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Diastereoisomeric Singly Bridged Cyclophosphazene-Macrocyclic Compounds

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^{31}P NMR spectroscopy and added chiral shift reagent (CSR) or chiral solvating agent (CSA) have been used to show that unsymmetrically substituted singly bridged macrocyclic phosphazene compounds exist as 1:1 diastereoisomers of two racemic mixtures, in contrast to previous work (ref 2) on symmetrically substituted diastereoisomeric analogues, which exist as meso and racemic forms. The cis-ansa cyclotriphosphazatriene-macrocycle, **1**, is meso and monosubstitution of the >P(O-macrocycle)Cl group with 2-naphthol gives a racemic product (**7**), in which the macrocyclic ring exists in a trans-ansa configuration. Reaction of **7** with the di-secondary amine, piperazine, gives an unsymmetrically disubstituted racemic compound (**8**) having a cis-ansa configuration of the macrocyclic ring. Reaction of **8** with a further quantity of **1** forms a singly bridged derivative (**9**) with the macrocyclic rings in cis–trans configurations, and further reaction of **9** with pyrrolidine gives compound **10** with the macrocyclic rings in cis–cis configurations. Both **9** and **10** have four stereogenic centers giving rise to diastereoisomeric compounds existing as mixtures of two racemates. The results are consistent with inversion of configuration at phosphorus at each step of the reaction of >P(OR)Cl groups with nucleophile Z (i.e., Z = naphthoxy, piperazino, pyrrolidino) to form >P(OR)Z derivatives.

Introduction

The possibility of optical isomerism in cyclophosphazenes was first discussed in a review about forty years ago, on realizing that the tetracoordinated phosphorus atoms in $(NPXY)_n$ are pentavalent and potentially stereogenic.[1] Confirmation of chirality in cyclophosphazenes has only recently been confirmed in an investigation of amination reactions of the cis-ansa macrocyclic-phosphazene compound, 2,4-oxy-(tetraethylenoxy)-2,4,6,6-tetrachlorocyclotriphosphazatriene (**1**)[2] and in an investigation of spermine-bridged gem-disubstituted cyclophosphazenes.[3] Chirality has also been considered in biphenoxy and binaphthoxy derivatives of cyclotriphosphazenes and their use in cyclolinear polymers.[4]

Reaction of **1** with the di-secondary amine, piperazine (pip, **2**), formed both singly bridged (**4**) and doubly bridged derivatives (**6**) by a sequence of reactions summarized in Scheme 1, which provided a convenient way to investigate the chiral configurational properties of cyclophosphazene compounds.[2] X-ray crystallographic and ^{31}P NMR spectroscopic studies showed that there are two stable configurational isomers of **4** (meso and racemate) and two stable configurational isomers of **6** (both meso, one with a plane and one with a center of symmetry).[2] The intermediates in Scheme 1, **3** and **5**, are very reactive and could not be isolated. The chiral configurational properties of compound

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(4) Dez, I.; Levalois-Mitjaville, J.; Grützmacher, H.; Gramlich, V.; De Jaeger, R. *Eur. J. Inorg. Chem.* **1999**, 1673−1684.

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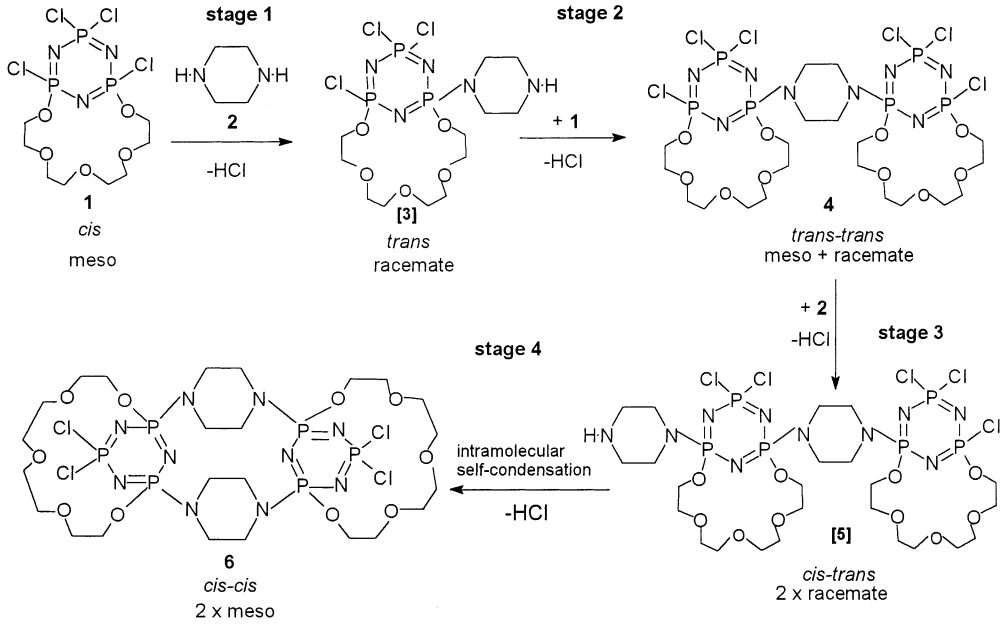
Scheme 1



