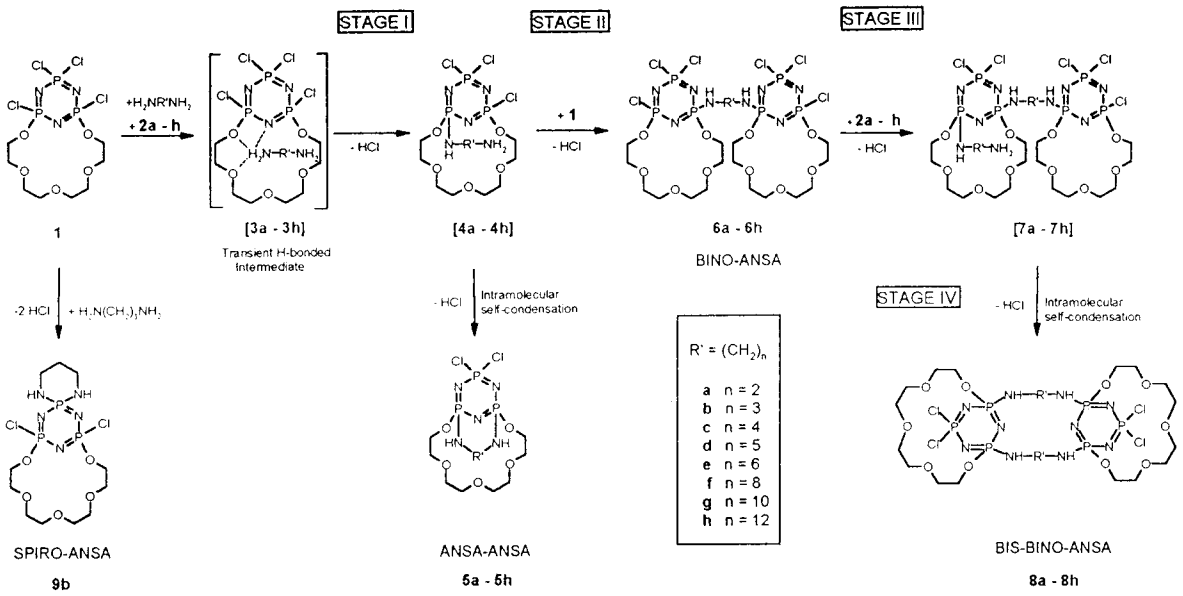
Scheme 1



present, together with earlier literature data) shows that a number of systems, in which the relative distribution of the X,Y substituents leads to pairs of chiral centers [in *R,S* (meso) or *R,R*/*S,S* (homotopic) relationships], have been described and characterized structurally.

[To avoid confusion between the use of the symbols R and S to designate configuration (plus the need later to designate a second set of configurations as R′ and S′) and the use of R to designate a general aliphatic substituent (plus the need to designate different aliphatic groups as R′ and R″), in this work chiral configurations are designated in italics as *R* and *S*, and so too the configurational descriptions *cis* and *trans*.]

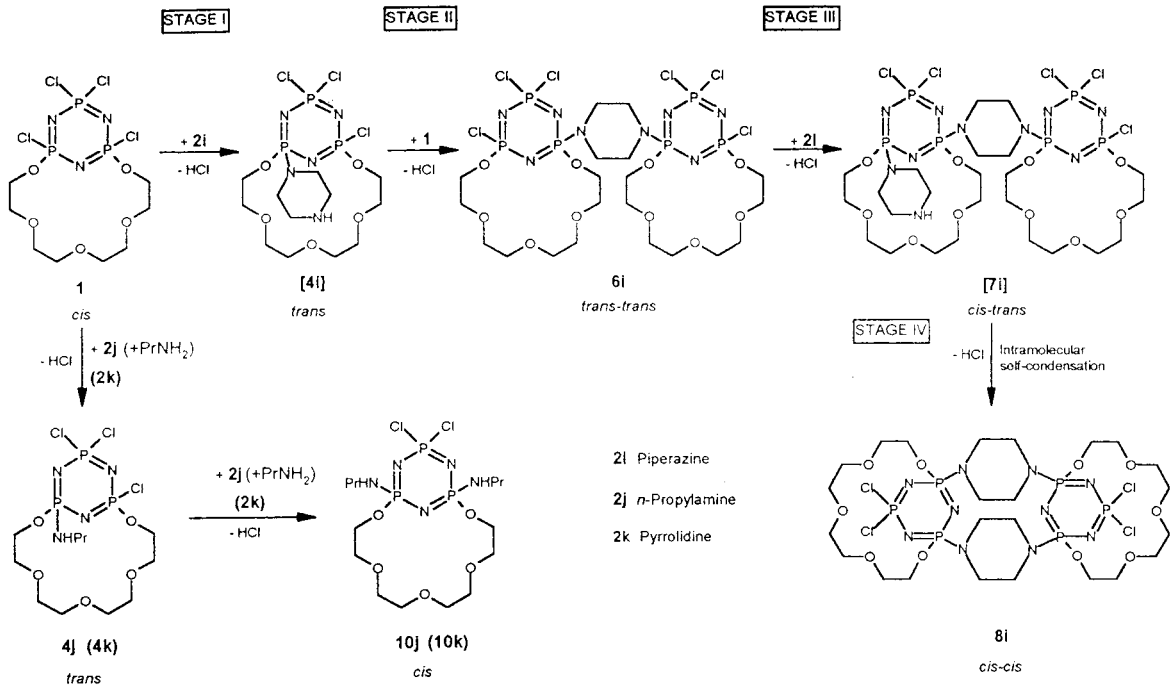
Examples of both types I and II have been examined crystallographically, for example geminal $N_3P_3Cl_3(NMe_2)_3$,[6] *trans*-$N_3P_3Cl_4(NMe_2)_2$,[10] and *trans*-$N_3P_3(NH_2)_2(OPr^n)_4$.[11] Additional complications can occur when a chiral molecule, which may be synthesized as a racemate, crystallizes through spontaneous resolution as a chiral crystal. An example of the latter type from our own work is 2,2-(1′,3′-propane-dioxy)-*trans*-4,6-dichloro-4,6-bis(pyrollidinyl)cyclotriphosphazatriene,[12] which crystallizes in space group $P2_12_12_1$. In each of these examples, chirality was not discussed, and even the implications of chirality do not seem to have been considered. In one other case, an optically active trimer derivative has been reported,[13] but this was based on cyclization of an optically active acyclic precursor. Recent studies of singly bridged derivatives containing two cyclophosphazene rings resulted in the unexpected observation by high-field NMR spectroscopy of two sets of signals with small chemical shift differences;[14] this paper deals with the explanation of these two sets of signals in terms of the presence of chiral configurational isomers and the implications for phosphazene chemistry in general.

The reactions of the cyclotriphosphazatriene-macrocyclic compound **1** with aliphatic diamines **2a**−**h** (n = 2−6, 8, 10, 12) in benzene solution[14,15] provide a very convenient way to investigate the chiral configurational properties of a series of cyclophosphazene compounds, partly because of their ease of formation and characterization, and partly because there are multiple chiral centers giving rise to diastereoisomers. The reactions summarized in Scheme 1 show the formation of a series of compounds[14,15] via the monosubstituted intermediates **4a**−**h**, viz. (i) intramolecular condensation to form the ansa-ansa compounds **5a**−**h**, (ii) intermolecular condensation with more **1** to form the singly bridged bino-compounds **6a**−**h**, (iii) further reaction of **6a**−**h** with diamine to form the intermediate compounds **7a**−**h**, and then (iv) intramolecular condensation of **7a**−**h** to form the doubly bridged bis-bino compounds **8a**−**h**.[14,15] [A spiro-ansa compound **9b** has also been isolated, but only for the reaction of **1** with 1,3-diaminopropane, **2b**].[14]

At each of the four stages (denoted I−IV) of the reaction, a >P(OR)Cl group reacts with amine R′NH$_2$ to form a >P(OR)-(NHR′) derivative as shown in Scheme 1; concomitantly, at each stage of the reaction HCl is formed which combines with a free amino group of the diamine to form the amine hydrochloride. Hence, formation of the bino compound **6** is favored at a 1:1 ratio of compound **1** and diamine, and formation of the bis-bino compound **8** is favored at a 1:2 ratio of the reactants.[14] Although each of these products was characterized by elemental analysis, MS, and ^{31}P NMR, no explanation was provided for one unusual feature of the ^{31}P NMR spectra of lower members of the series of bino-compounds **6a**−**d** (n = 2−6), viz. the proton-decoupled ^{31}P NMR spectra were observed as the expected AMX spin-coupling patterns but, unexpectedly, each phosphorus signal was observed as a pair of signals in a 1:1 ratio with a small chemical shift separation, $\Delta\delta$ ∼0.02−0.05 ppm.[14] On the other hand, the ^{31}P NMR spectra of higher members of the series of bino-compounds **6e**−**h** (n = 8, 10, 12) were observed as the expected single AMX spin systems. Similar NMR behavior has been observed previously for two analogous series of singly bridged cyclotriphosphazatriene-diamine derivatives (denoted as 3n3 and 4n4 series with n = 6,

(10) Ahmed, F. R.; Fortier, S. *Acta Crystallogr.* **1980**, *B36*, 1456−1460.
(11) Fincham, J. K.; Hursthouse, M. B.; Parkes, H. G.; Shaw (nee Gözen), L. S.; Shaw, R. A. *J. Chem. Soc., Dalton Trans.* **1988**, 1169−1178.
(12) Alkubaisi, A. H.; Hursthouse, M. B.; Shaw (nee Gözen), L. S.; Shaw, R. A. *Acta Crystallogr. Sect. B* **1988**, *44*, 16−22.
(13) Schmulbach, C. D.; Dereian, C.; Zeck, C.; Sahuri, S. *Inorg. Chem.* **1971**, *10*, 195−196.
(14) Brandt, K.; Porwolik, I.; Siwy, M.; Kupka, T.; Shaw, R. A.; Davies, D. B.; Hursthouse, M.; Sykara, G. *J. Org. Chem.* **1999**, *64*, 7299−7304.
(15) Brandt, K.; Porwolik-Czomperlik, I.; Siwy, M.; Kupka, T.; Shaw, R. A.; Davies, D. B.; Hursthouse, M.; Sykara, G. *J. Am. Chem Soc.* **1997**, *119*, 1143−1144.