3 were investigated by using monosubstituted analogues (with *n*-propylamine and pyrrolidine) that would not react further with **1** to form a bridged compound. It was confirmed by ^{31}P NMR on addition of chiral shift reagent (CSR),[5,6] tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III), Eu(hfc)$_3$, that each of the analogues of compound **3** exists as a racemate with the macrocyclic ring in the trans configuration.[2] The chiral configurational properties of compound **5** (predicted to exist as two racemates with macrocyclic rings in cis−trans configurations) were not confirmed directly, though indirect confirmation was given by characterization of the two different configurational isomers of the doubly bridged derivative **6**, which had to be produced by intramolecular condensation of the two racemic forms of **5**.[2]

In this work two stable configurational analogues of compound **5**, viz., **9** and **10**, have been synthesized and their stereogenic properties investigated by ^{31}P NMR spectroscopy with use of added chiral shift reagent (CSR)[5,6] and the chiral solvating agent (CSA),[6,7] (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. In both compounds **9** and **10** the two stereogenic cyclophosphazene rings have different substituents, Z, for the >P(O-macrocycle)Z moiety, which enables the diastereoisomeric properties of unsymmetrically substituted singly bridged cyclophophazene rings to be compared with those for symmetrically substituted analogues studied previously.[2]

Results and Discussion

Formation and Characterization of Mono- and Di-substituted bino(pip) Compounds (9, 10; Scheme 2). To investigate the chiral configurational properties of the "reactive intermediate" **5** in Scheme 1, it is desirable that the stable analogue provides a relatively simple ^{31}P NMR spectrum for analysis. This was achieved by a reversed-order formation of a 2-naphthoxy derivative, denoted by (OAr), of the bino-piperazino compound **9**, as summarized in Scheme 2. The known 2-naphthoxy macrocyclic-phosphazene starting compound, **7**,[8] was chosen so that the ^{31}P NMR spectrum of one cyclophosphazene ring, with >P(OR)(OAr) and >P(OR)-(pip) groups, would be significantly different from that of the other ring, with >P(OR)Cl and >P(OR)(pip) groups (where pip signifies piperazino). Although details of the reaction of 2-naphthol with **1** to form **7** have recently been published,[8] the chiral configurational properties, necessary for the present investigation, have not been elucidated.

To avoid formation of a piperazine-bridge between two molecules of compound **7** in step 2 of the reaction in Scheme 2, a solution of **7** was added slowly to an excess of piperazine to form the unsymmetrically disubstituted derivative **8**, which was stabilized by addition of concentrated HCl to neutralize the excess of **2** and form the hydrochloride derivative of **8**. The required singly bridged compound **9** was formed by reaction of **8** with **1** in a 1:1 ratio in the presence of sufficient NaH to neutralize the hydrochloride already present and that formed on reaction of a >P(OR)Cl group with one NH group of piperazine to give the >P(OR)(pip) derivative. The final step was reaction of compound **9** with an excess of pyrrolidine (pyr) to form the fully substituted compound **10**. Each of the compounds in Scheme 2 was characterized by MS and NMR spectroscopy (Supporting Information: Table S1, ESI-MS and ^{1}H NMR data; Table S2, ^{13}C NMR data) and the ^{31}P NMR chemical shifts and ^2J(P−P) magnitudes of each of the compounds in $CDCl_3$ and toluene-d_8 solution are summarized in Table 1.

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Scheme 2

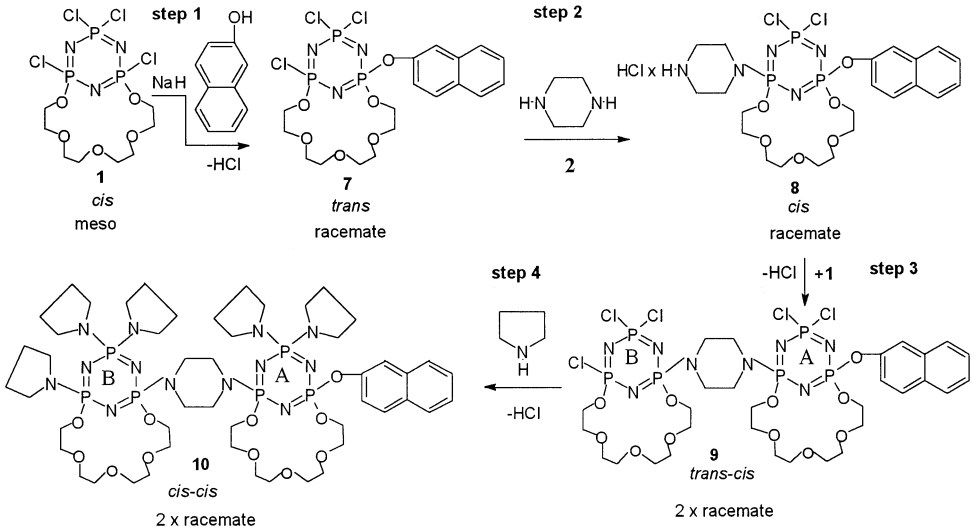

Table 1. ^{31}P NMR Data for the Macrocyclic-Phosphazene Compounds **7**−**10** in Scheme 2[a]

		chemical shifts/ppm [$\sum J(POCH_2)$/Hz][b]						coupling constants, ^2J(P−P)/Hz				
		>PCl_2	>P(OR)Cl	>P(OR)(pip)	>P(OR)(OAr)							
compd	solvent	1	2	3	4	ring config	isomer	1,2	1,3	1,4	2,3	(n,m)[c]
7[d].	Chl	27.4	21.2 [34.8]		6.6 [25.7]	trans		80.8		74.5		68.7 (2,4)
	Tol	27.0	21.6		6.5			82.6		79.0		68.2 (2,4)
8[e]	Chl	26.4		16.2	8.8 [15.2]	cis			57.9	70.3		67.7 (3,4)
	Tol	26.7		17.1	9.4				60.2	70.2		66.2 (3,4)
9	Chl	26.2		16.8	8.7 [16.1]	cis	r_1		55.0_8	70.3_8		67.6_8 (3,4)
							r_2		55.4_6	70.4_5		67.4_2 (3,4)
		26.2	20.3 [36.1]	14.7		trans	r_1	78.8_7	58.2_4		56.1_3	
							r_2	79.0_5	58.2_6		56.4_2	
9	Tol	25.7		17.1	9.1 [15.6]	cis	r_1		56.9_2	71.2_8		68.0_3 (3,4)
				14.8			r_2		57.1_9	71.4_8		67.9_7 (3,4)
		25.7	20.5 [34.2]			trans	r_1	80.1_0	60.4_1		55.3_3	
							r_2	80.2_7	60.5_9		55.7_1	

		chemical shifts/ppm [$\sum J(POCH_2)$/Hz][b]						coupling constants, ^2J(P−P)/Hz				
		>$P(pyr)_2$	>P(OR)(pyr)	>P(OR)(pip)	>P(OR)(OAr)							
compd	solvent	1	2	3	4	ring config	isomer	1,2	1,3	1,4	2,3	(n,m)[c]
10	Chl	19.3		22.4	15.1 [12.1]	cis			49.0	57.0		65.5 (3,4)
		19.2	21.6 [*f*]	22.3		cis		*f*	*f*		*f*	
10	Tol	19.8		22.6	15.3 [10.8]	cis			50.8	59.2		67.4 (3,4)
		19.9	22.0 [13.5]	22.7		cis		49.0	47.8		54.1	

[a] 200-MHz NMR measurements at ambient temperatures in $CDCl_3$ (Chl) and toluene-d_8 (Tol) at 298 K. [b] $\sum J(POCH_2)$ correspond to the sum of vicinal coupling constants from the phosphorus atom to the macrocyclic methylene group. Key: pip = piperazino, pyr = pyrrolidino, OAr = 2-naphthoxy. [c] n,m correspond to other phosphorus atoms with geminal coupling. [d] Initial ^{31}P NMR data at 120 MHz of compound **7** in chloroform given in ref 8. [e] Protonated form of **8**, i.e., **8**·*n*HCl. [f] Magnitude of coupling constants could not be determined owing to line broadening.