Scheme 2



7, 8, 9) by Labarre et al.,[16] who suggested that the doubling-up of ^{31}P NMR signals is caused by different folded conformations of the molecules resulting from intramolecular NH···Cl hydrogen-bonding. The latter explanation is found to be incorrect, and it is shown, in this work, that the doubling-up of ^{31}P NMR signals for the bino-series of compounds **6a**−**d**[14] (plus other phenomena, see below) and for the series of bridged cyclophosphazene compounds observed by Labarre et al.,[16] can be explained in terms of the chiral configurational properties of the cyclophosphazene compounds. This explanation, in turn, has general significance for understanding the chiral configurational properties of cyclophosphazene compounds.

Results

Reactions of Compound 1 with the Di-secondary Amine, Piperazine, 2i (Scheme 2). An attempt was made to investigate the origin of the doubling-up of the ^{31}P NMR signals of singly bridged cyclophosphazene compounds using the series of cyclophosphazene-macrocyclic compounds **6a**−**c**, because they contain P−Cl and P−NH groups and might be capable of forming hydrogen-bonded conformations analogous to the series of compounds investigated by Labarre et al.[16] However, it is found that the diamino-bridged bino compounds **6a**−**c** are unstable in solution at higher temperatures and so are unsuitable to study the possibility of hydrogen-bonded conformations. It is also found that the solid form of compounds **6a**−**c** are unstable in air/moisture and the crystals are, in the main, unsuitable for X-ray crystallography. It is likely that the instability results from having both reactive P−Cl and P−NH groups in a cyclophosphazene containing a macrocyclic ring, and that the stability might be increased if the bridge could be formed with a di-secondary amine. Hydogen bonds are also precluded in cyclophosphazene-macrocyclic compounds bridged by a di-secondary amine. In this work it was found that both the singly bridged and doubly bridged cyclophosphazene-macrocyclic derivatives could be formed with the di-secondary amine, piperazine. The series of reactions of **1** with piperazine summarized in Scheme 2 is similar to those with primary diamines in Scheme 1, except that the reactions with piperazine do not lead to formation of compounds analogous either to the ansa−ansa series (**5a**−**h**) or to the spiro−ansa compound **9b**.

Formation of the Bino(piperazine) Phosphazene-macrocyclic Compound, 6i. A bino-compound **6i** was readily formed by the reaction of **1** with piperazine **2i** in a 1:1 ratio at room temperature as summarized in Scheme 2. It has been shown previously that the structures of cyclophosphazene derivatives (such as the macrocyclic compounds **1**, **5**, **6**, **8**) can be determined by a combination of proton-coupled and proton-decoupled ^{31}P NMR spectroscopy.[14,17] ^{31}P NMR spectroscopy of the reaction mixture of **1** and **2i** in toluene-d_8 in Figure 1a shows the presence of a small amount of the monosubstituted intermediate **4i** (Stage I of reaction), a significant proportion of the bino-compound **6i** (Stage II) and, because the reaction had not yet gone to completion, some of the starting material **1**.

At the completion of the reaction **6i** is formed in ∼90% yield, and signals for the starting compound **1** and the intermediate compound **4i** are not observed; **6i** is obtained in high yield because no side reactions to form the spiro−ansa compound (cf. compound **9b** in Scheme 1) nor the ansa−ansa compound (cf. compounds **5a**−**h** in Scheme 1) were observed with piperazine. The ^{31}P NMR spectrum of **6i** in Figure 1a exhibits two AMX spin systems in a 1:1 ratio similar to those found previously for the bino series of compounds **6a**−**d** with bridges formed from primary diamines.[14] There is also evidence for the intermediate compound **4i**, which exhibits an AMX spin system with similar chemical shifts and coupling constants to **6i**. The ^{31}P NMR chemical shifts and ^{2}J(P−P) spin coupling constants of each of the compounds in the crude reaction mixture in toluene-d_8 are summarized in Table 1. The bino(piperazine) compound **6i** was purified on a silica gel column by elution with acetone:isooctane (1:2), and crystals of **6i** formed in a

(16) Perly, B.; Berthault, P.; Vivaud, L.; Guerch, G.; Labarre, J.-F.; Sournies, F. *J. Mol. Struct.* **1987**, *162*, 87−95.

(17) Labarre, M.-Ch.; Labarre, J.-F. *J. Mol. Struct.* **1993**, *300*, 593−606.

Table 1. ^{31}P NMR Data of Derivatives of the Reactions of Piperazine with the Phosphazene-macrocyclic Compound (**1**) in Scheme 2[a]

	chemical shifts (ppm)			^2J(P−P), Hz			
cpd	>PCl_2 1	>P(OR′)Cl 2	>P(OR′)(NR) 3	1,2	1,3	2,3	(*n*,*m*)[b]
1	25.3_0	19.3_5		70.8			66.4 (2,2)
4i	26.7_4	20.9_3	15.4_2	78.3	62.7	55.5	
6i	26.3_2	21.0_9	15.4_9	79.8	60.3	55.7	
	26.2_9	20.9_3	15.4_8	79.5	60.1	55.7	
[**7i**]	26.2_5	20.9_8	15.3_6	79.8	60.0	56.0	
(*trans*)	26.2_3	20.9_5	15.3_3	79.8	59.9	56.1	
[**7i**](*cis*)	∼25.5	∼16−18[c]					
8i(m_1)	27.9		17.8_5		57.5		(3,3)[d]
8i(m_2)	27.1		17.2_5		55.5		(3,3)[d]

[a] 160 MHz NMR measurements at ambient temperatures in toluene-d_8. Chemical shifts are referenced to triphenylphosphine as an internal standard ($\delta = -4.5$ ppm). [b] *n*,*m* correspond to other phosphorus atoms with geminal coupling. [c] Very complicated sets of overlapping ABX spin systems not analyzed. [d] Coupling constant not observed in A_2X spin system.

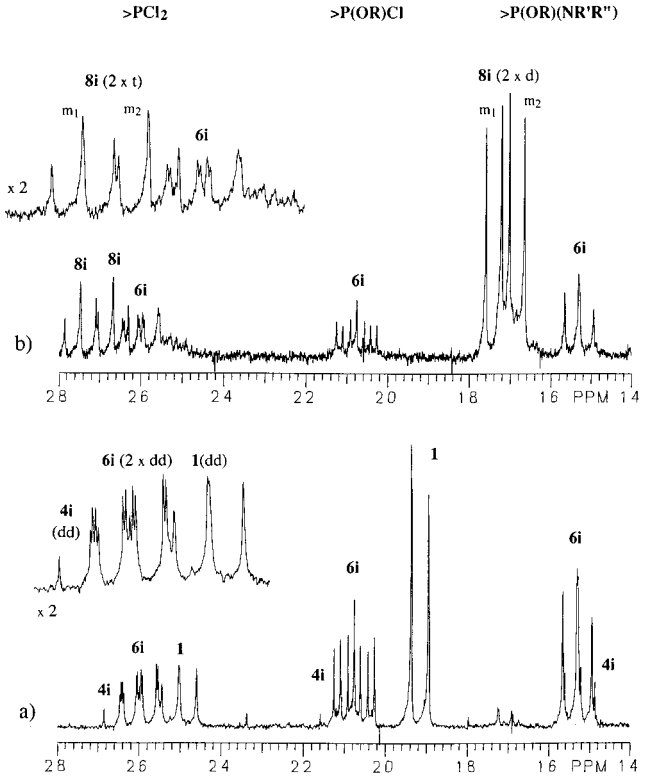


Figure 1. ^{31}P NMR spectrum (160 MHz proton-decoupled) of the room-temperature reaction of the phosphazene-macrocyclic compound **1** with piperazine, **2i**, in toluene-d_8 solution. (a) Addition of **2i** to **1** in ∼1:1 ratio shows formation of the singly bridged compound **6i** (corresponding to meso and racemic forms), some unreacted **1**, and evidence for the intermediate **4i**. (b) Addition of **2i** to **6i** in ∼1:1 ratio shows formation of the bis-bino compound **8i** (consisting of two sets of A_2X spin systems, labeled m_1 and m_2) in the presence of unreacted **6i**.

number of collected fractions on standing for 48 h. Two crystalline forms were obtained, one as plates and the other as needles, which could be readily separated by hand.

X-ray Crystal Structure(s) of the Bino(piperazine) Compounds, 6i. X-ray structure determination of the needlelike crystals of **6i** shows in Figure 2a that the molecule contains two phosphazene-macrocyclic units bridged by a piperazine molecule. The complex sits on a center of inversion in the unit cell, and the molecule is a meso form, in which the phosphorus atoms in the diamine bridge of both molecules in the unit cell have *RS* configurations. The structure in Figure 2a shows that the phosphazene-macrocyclic units are in an antiparallel arrangement, and each of the macrocyclic rings is in the *trans* configuration with respect to the plane of the cyclophosphazene ring.

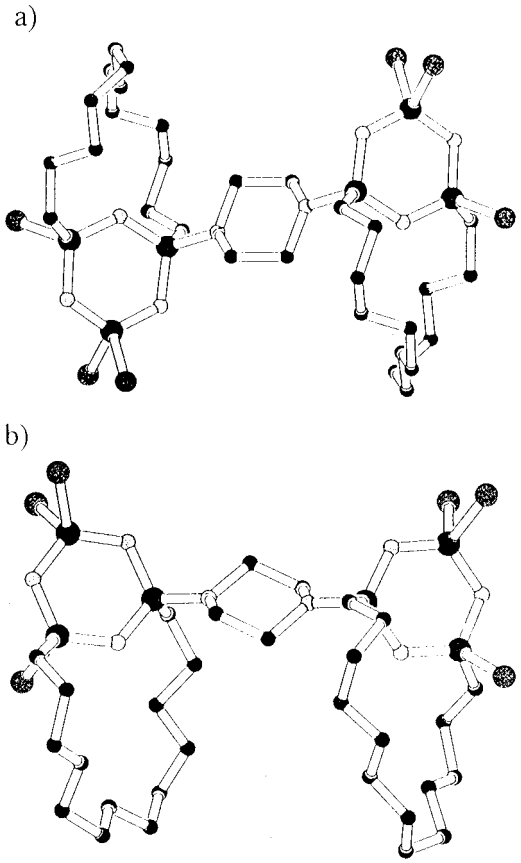


Figure 2. X-ray crystallographic structures of the two forms (needles and plates) of the singly bridged bino compound **6i**, in which each of the macrocyclic rings has a *trans* configuration with respect to the plane of the cyclophosphazene rings. (a) The needlelike crystals result from the meso form of the bino(pip) compound **6i**, in which the phosphorus atoms bridged by the piperazine ring have opposite configurations (*R* and *S*). (b) The platelike crystals result from the racemic form of **6i**, in which the phosphorus atoms bridged by the piperazine ring have the same configurations (*RR* or *SS*).

The platelike crystals of **6i** also have a centrosymmetric crystal structure, but in this case, the individual molecules comprise two phosphazene-macrocyclic units of the same chirality. The unit cell thus contains two chiral molecules, one having an *RR* and the other an *SS* configuration of the phosphorus atoms of the bridge. A diagram of one of the molecules is shown in Figure 2b, from which the approximate C2 rotational symmetry relationship between the phosphazene components can be seen. The conformation adopted by the molecule in the solid state has a syn arrangement of the

phosphazene-macrocyclic units; an anti conformation would be accessible by rotation about either of the N(pip)−P bonds.

Formation of the Bis-bino(piperazine) Phosphazene-macrocyclic Compounds, 8i. To optimize formation of the bis-bino compound, **8i**, piperazine **2i** was added in a 1:1 mole ratio to previously prepared and purified **6i**, and because the last step of the desired reaction (**7i** → **8i**) is *intramolecular* condensation (Scheme 2), the reaction was performed at about 80 times the dilution of the normal reaction conditions for intermolecular substitution reactions in these systems. After the reaction mixture was concentrated, the ^{31}P NMR spectrum of the crude reaction mixture in THF-d_8 in Figure 1b showed about 30% of the unreacted starting material **6i** and two similar A_2X spin systems for **8i** in a 1:1 ratio. The signals of **8i** have slightly different chemical shift differences between the >PCl_2 and >P(OR)-(NR′R″) signals (10.2 vs 9.8 ppm) and slightly different values of the ^2J(P−P) spin−spin coupling constants (55.5 vs 57.5 Hz). The different NMR characteristics were used to assign the two sets of signals and indicated that there might be two different bis-bino compounds, **8i**. Silica gel column chromatography was used to separate the unreacted starting compound **6i** from **8i**, and the recovered **8i** products were partially separated by differential solubility in toluene and finally purified by column chromatography. The two bis-bino compounds were characterized by NMR and MS; in particular, the ^{31}P NMR of each compound showed the characteristic A_2X spin systems with small differences in $\Delta\delta$ and ^2J(P−P) values, as found in the crude reaction mixture (Table 1). The two bis-bino compounds were slowly crystallized from THF over a period of about 2 months; two crystal forms were found, one as needles and the other as plates.

X-ray Crystal Structure(s) of Bis-bino(piperazine) Compounds 8i. X-ray crystal structure analysis revealed that bis-bino (plates) is the meso form with a crystallographic center of symmetry and bis-bino (needles) is the meso form with a pseudoplane of symmetry. Diagrams of the two molecular structures are shown in Figure 3.

The structure of bis-bino(plates) in Figure 3a shows that the macrocyclic rings are in the *cis*-configuration, the two cyclophosphazene rings are in an anti arrangement with respect to the plane of the ring formed from the two piperazine bridges, and the phosphorus atoms attached to the piperazine bridges have the *RR* and *SS* configurations, resulting in a center of symmetry for the molecule. The structure of bis-bino(needles) in Figure 3b is of low precision due to the poor quality of the crystal and diffraction data, probably reflecting the presence of severe disorder. Nevertheless, the data are good enough to establish the structure and configuration of the compound, viz. the macrocyclic rings are in the *cis* configuration, the phosphorus atoms attached to the piperazine bridges have the *RS* configurations, and the cyclophosphazene rings are in a syn arrangement with respect to the plane of the ring formed from the two piperazine bridges resulting in a plane of symmetry for the molecule.

Discussion

X-ray crystallographic studies of the starting compound **1** have shown that the macrocyclic ring is in the *cis*-ansa configuration with respect to the cyclophosphazene ring.[18] Although each macrocyclic-ring phosphorus atom of compound **1** is chiral, the molecule is the meso form. In this work, aminolysis of compound **1** with piperazine **2i** results in formation of the relatively stable singly bridged bino compounds **6i** and the doubly bridged compounds **8i**. X-ray crystallographic investigations show that **6i** exists as a mixture of meso and racemic forms with the macrocyclic rings in *trans*-configurations and **8i** exists as a mixture of two different meso forms, each with the macrocyclic rings in *cis*-configurations. These results can be rationalized by consideration of the configurational properties of each stage (I−IV) of the reaction of the aminolysis of compound **1**, as summarized in Schemes 1 and 2, and have been confirmed in this work, together with the configurational properties of the intermediate compounds **4** and **7**, by ^{31}P NMR spectroscopy on addition of chiral shift reagent (CSR).[19] For NMR CSR investigations of the chiral configurational properties of the compounds in this work, it is important to use a solution of a mixture of products to provide some ^{31}P NMR signals where no effect is expected to compare with those where different chiral signals should be observed.

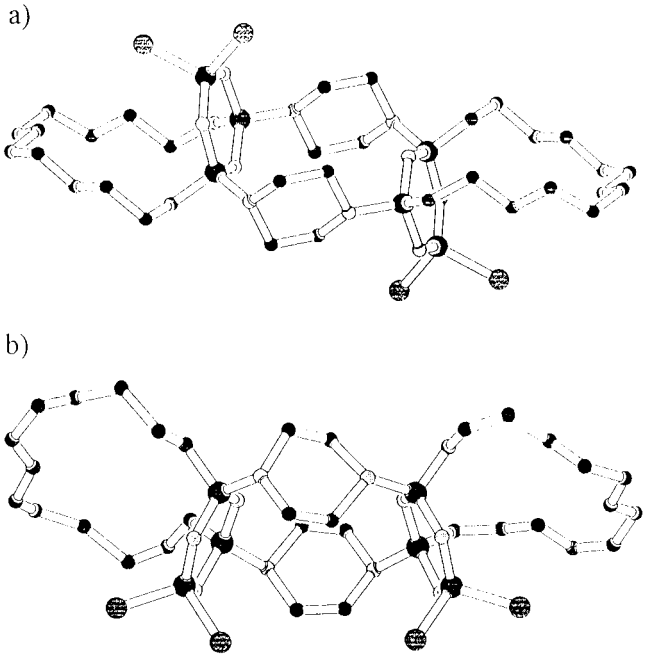


Figure 3. X-ray crystallographic structures of the two forms (needles and plates) of the doubly bridged bis-bino compound **8i**, in which each of the macrocyclic rings has a *cis* configuration with respect to the plane of the cyclophosphazene rings. (a) The platelike crystals result from the meso form with a center of symmetry in which the phosphorus atoms attached to one piperazine bridge have the same configuration (*RR* or *SS*) and the two cyclophosphazene rings are in an anti arrangement. (b) The structure of bis-bino(needles) is a meso form with a plane of symmetry, in which the phosphorus atoms at the ends of the piperazine bridge have opposite configurations (both *RS*) and the two cyclophosphazene rings are in a syn arrangement.