Assignment of ^{31}P NMR signals of substituted cyclophosphazene compounds is usually accomplished by analysis of proton-coupled and proton-decoupled spectra[9] and is straightforward for both compounds **7** and **8**, which have different substituents on each phosphorus atom of the single cyclophosphazene ring. Singly bridged compounds **9** and **10** have two different phosphazene moieties, leading to slightly more complicated ^{31}P NMR spectra and signal assignment. For example, the proton-decoupled ^{31}P NMR of compound **9** in Figure 1a shows the sum of two different AMX spin systems for two >PCl_2 groups δ ca. 26 ppm, one >P(OR)Cl δ ca. 20 ppm, two >P(OR)(pip) signals δ ca.15 and 17 ppm, and a >P(OR)(OAr) signal δ ca. 9 ppm. The proton-coupled ^{31}P NMR spectrum of compound **9** in Figure 1b shows that there is no proton coupling for the two >PCl_2 signals, clear triplets with large vicinal proton−phosphorus coupling for the >P(OR)Cl group [expanded signals give $\sum^3 J(POCH_2) = 36.1$ Hz], a multiplet with relatively small coupling constants for one >P(OR)(pip) group and broad multiplets for the other, and triplets with small coupling constants for the >P(OR)(OAr) group [expanded signals give $\sum^3 J(POCH_2) = 16.1$ Hz]; each of the latter signals was slightly broadened as a result of the very small four-bond coupling to the 2-naphthoxy substituent. Detailed analysis of the ^{31}P NMR spectrum in the two sets of AMX spin systems of compound **9** shows

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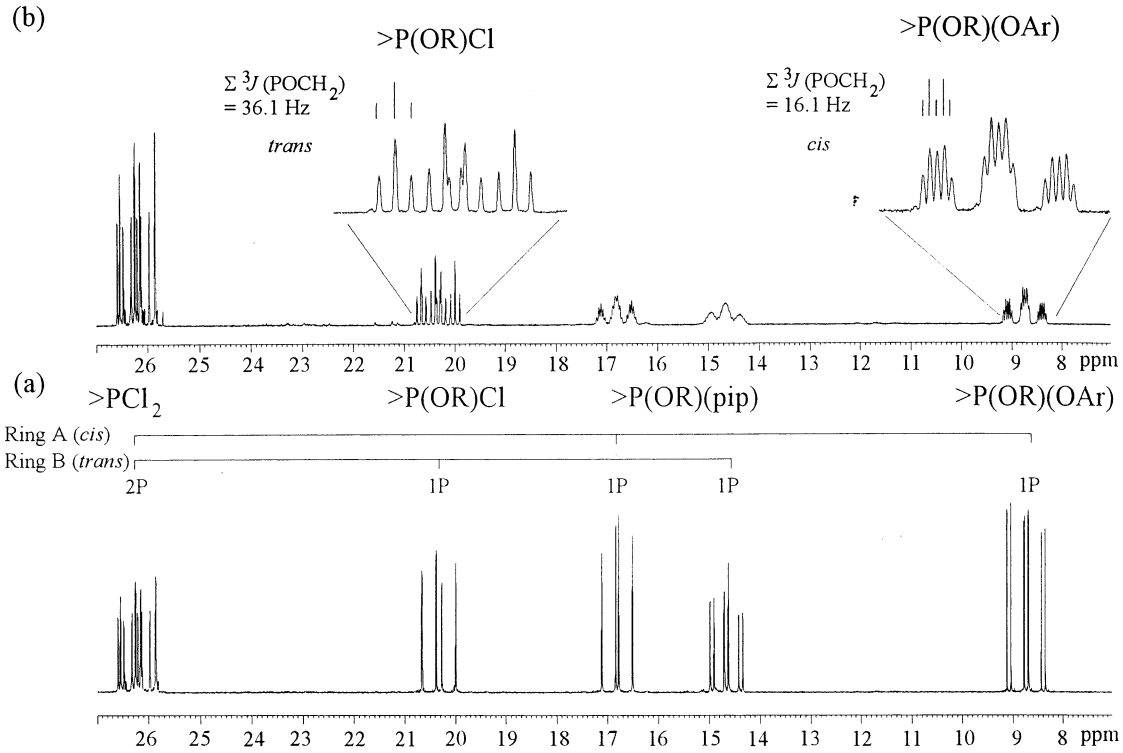