It is convenient to follow the reaction scheme in terms of the *R* and *S* configuration at each phosphorus atom of the cyclophosphazene-macrocyclic ring. The absolute configurations of the two chiral centers in the starting compound **1** can be designated as *R* and *S*, noting that, for each chiral P atom, the Cahn−Ingold−Prelog(CIP)[20] priority order of groups is Cl > OR > N[PCl_2] > N[P(OR)Cl]. On aminolysis of compound **1** with HNR′R″ the P−Cl group in >P(OR)Cl is replaced by P−NR′R″ to form >P(OR)(NR′R″). There is a potential

(18) Brandt, K.; Kupka, T.; Drozd, J.; van de Grampel, J. C.; Meetsma, A.; Jekel, A. P. *Inorg. Chim. Acta* **1995**, *228*, 187−192.

(19) Rinaldi, P. L. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *16*, 291−352 and references therein.

(20) Cahn, R. S.; Ingold, C. K.; Prelog, V. IUPAC Rules for the Nomenclature of Organic Chemistry, Section E, Stereochemistry. *Pure Appl. Chem.* **1976**, *45*, 10−30.

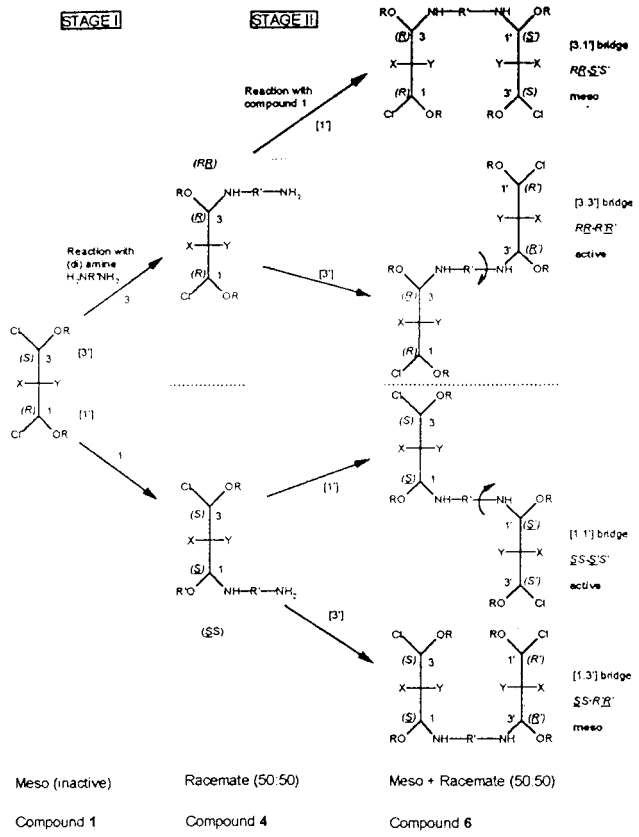


Figure 4. Diagrammatic representation of the configurational properties of Stages I and II of the reaction of diamines, **2**, with the phosphazene-macrocyclic compound **1** as summarized in Scheme 1. The configurational notation *R*/*S*, $\underline{R}/\underline{S}$, *R*′/*S*′ and $\underline{R}'/\underline{S}'$ is described in the text.

problem in denoting the absolute configuration of the phosphorus atoms in >P(OR)Z groups, because of the priority order in the CIP series of substituent groups Z in this work (i.e., Cl > OR > NR′R″).[20] In the present work this problem is avoided by relating all configurations to the *RS* configuration of the starting compound **1** and denoting subsequent changes in configuration by modifying *R* and *S* as $\underline{R}/\underline{S}$ (and $\underline{\boldsymbol{R}}/\underline{\boldsymbol{S}}$ later) to take account of the different substitution patterns of >P(OR)Z groups.

To simplify subsequent representations of the *cis* and *trans* configurations of the macrocyclic ring, the linkage positions of the *cis*-ansa configuration of the >P(O-macrocycle) groups in the structure of the starting compound **1** are represented in Figure 4 by OR in the 2D stick diagram of cyclotriphosphazatriene derivatives.

In addition, so that the orientations of the cyclotriphosphazatriene rings can be followed throughout the analysis, the $>PCl_2$ groups have been represented by >P(X)(Y), that is, in this work X = Y = Cl. [note well: If X ≠ Y, the >P(X)(Y) group is also chiral, and this would lead to an even more complicated chiral configurational analysis.]

In any 2D diagrammatic represention of a 3D structure, it is necessary to define groups which are above and below the plane, similar to that for Fischer projections of carbon compounds. In this work the phosphorus atoms (labeled 1 and 3 in Figure 4) and the attached OR/Cl groups are in-the-plane and the >P(X)(Y) group, with P−X and P−Y bonds attached by solid lines, points forward out-of-the-plane. Following these rules the *R* and *S* configurations are denoted in Figure 4 for the two chiral >P(OR)Cl groups of the meso form of compound **1**.

Confirmation by ^{31}P NMR Spectroscopy of the Chiral Configurational Properties of the Reaction of Phosphazene-Macrocyclic Compounds with Amines. The chiral configurational properties of each stage of the reaction can be understood, if it is assumed that the substitution reaction of each >P(OR)Cl group with HNR′R″ (which covers both primary and secondary amines) proceeds with inversion of configuration, that is,the Walden Inversion.[21] It is convenient to investigate the chiral configurational properties of the reaction of **1** with amines in terms of the four stages (I−IV) of the reaction as outlined in Schemes 1 and 2, and using a primary diamine, $H_2NR'NH_2$, as an example, in Figure 4.

Stage I. Reaction of amine HNR′R″ with the >P(OR)Cl groups of **1** to form >P(OR)(NR′R″) at either the 1 or 3 positions (Figure 4) gives the monosubstituted compound **4** in which there is inversion of configuration at the reaction center and the macrocyclic ring, represented by the >P(OR) groups, exists in a *trans*-configuration. The two macrocyclic-phosphorus atoms now have different substituents, >P(OR)Cl and >P(OR)-(NR′R″), which are expected to exhibit different optical activities. The chirality of the P atoms for the >P(OR)(NR′R″) group is denoted by $\underline{R}$ or $\underline{S}$ (underlined) compared to *R* or *S* (normal type) for the original >P(OR)Cl group. Reactions are equally likely at either >P(OR)Cl group of **1**, which has an *RS* configuration, to give optically active products $\underline{RR}$ and $\underline{SS}$, in which the inverted optically active phosphorus atom is denoted by underlining, that is, $\underline{R}$ or $\underline{S}$. By only allowing rotation of structures in the plane (as with Fischer projections of carbon compounds) it is seen in Figure 4 that the two structures of the monosubstituted compound **4** cannot be superimposed and thus are enantiomers; the mirror plane is shown by the broken line.

^{31}P NMR Spectroscopy of the "Intermediate" Compound 4. The chiral configurational properties of the monosubstituted-derivative **4** (expected to exist as a racemate) were investigated by the reaction of **1** with amines for which no further reaction is possible, viz. a monofunctional primary amine such as *n*-propylamine, **2j**, as shown in Scheme 2, and a secondary amine such as pyrrolidine, **2k**. As an example, the reaction of *n*-propylamine, **2j**, at a 2:1 ratio with the cyclophosphazene-macrocyclic compound **1** in benzene leads to formation of both the monosubstituted compound **4j** and the di-substituted compound **10j**, which were separated by column chromatography and characterized by MS and ^{31}P NMR spectroscopy (to be published). In the present example, the partially separated fractions of compounds **4j** and **10j** were used for NMR CSR experiments.

The 160 MHz proton-decoupled ^{31}P NMR of a ∼50:50 mixture of compounds **4j** and **10j** is shown in Figure 5a. The spectrum of the monosubstituted derivative **4j** is observed as an AMX spin system [>P(OR)(NR′R″) δ ∼16.2 ppm, >P(OR)-Cl δ ∼21.8 ppm and $>PCl_2$ δ ∼26.0 ppm], and the spectrum of the di-substituted derivative **10j** is observed as an A_2X-like spin system [>P(OR)(NR′R″) δ ∼17 ppm and $>PCl_2$ δ ∼25.8 ppm]. The proton-coupled ^{31}P NMR spectrum in Figure 5b is consistent with the assignment of signals in that no coupling is observed on the $>PCl_2$ group, triplets are observed on the >P-(OR)Cl signals due to vicinal $POCH_2$ coupling, and broad lines are observed for the >P(OR)(NR′R″) signals due to vicinal $POCH_2$ and two $PNCH_2$ coupling paths. On gradual addition of the chiral shift reagent, Eu(hfc)$_3$, there are greater changes in chemical shifts of the ^{31}P NMR signals of **10j** compared with **4j**, but eventually, as shown in Figure 5c, the >P(OR)Cl signal of **4j** separates into a pair of signals of equal intensity

(21) Walden, B. *Ber.* **1893**, *26*, 210; **1896**, *29*, 133; **1899**, 32, 1855.

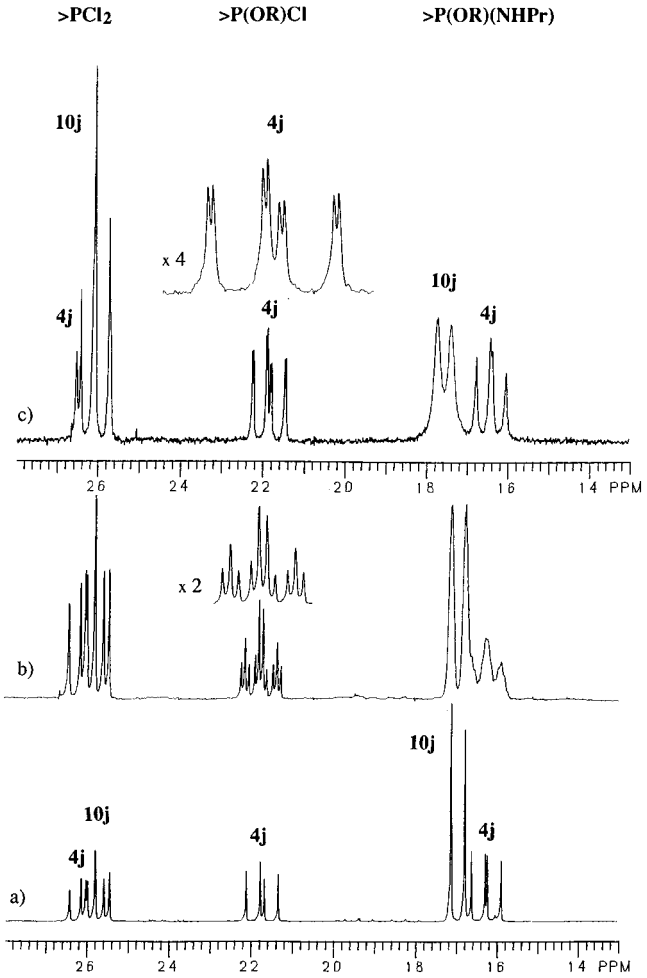


Figure 5. (a) ^{31}P NMR spectrum (160 MHz proton-decoupled) in $CDCl_3$ solution of compound **4j**, the mono-*n*-propylamine derivative of **1**, in the presence of the di-*n*-propylamine derivative, **10j**. (b) Proton-coupled spectrum shows the larger $POCH_2$ coupling to the >P(OR)Cl signal of **4j** (ΣJ ~30 Hz) with the macrocyclic ring in the *trans*-configuration, and the smaller ΣJ coupling to the >P(OR)(NR′R″) signal of **10j** with the macrocyclic ring in the *cis*-configuration. (c) Addition of chiral shift reagent, Eu(hfc)$_3$, separates the >P(OR)Cl signal of **4j** into two signals at a 1:1 ratio, corresponding to *RR* and *SS* configurational isomers of the racemic mixture.

corresponding to the *RR* and *SS* isomers, whereas no separation of signals (only broadening due to complexation with the paramagnetic CSR) is observed for **10j**. This experiment confirms the expected chiral configurational properties of Stage I of the reaction.

Stage II. The chiral configurational properties for formation of the bino-compound **6** from the "intermediate" **4** are shown for Stage II of the reaction in Figure 4. *For convenience*, the chiral phosphorus atoms of the original cyclophosphazene moiety (**1**) are labeled 1−3, and those for the second cyclophosphazene moiety (**1′**) are labeled 1′−3′. Similarly, the unprimed *R* and *S* configurational designations of the original molecule are primed for the second moiety, *R*′ and *S*′. Each "intermediate" compound **4** (*SS* and *RR*) gives rise to two singly bridged bino-compounds **6** by reaction with equal probability at the 1′ or 3′ positions to give four structures denoted as *SS*·*S*′*S*′, *SS*·*R*′*R*′, *RR*·*S*′*S*′ and *RR*·*R*′*R*′. By symmetry considerations two of the structures with *R*·*S* configurations of the bridge have planes of symmetry and are the same meso-compound (i.e., *SS*·*R*′*R*′ and *RR*·*S*′*S*′), and it can be seen in Figure 4 that these two structures are the same by rotating one molecule 180° in-the-plane to give the other structure. The structures of the two other isomers with *R*·*R* and *S*·*S* bridges (*RR*·*R*′*R*′ and *SS*·*S*′*S*′) cannot be superimposed and exist as a racemate; the mirror plane between the enantiomeric forms is shown in Figure 4. The configurational analysis at this stage of the reaction is confirmed in this work by X-ray crystallographic observation of the meso and racemic forms of the bino(piperazine) compound **6i** summarized in Figure 2. On statistical grounds it is expected that each isomer is formed with the same probability, and as there are "two" meso forms and two enantiomers, there will be equal amounts of the meso and racemate.

It should be noted that the single di-amine bridge is denoted by a dot (·) in the configurational designations of molecules in Figure 4 and that, as it is *only a matter of convenience* which phosphazene moiety in the bridged compound is designated by primes (P atoms and *R*/*S* configurations), the configurational properties of each pair of macrocyclic-P atoms can be interchanged across the diamine bridge, that is, taking the optically active *SS*·*S*′*S*′ isomer (or the *RR*·*R*′*R*′ isomer) and interchanging the pair of *S*′*S*′ with the *SS* configurations gives the same configuration of the molecule. Similarly, for the meso-form *SS*·*R*′*R*′ (or *RR*·*S*′*S*′) interchanging the pairs of *SS* and *R*′*R*′ configurations across the diamine bridge gives the same meso form.

^{31}P NMR Spectrocopy of the Bino-derivative, 6i. The ^{31}P NMR spectrum of the bino(piperazine) compound **6i** is observed in Figure 1a as two similar AMX spin systems which exist with small chemical shift differences in a 1:1 ratio, similar to the series of bino-compounds formed from diamines with $n \leq 6$.[14] As crystal structure determinations were performed on the bino compound **6i**, it is expected that the two sets of signals for the singly bridged compounds **6** correspond to the meso and racemic forms, with different chemical shifts for the diastereoisomers.

The configurational properties of Stage II of the reaction were confirmed by addition of the chiral shift reagent, Eu(hfc)$_3$, to the bino-compound **6i** in chloroform solution (in the presence of a small proportion of one meso form of the bis-bino compound **8i**) as shown in Figure 6. The proton-decoupled ^{31}P NMR spectrum in Figure 6a shows the A_2X-like spin system of **8i** and the two sets of AMX spin systems of **6i**. Addition of Eu(hfc)$_3$ causes some chemical shift changes and slight broadening of the >P(OR)(NR′R″) signals as shown in Figure 6b, whereas the >P(OR)Cl and $>PCl_2$ signals are separated into *m* and *r* forms. The chiral shift behavior can be seen clearly on the $>PCl_2$ signal (expanded inset), which shows that the signals of the racemate are in a 1:1 ratio and half the intensity of the meso signals, confirming the predicted configurational properties of Stage II of the reaction.

It should be noted that for compound **6i** the meso, *m*, signals for >P(OR)Cl and >P(OR)(NR′R″) groups are to higher frequency than those for the racemate, *r*, but vice versa for the $>PCl_2$ signal. [The relative assignment of signals of the *m* and *r* forms of **6b** has also been confirmed by ^{31}P NMR spectroscopy of the chromatographic fractions corresponding to the partial separation of these isomers as shown in Fig.S1 and by addition of chiral shift reagent, Eu(hfc)$_3$.]

Stage III. Reaction at one of the two remaining >P(OR)Cl groups of the bino compound **6** with an amino group of a second diamine molecule forms a monosubstituted bino compound **7** as an intermediate in the reactions shown in Schemes 1 and 2. The chiral configurational properties of the reaction are summarized in Figure 7.