Figure 1. ^{31}P NMR (200 MHz) spectrum of compound **9** in $CDCl_3$ solution at 298 K. (a) The proton-decoupled spectrum showing two sets of AMX signals corresponding to the expected two racemic mixtures and (b) the proton-coupled spectrum. Expansions of the >P(OR)Cl signal exhibit triplets with $\sum J$(P−O−CH_2) = 36.1 Hz corresponding to trans configurations of the macrocyclic ring and the >P(OR)(OAr) signal exhibits triplets with $\sum J$(P−O−CH_2) = 16.1 Hz corresponding to cis configurations of the macrocyclic ring.

that there are significant differences in the magnitudes of the ^2J(P−P) coupling constants between the two >PCl_2 and two P(OR)(pip) groups (viz. 55 vs 58 Hz in chloroform and 57 vs 60 Hz in toluene, Table 1), which enables these signals to be assigned to the phosphazene rings containing >P(OR)Cl or >P(OR)(OAr) groups, respectively.

The proton-decoupled ^{31}P NMR spectrum of each >PXY group of diastereoisomeric compound **9** is observed as a pair of signals in a 1:1 ratio. The two sets of signals of the >P(OR)(OAr) group of **9** are readily seen in Figure 2a, as are those for signals of the >P(OR)Cl and both >P(OR)(pip) groups (not shown). Although the overlapping multiplets of the >PCl_2 groups in Figure 2a are more complicated, they also show doubling of signals and, to aid discussion, the signals of the cyclophosphazene ring containing the >P(OR)(OAr) group are labeled A and those from the other ring are labeled B (the two cyclophosphazene rings of compound **10** are similarly labeled). Careful analysis of the spectrum, observed with good data resolution and resolution enhancement, shows that there are very small differences in the magnitudes of the ^2J(P−P) coupling constants in the two sets of ^{31}P NMR AMX systems for each isomer of compound **9** (Table 1), which enables the separate signals of each isomer to be assigned. The isomers are designated r_1 and r_2, for convenience, and labeled for the signals of the >P(OR)(OAr) group in Figure 2a, whereas those for the two >PCl_2 groups are not as clear at this stage of the analysis.

The proton-decoupled ^{31}P NMR of compound **10** [Figure S1a] shows the sum of an AMX spin system for the phosphorus atoms of the 2-naphthoxy-substituted cyclophosphazene ring (A) and an ABX spin system for the second cyclophosphazene ring (B). Comparison of the proton-coupled and proton-decoupled spectra leads to the assignment of signals and geminal phosphorus−phosphorus coupling constants (Table 1), together with the $\sum^3J$($POCH_2$) magnitudes for the >P(OR)(OAr) group of ring A (10.8 Hz) and the >P(OR)(pyr) group of ring B (13.5 Hz). All the expanded AMX/ABX signals of compound **10** in Figure S1a exhibit doubling due to diastereoisomers, particularly for the signals of the >P(OR)(OAr) group at ca. 15.3 ppm and the two >P(pyr)$_2$ groups at ca. 19.8 and 19.9 ppm.

The observed nonequivalence of the ^{31}P NMR signals of the two racemic forms of both compounds **9** and **10** are different for each signal and vary with solvents such as chloroform and toluene, and the magnitudes of the chemical shift separations $\Delta\delta$ ($=\delta r_1 - \delta r_2$) are summarized in Table 2.

The ^{13}C NMR spectra of both compounds **9** and **10** also exhibit nonequivalence of some carbon atoms, especially those close to the stereogenic phosphorus centers, e.g., C1−C3 of the naphthoxy moiety and C1′/C8′ of the macrocyclic ring (Table S2).