It can be seen that for the meso form of the bino compound **6** in Figure 4 the separate P−(OR) and P−Cl groups at the ends

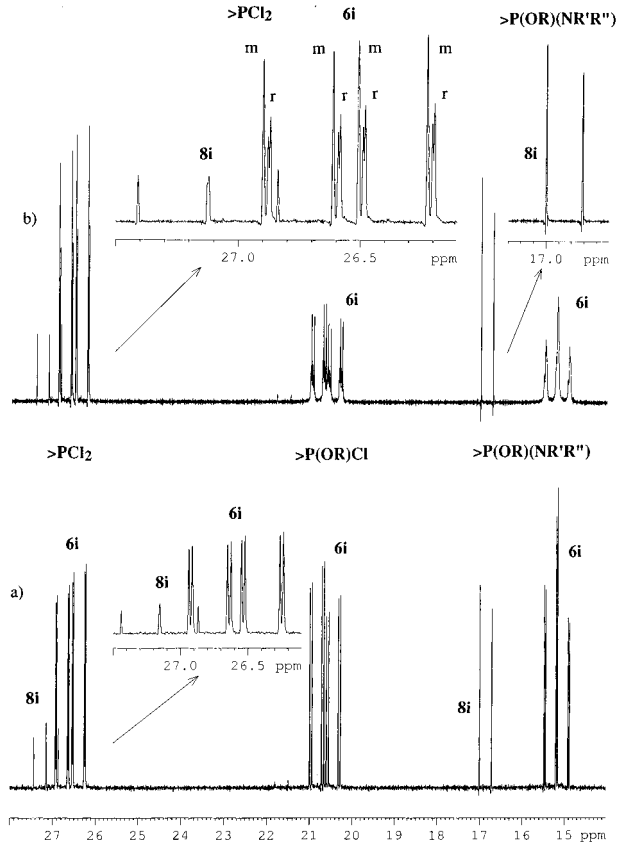


Figure 6. (a) ^{31}P NMR spectrum (200 MHz proton-decoupled) of the bino compound **6i** in chloroform-*d* solution in the presence of a small amount of the syn meso form of the phosphazene-macrocyclic compound **8i**. (b) Addition of Eu(hfc)$_3$ separates the ^{31}P NMR signals of **6i** into one set of doublet of doublets corresponding to the meso form (labeled m) and two sets of doublet of doublets at a 1:1 ratio, corresponding to the racemate (r). The fact that the signals of compound **8i** remain the same on addition of the chiral shift reagent is consistent with compound **8i** being a meso form.

of the molecule are conveniently aligned so that aminolysis can take place with the diamine to form a second >P(OR)(NR′R″) group in the molecule, compound **7**. Reaction takes place with inversion of configuration and the resulting configurations are designated in bold-faced type as ***R*** and ***S*** to differentiate them from the configurations (*R* and *S*) of the first diamine bridge as shown in Figure 7a. For example, the *SS*·*R*′*R*′ meso form of the singly bridged bino compound **6** reacts with amine at the vacant 3-position of the first cyclophosphazene ring to give the *S**R***·*R*′*R*′ form or at the vacant 1′-position of the second cyclophosphazene ring to give the *SS*·*S*′***R***′ isomer, as shown in Figure 7a. The two isomers are enantiomers, and as each of the configurational isomers of the bino compound **6** reacts with equal probability, it is expected that the meso form of compound **6** leads to a racemic mixture (designated r_1).

It can be seen for the optically active forms of the bino compound **6** in Figure 4 that the separate P−(OR) and P−Cl groups at the ends of the molecule can only be aligned for aminolysis to take place, if one cyclophosphazene moiety is rotated out-of-the-plane by 180° (as shown by the curly arrow). In this case, the >P(X)(Y) group of the rotated cyclophosphazene moiety is now below-the-plane, which is represented in Figure 7b by broken lines for P−X and P−Y bonds. Hence, the optically active *SS*·*S*′*S*′ isomer of compound **6** in Figure 7b reacts with amine at the vacant 3-position of the first cyclophosphazene ring to give the *S**R***·*S*′*S*′ isomer or at the vacant 3′-position to give the *SS*·*S*′***R***′ isomer. These two configurational isomers are the same, because pairs of chiral configurations can be interchanged across the diamine bridge. A similar situation is found for amination of the optically active *RR*·*R*′*R*′ isomer of compound **6**, as shown in Figure 7b. The two configurational isomers are enantiomers, and as each of the configurational isomers of the bino compound **6** reacts with equal probability, it is expected that aminolysis of the active form of compound **6** leads to a racemic mixture (designated r_2) of compound **7**. The two sets of optical isomers of compound **7** in Figure 7a and b are diastereoisomers. Again, as each amination reaction is expected to occur with equal probability, the chiral configurational properties of compound **7** are predicted to exist as two sets of racemates (r_1 and r_2) in a 1:1 ratio.

The chiral configurational properties of Stage III of the reaction were confirmed by formation of a stable "intermediate" type of compound **7**, which could not react further and which would provide a relatively simple ^{31}P NMR spectrum for analysis. This was achieved by a reversed-order formation of a *β*-*O*-naphthoyl derivative of the bino-piperazine compound **6i** whose ^{31}P NMR spectrum consisted of 2 pairs of AMX signals in a 1:1 ratio corresponding to two racemic mixtures, as confirmed by addition of the chiral shift reagent, Eu(hfc)$_3$ (to be published).

Stage IV. The chiral configurational analysis for Stage IV of the reaction in Figure 7 indicates that intramolecular condensation of the "intermediates" **7** leads to two different bis-bino compounds **8**, each being a meso-form, but with different configurations of the phosphorus atoms of the bridging group. The prediction of two meso forms of the doubly bridged compound **8** has been confirmed by the X-ray crystal structures of **8i** in this work.

In terms of the mechanism of the reaction, it is shown in Figure 7a that monosubstitution of the meso form of the bino compound **6** by diamine (Stage III) gives a racemic mixture (labeled r_1) for compound **7**, and then an intramolecular reaction with the remaining free amino group of **7** to form the second *RS* bridge of the bis-bino compound **8** (Stage IV). This bis-bino form (labeled m_1) is meso by virtue of a plane of symmetry, and corresponds to the X-ray crystal structure of bis-bino(pip) in Figure 3b, having the cyclophosphazene rings in a syn arrangement with respect to the bridging groups, as shown by the >P(X)(Y) groups of both cyclotriphosphazatriene rings projecting (up) out-of the-plane. Similarly, it is shown in Figure 7b that monosubstitution of the racemic form (*RR/SS* bridges) of compound **6** gives a racemic mixture (labeled r_2) for compound **7** and then a second meso form (labeled m_2) of the bis-bino compound **8**, corresponding to the X-ray crystal structure in Figure 3b with both *RR* and *SS* bridges. This molecule has a center of symmetry in which the cyclophosphazene rings are in an anti arrangement with respect to the bridging groups, as shown by the structure in Figure 7b where the >P(X)(Y) group of one cyclotriphosphazatriene ring projects (up) out-of-the-plane and the other projects below-the-plane.

It should be noted that, by labeling the central >PCl$_2$ group as >P(X)(Y) for the cyclophosphazene-macrocyclic compounds in Figures 4 and 7, it can be seen that the initial *cis*-configuration of the starting compound **1**, where the OR groups are on the same side of the cyclophosphazene ring as the Y group (Figure 4), undergoes double inversion of configuration in the formation of the doubly bridged compounds **8**, in which the macrocyclic rings of compounds **8** regain the *cis*-configuration, but now the OR groups are on the same side of the cyclophosphazene ring as the X group (Figure 7).

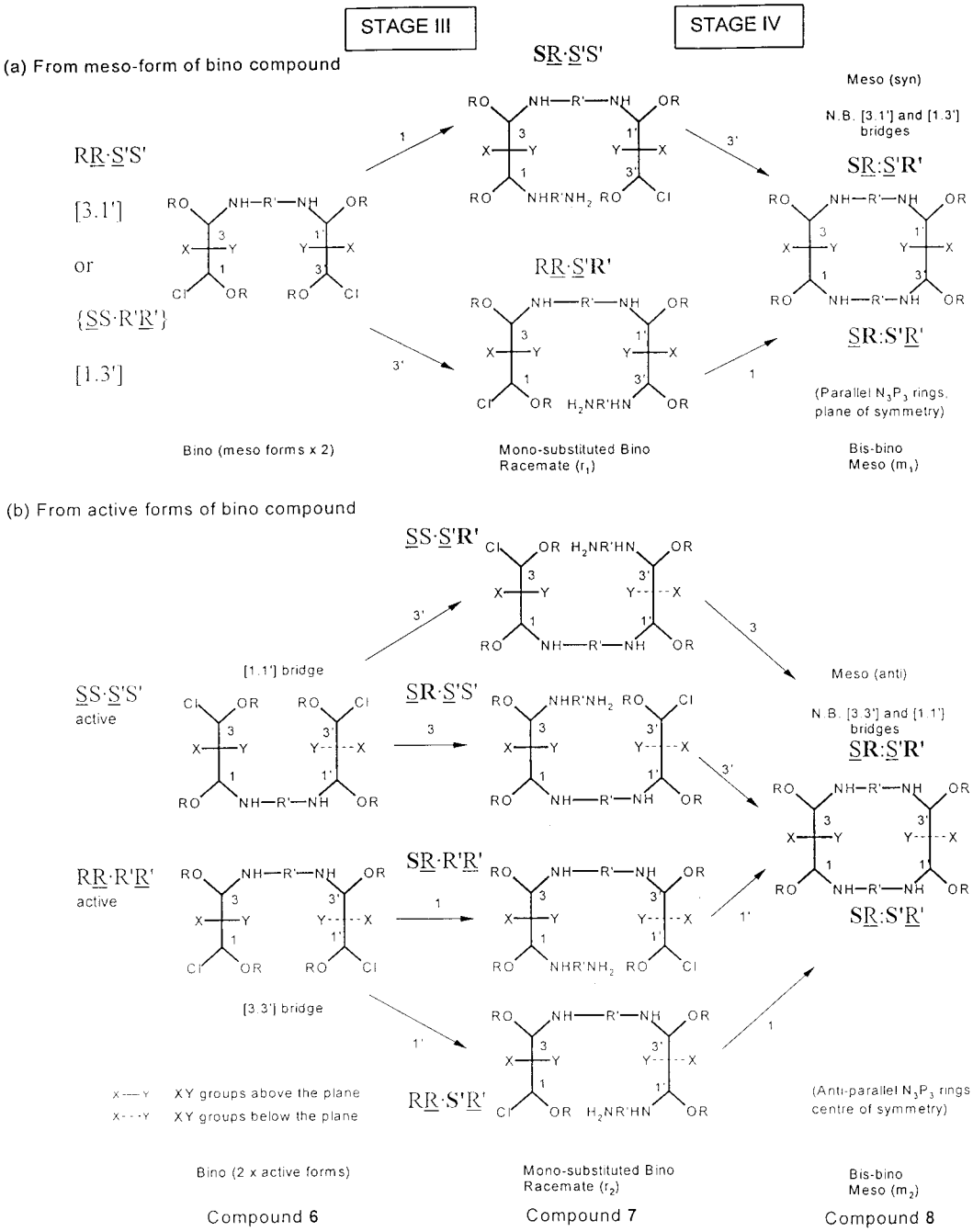


Figure 7. Diagrammatic representation of the configurational properties of Stages III and IV of the reaction of diamines, **2**, with the phosphazene-macrocyclic compound **6** summarized in Schemes 1 and 2. (a) Aminolysis of the meso (*RS*) form of the bino compound **6** first gives rise to the monosubstituted bino compound **7** (as a racemate, labeled r_1) and then intramolecular condensation to form the syn meso form of bis-bino compound **8** (labeled m_1). (b) Aminolysis of the racemic (*RR* or *SS*) form of the bino compound **6** gives rise to the monosubstituted bino compound **7** (as a different racemate, labeled r_2) and then intramolecular condensation to form the anti meso form of bis-bino compound **8** (m_2).

^{31}P NMR Spectroscopy of the Bis-bino Compound 8. The chiral configurational analysis for Stage IV of the reaction is supported in this work by the observation of two sets of A_2X signals (Figure 1b) for the two meso forms of the doubly bridged bis-bino(piperazine) compound **8i**. Under conditions where chiral shift effects are observed on signals of **6i** (in Figure 6b) there is no chiral effect on signals of the **8i** compound, which is consistent with **8i** existing as a meso form and is consistent with the predicted configurational properties of Stage IV of the reaction.

It should be noted that in the reaction of the phosphazene-macrocyclic compound **1** with *n*-propylamine **2j**, a small proportion of the di-*n*-propylamine compound **10j** was formed, which is analogous to the bis-bino compound **8** in that the phosphazene-macrocyclic rings are di-substituted with amine and are expected to have their macrocyclic rings in *cis*-configurations, that is, the compounds are optically inactive (meso-form) and exhibit one set of ^{31}P NMR signals. These predictions were confirmed for the di-*n*-propylamine compound **10j**. Addition of the chiral shift reagent, Eu(hfc)$_3$, to the mixture of **4j** and **10j** under conditions where the four ^{31}P NMR lines of the >P(OR)Cl signal for **4j** resolved into two sets of signals for the enantiomers in Figure 5c, showed only one set of ^{31}P NMR signals for compound **10j**, as expected for a meso compound.

In summary, X-ray crystallographic studies have provided

definitive proof of the existence of chiral configurational isomers of compounds at key stages of the reaction sequence and definitive proof of the configuration of the macrocyclic ring, viz. the starting material **1** is the meso-form with a *cis*-configuration of the macrocyclic ring,[18] the bino-compound **6** has both meso and racemic forms with each macrocyclic ring in the *trans*-configuration, and the bis-bino compound **8** exists in two meso-forms with the two macrocyclic rings having reverted to the *cis*-configuration. The number and spin-type of ^{31}P NMR signals observed for each of these compounds is consistent with the configurational analysis and addition of chiral shift reagent confirms the number of racemates and meso compounds. In addition, the behavior of the compounds acting as models of the reaction intermediates **4** and **7**, when investigated by ^{31}P NMR and chiral shift reagent, also confirms the chiral configurations of each of the intermediate stages of the reaction. To our knowledge this is the first time that the existence of chiral configurational isomers has been elucidated systematically in the field of cyclo-phosphazene chemistry.

The configurational analysis can be applied to any appropriate derivatives of cyclotriphosphazatrienes, that is, di-, tri-, tetra-substituted compounds represented by structures I and II in the Introduction. It has been found that the chiral configurational properties of cyclotriphosphazatriene derivatives are often easier to appreciate, in practice, by representing the cyclotriphosphazatriene ring by a cyclopropane-type structure with groups above and below the plane of the ring. Similarly, it is found that a cyclobutane-type structure is useful for visualizing the configurational properties of cyclotetraphosphazatetraene derivatives.

Confirmation of the *cis*- and *trans*-Configurations of Cyclophosphazene-macrocyclic Rings by ^{31}P NMR Spectroscopy. The configurational analysis of the reactions summarized in Figures 4 and 7 is based on inversion of configuration for each substitution of a P−Cl group by amine as summarized in Stages I−IV of the aminolysis of compound **1**. Although the structures of some of the compounds (i.e., **1**, **6i**, and **8i)** in Schemes 1 and 2 have been confirmed by X-ray crystallography, it is not feasible to check the configuration of each new compound in the series by this technique, and it would be helpful to use a routine NMR method to distinguish between *cis*- and *trans*-configurations of the macrocyclic rings.

Proton-coupled ^{31}P NMR signals of phosphazene rings are used to assist the assignment of signals,[14,17] but it is also found, in this work, that the magnitudes of the P−O−CH_2(macrocyclic ring) coupling constants are diagnostic for the *cis*- and *trans*-configurations of the cyclophosphazene-macrocyclic ring substitution pattern. The proton-coupled ^{31}P NMR signal of >P(OR)Cl groups are usually observed as "triplets" resulting from P−O−CH_2 coupling. The "triplet" nature of the signal depends on the symmetry properties of the molecule and on the *cis*- or *trans*-configuration of the macrocyclic ring, that is, whether the proton-decoupled spectrum is AMX, A_2X, or sometimes AA′X, the latter giving rise to virtual coupling in proton-coupled spectra.[22] It is found, in this work, for compounds with authenticated *trans*-configurations of the cyclophosphazene-macrocyclic ring (e.g., the bino compound **6i**) that the sum of vicinal P−O−CH_2 coupling constants for >P(OR)-Cl groups is $\Sigma J \approx 30$ Hz, whereas for compounds with authenticated *cis*-configurations of the cyclophosphazene-macrocyclic ring (e.g., the bis-bino compound **8i**) that the sum of vicinal P−O−CH_2 coupling constants for >P(OR)Cl groups is much smaller, $\Sigma J = 10-15$ Hz; the latter magnitude is difficult to determine due to multiple coupling paths in compounds such as **5** or **8** but has been confirmed to be $\Sigma J \approx 15$ Hz for compounds having nonsymmetrically substituted macrocyclic rings in the *cis* configuration, [e.g., pernaphthoylated derivatives of compounds **6a**,**b**, containing >P(OR)(NHR′) and >P(OR)-(OAr) groups, to be published]. Hence, it is found in practice that the proton-coupled ^{31}P NMR signals of >P(OR)(NHR′) groups are significantly narrower for compounds with *cis*-configurations (e.g., **1**, **5** and **8i**), compared to those with authentic *trans*-configurations of the macrocyclic rings such as compound **6i**. An example is shown in Figure 5b where the proton coupling on the >P(OR)Cl group of the monosubstituted compound **4j** is observed as a clear triplet with $\Sigma J \approx 30$ reflecting the macrocyclic ring in the *trans*-configuration, whereas the proton coupling on the >P(OR)(NHPr) signal of the di-*n*-propylamine derivative **10j** is observed as a broad signal resulting from the macrocyclic ring in the *cis* configuration and multiple coupling paths.

Using the magnitude of ΣJ(P−O−CH_2) as the criterion of *cis*- and *trans*-configurations of the macrocyclic rings, it is confirmed that there is inversion of configuration at each substitution step of the aminolysis of compound **1**, as summarized in the reaction Schemes 1 and 2; that is the *cis*-configuration of the macrocyclic ring of **1** is converted to the *trans*-configuration for monosubstitution (as in "intermediate" compounds **4j**,**k**) and back to the *cis*-configuration for di-substitution (as in the ansa−ansa compounds **5a**−**5h**[14] and compound **10j**). When two phosphazene-macrocyclic rings are involved, the configuration of the two macrocyclic rings are *trans*−*trans* when both are monosubstituted as in the bino-compounds **6**, *cis*−*trans* for the "intermediate" compound **7**, and *cis*−*cis* for the bis-bino compounds **8**, when both macrocyclic rings are di-substituted. These NMR results provide further confirmation of the chiral configurational properties of Stages I−IV of the reaction in Schemes 1 and 2.