Confirmation by ^{31}P NMR Spectroscopy of the Chiral Configurational Properties of the Sequence of Compounds in Scheme 2. The chiral configurational properties of each step of the reaction in Scheme 2 can be understood, if it is assumed that the substitution reaction of the P−Cl bond of each >P(OR)Cl group with Z to form >P(OR)Z proceeds with inversion of configuration, which covers both aryloxy and secondary amino derivatives in this work. An

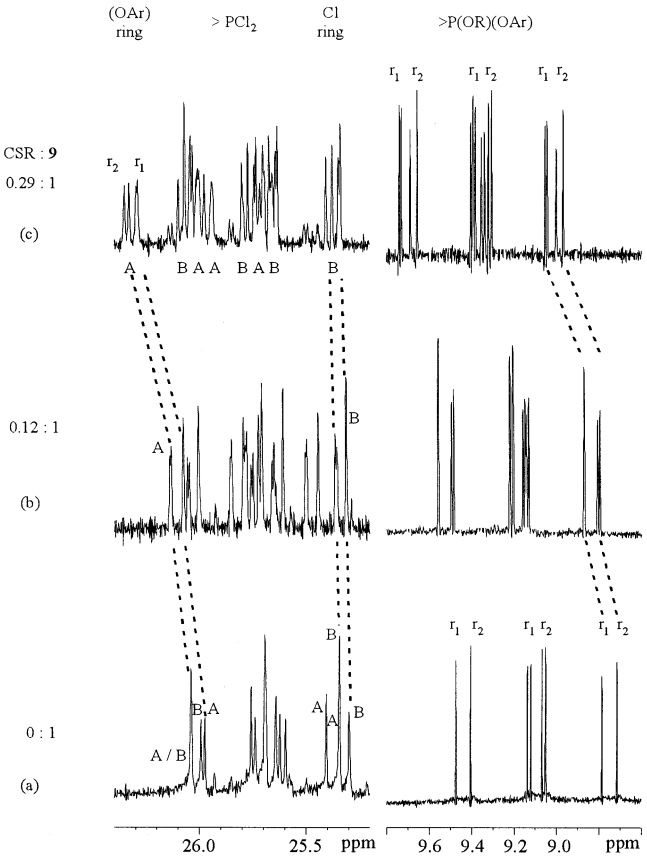

Figure 2. ^{31}P NMR (200 MHz) confirmation of the chiral configurational properties of the diastereoisomeric compound **9** in toluene-d_8 solution on addition of chiral shift reagent (CSR), Eu(tfc)$_3$, at 298 K. (a) Expansion of the proton-decoupled spectrum of the >P(OR)(OAr) and >PCl$_2$ groups shows two sets of signals corresponding to the two different racemic mixtures (labeled r_1 and r_2). (b) Addition of CSR in ca. 0.1:1 mol ratio results in signals of the r_2 isomer separating into two lines of equal intensity and (c) at an ca. 0.3:1 mol ratio of separation of signals of the r_1 isomer into two lines of equal intensity (and increased separation of r_2 signals).

analysis of the *R* and *S* configuration of each >P(OR)Z moiety of the cyclophosphazene-macrocyclic ring for each step of the reaction in Scheme 2 is provided in the Supporting Information.

Although enantiomers have the same NMR spectrum, diastereoisomers are 1:1 mixtures of two different racemates (or meso and racemic forms) and should give rise to different NMR spectra.[10] This is observed for the proton-decoupled ^{31}P NMR spectra of the present set of compounds in Scheme 2, where racemic compounds **7** and **8** are found to exhibit single AMX spectra, but the diastereoisomeric compound **9** exhibits doubling up of all signals of the two sets of AMX spectra (Figure 2) and the diastereoisomeric compound **10** also exhibits doubling up of signals in the more complex sum of AMX/ABX spectra (shown in Figure S1).