Rationalization of the Doubling-Up of ^{31}P NMR Signals in the Bino-series of Compounds, 6. ^{31}P NMR spectroscopy (121 MHz) of each of the singly bridged bino-compounds **6a**−**h** (having unbranched primary diamine bridges NH−$(CH_2)_n$−NH with $n = 2$, 3, 4, 6, 8, 10, and 12) exhibited three ^{31}P signals with AMX spin-coupling patterns; lower members of the series (i.e., **6a**−**d**, $n = 2$, 3, 4 and 6) exhibited a doubling-up of signals, whereas the higher members of the series (i.e., **6e**−**h**, $n = 8$, 10, and 12) were observed as single sets of signals with AMX spin-coupling patterns.[14] As a result of the present study it is now known that the doubling-up of signals in compound **6i** is due to the presence of chiral configurational isomers (meso and racemic) and this behavior has been confirmed by addition of CSR for the two lowest members of the bino-diamine series **6a**,**b**. From the results summarized for the bino compounds **6** in Table 2 it can be seen that the configurational nonequivalence is different for different ^{31}P NMR signals, and in general, the effect decreases with an increase in *n*, the number of CH_2 groups linking the two cyclophosphazene rings. This observation can be explained in terms of the expected decrease in the magnitude of the effect of differences in configurations of the two >P-(OR)(NR′R″) groups, *RS/SR* versus *RR/SS*, on the ^{31}P NMR signals of the cyclophosphazene rings, as the number of CH_2

(22) (a) Hewlett, C.; Shaw, R. A. *J. Chem. Soc.* **1966**, 56−59. (b) Finer, E. G.; Harris, R. K.; Bond, M. R.; Keat, R.; Shaw, R. A. *J. Mol. Spectrosc.* **1970**, *33*, 72−83. (c) Alkubaisi, A. H.; Parkes, H. G.; Shaw, R. A. *Heterocycles* **1989**, *28*, 347−358.

(23) Pflugrath, J. W.; Messerschmidt, A. MADNES, version 11, September 1989; Delft Instruments: Delft, The Netherlands, 1989.

(24) (a) Sheldrick, G. M. SHELX-86: Program for crystal structure solution; University of Göttingen: Germany, 1986. (b) Sheldrick, G. M. SHELX-93, unpublished work; University of Göttingen: Germany, 1993.

Table 2. Observed Nonequivalence ($\Delta\delta$ ppm) of ^{31}P NMR Signals of Bridged Phosphazene-macrocyclic Compounds[a]

compound	*n*	>PCl_2	>P(OR)Cl	>P(OR)(NR′R″)
	Stage II ($\Delta\delta$ of meso and racemic isomers)[b,c]			
6a	2	**−0.028**	**0.072**	**0.024**
6b	3	*c*	0.050	0.077
6c	4	*c*	0.016	*c*
6e	6	0.019	0.017	*c*
6i	pip	**0.086**	0.061	*c*
		solvent	>PCl_2	>P(OR)(NR′R″)
	Stage IV ($\Delta\delta$ for two meso isomers)[d]			
8b	3	$CDCl_3$	*c*	0.141
8i	pip	$CDCl_3$	0.146	0.151
		THF	**0.794**	**0.569**

[a] In those cases where the configurational isomers have been assigned unequivocally, the $\Delta\delta$ values are denoted in bold-face type, otherwise magnitudes of $\Delta\delta$ corresponds to the absolute value of chemical shift difference; pip = piperazine. [b] 121 MHz measurements made in $CDCl_3$ solution at 298 K. For compounds **6a** and **6i** the meso and racemic forms have been assigned unequivocally by addition of chiral shift reagent and the $\Delta\delta$ ($= \delta_m - \delta_r$) values are denoted in bold face type. [c] Nonequivalence too small to observe at 121 MHz. [d] For **8i** the two meso forms have been assigned unequivocally from X-ray structure determinations. The ^{31}P NMR signals of the meso form m_1 (which has a plane of symmetry and P-bridge-P with *RS* configurations) are to high frequency of those from the meso form m_2 (which has a center of symmetry and *RR/SS* configurations of the P-bridge-P moieties), i.e. $\Delta\delta = (\delta_{m1} - \delta_{m2})$ magnitudes are denoted in bold-faced type.

groups increases and, concomitantly, an increase in the distance apart of the centers of configuration.

A similar explanation is able to rationalize the ^{31}P NMR effects observed previously by Labarre et al.[16] for the 3*n*3 and 4*n*4 series of molecules. 202 MHz ^{31}P NMR signals were also observed as pairs of signals in a 50:50 ratio for the lowest member (i.e., $n = 6$) of each series (with $m = 3$ or 4) and then observed on various signals for higher members of each series, but not at all for the 393 ($n = 9$) compound,[16] analogous to the behavior observed for the bino-series of compounds in this work. The bridged 3*n*3 and 4*n*4 compounds have cyclotriphosphazatriene rings linked by diamines. The bridging phosphorus atoms are chiral and thus exist in either *R* or *S* configurations for each cyclophosphazene ring. The two chiral centers of the bridged compounds lead to *RR*, *SS*, *RS*, and *SR* configurations in which *RS* and *SR* are the same compound (meso) and *RR* and *SS* are enantiomers, existing as a racemic mixture. Hence, configurational analysis rather than conformational analysis explains the ^{31}P NMR spectra of 3*n*3- and 4*n*4-bridged compounds as a pair of signals in a 50:50 ratio and the fact that differences in chemical shift nonequivalence are found for the different compounds observed previously by Labarre et al.[16] The trends in configurational nonequivalence of 3*n*3- and 4*n*4-bridged compounds are similar to those observed for the bino compounds **6** in this work, that is, the magnitude of the effect decreases with an increase in *n*, resulting from an increase in the distance apart of the centers of configuration.

Conclusions

1. In this work the chiral configurational properties of derivatives of cyclo-triphosphazatriene rings with two (one N_3P_3 unit) or four (two N_3P_3 units) chiral centers have been elucidated by investigation of the amination reaction of the cyclotriphosphazatriene-macrocyclic compound **1** with the di-secondary amine, piperazine. First, the monosubstituted derivative **4** is formed as an intermediate, and then the singly bridged bino compound(s) **6**, which has been isolated and characterized. Reaction of **6** with piperazine, first forms the monosubstituted compound **7** as an intermediate and then the doubly bridged bis-bino compound(s) **8**, which have also been isolated and characterized.

2. The chiral configurational properties of the reaction scheme have been elucidated by X-ray crystallographic analysis of stable isolated forms of compounds **6** and **8** and supported by ^{31}P NMR spectroscopic studies using chiral shift reagents. It is found that compound **6** exists as a 50:50 mixture of meso and racemic forms and that compound **8** exists as a 50:50 mixture of two meso forms, one with a center of symmetry and one with a plane of symmetry. The chiral configurational properties of models of each of the intermediates **4** (racemate) and **7** (two racemates) in the reaction were also confirmed by ^{31}P NMR spectroscopy using chiral shift reagents.

3. The chiral configurational analysis of the reaction scheme is consistent with inversion of configuration at each step of the reaction of >P(OR)Cl with HNR′R″ to form >P(OR)(NR′R″). The original *cis*-configuration of the macrocyclic ring in **1** is inverted to *trans* for monosubstituted derivatives, and then to another *cis*-configuration (now on the opposite side of that of **1**) for di-substituted derivatives.

4. It is found that chiral cyclophosphazenes may be represented by 2D structural diagrams, if the Fischer rules for 2D representations of tetrahedral carbon atoms are followed for pentavalent phosphorus atoms in cyclotriphosphazatriene rings, for example, structures may only be rotated in-the-plane. However, it is necessary to define which 3D chiral structure is represented by the 2D diagram. For example, in using the 2D stick diagram representation of the cyclotriphosphazatriene ring, where all bonds have unbroken lines, it is recommended that the phosphorus atom at the ends of the planar ring and the associated attached groups are in-the-plane, whereas the phosphorus atom in the middle of the planar ring and the associated attached groups are above-the-plane. In cases where it is necessary to rotate the 2D structural diagram out-of-the-plane, it is found that the chiral configurational properties are faithfully represented by the 2D diagram, if groups now below-the-plane are denoted by dotted lines.

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Supporting Information Available: Experimental details (Materials and Methods, X-ray Crystallography, and Synthesis); Tables of crystal data and structure refinement, anisotropic displacement parameters, bond lengths and angles, selected torsion angles, and least-squares planes for compounds **6i** and **8i**; Tables of observed and calculated structure factors for compounds **6i** and **8i**; Figure S1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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