The chiral configurational properties of compounds **7**, **9**, and **10** in both chloroform and toluene solutions have been confirmed by ^{31}P NMR spectroscopy on addition of chiral shift reagent (CSR),[5,6] Eu(hfc)$_3$, in the same solvent. On gradual addition of CSR to a solution of compound **7**, each line of the ^{31}P NMR signals in the proton-decoupled AMX spectra separated into two lines of equal intensity, whose separation increased with titration of CSR similar to the *n*-propylamine derivative of compound **1** shown previously.[2] This behavior is consistent with compound **7** being chiral and existing as a racemic mixture. Similarly, on gradual addition of CSR to solutions of compounds **9** and **10**, each signal of the complex proton-decoupled ^{31}P NMR spectra separated into two lines of equal intensity, whose separation increased with titration of CSR. This behavior is consistent with both diastereoisomeric compounds **9** and **10** existing as two racemic mixtures. As an example, the effect of addition of Eu(hfc)$_3$ is shown in Figure 2 for the expanded signals of the >P(OR)(OAr) and >PCl$_2$ groups of compound **9** in toluene-d_8 solution. The effect is clearly seen in Figure 2b for the >P(OR)(OAr) signals at ca. 9 ppm, where addition of CSR to compound **9** in ca. 0.1:1 mol ratio shows doubling of the r_2 set of signals. On further addition of CSR the separation of lines increases and at an ca. 0.3:1 mol ratio the ^{31}P NMR lines of the other isomer separate into two closely spaced signals for the second racemate (labeled r_1) as shown in Figure 2c. Similar behavior is observed for signals of the two >PCl$_2$ groups of compound **9** at ca. 25−26 ppm, although the spectrum is more complicated owing to signal overlap (Figure 2). It can be seen that the signals of the >PCl$_2$ group in the phosphazene ring containing the naphthoxy group (labeled A) move to high frequency on addition of CSR, that those for the r_2 isomers separate into two signals at an ca. 0.1:1 mol ratio, and those for the r_1 isomers separate into two signals at an ca. 0.3:1 mol ratio of CSR to compound **9**. Analogous behavior is observed for the signals of the >PCl$_2$ group in the phosphazene ring containing the >P(OR)Cl group (labeled B), which can be seen most clearly for the low-frequency multiplet at ca. 23.3−23.4 ppm of compound **9** in Figure 2, parts b and c. Similar chiral behavior is exhibited by compound **10,** although separation into two signals with a 1:1 ratio was only observed on each of the signals of the AMX spectrum of the 2-naphthoxy-substituted cyclophosphazene ring (A), because the signals of the other cyclophosphazene ring (B) broadened immediately on addition of CSR, probably as a result of preferential complexation with the less-hindered and more basic cyclophosphazene ring. Nevertheless, addition of CSR shows that both compounds **9** and **10** are diastereoisomeric and both exist as two different racemic mixtures in line with the configurational analysis.

Although compound **8** is expected to exist as a racemate, it was found that addition of CSR in either chloroform or toluene solutions did not lead to any observed doubling of ^{31}P NMR signals. This may be a consequence of preferential complexation of the ligand with the free NH·HCl group in piperazine that is somewhat remote from the phosphorus atoms in the cyclophosphazene ring. On the other hand, it was found that the stereogenic properties of compound **8** were manifested by addition of the chiral solvating agent (CSA), (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol,[6,7] which also had been found previously to be more effective than CSR for a series of spermine-bridged cyclophosphazenes.[3] The chiral configurational properties of compounds **7**, **9**, and

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Table 2. Observed Nonequivalence of ^{31}P NMR Signals of Two Racemic Forms of Diastereoisomeric Bridged Macrocyclic-Phosphazene Compounds[a,b]

				chemical shift difference $[\Delta\delta(r_1-r_2)]$/ppb[c]			
compd	solvent	ring config	X	>PX_2	>P(OR)(OAr)	>P(OR)(pip)	>P(OR)X
9	Chl	cis	Cl	117	81	6	
	Tol			66	74	27[d]	
9	Chl	trans	Cl	6		80[d]	8
	Tol			46		98	43
10	Chl	cis	pyr	*e*	21	17[f]	
				g		20[f]	*g*
10	Tol	cis	pyr	12	15	8	
				83		71[f]	25

[a] Measurements made at 200 MHz in $CDCl_3$ (Chl) and toluene-d_8 (Tol) solution at 298 K; OAr = 2-naphthoxy, pip = piperazino, pyr = pyrrolidino. [b] The two racemic forms (r_1 and r_2) have not been assigned unequivocally [c] $\Delta\delta$ corresponds to the absolute value of chemical shift difference of the two racemic forms. [d] Exhibits another effect with $\Delta\delta$ ca. 6 ppb. [e] Nonequivalence too small to observe at 200 MHz. [f] Exhibits another effect with $\Delta\delta$ ca. 9 ppb. [g] Not observed as a result of line broadening, probably due to protonation effects (ref 13).

10 in toluene solutions also have been confirmed by ^{31}P NMR spectroscopy on addition of CSA. An example is shown for the >P(OR)(OAr) and >$P(pyr)_2$ signals of compound **10** in Figure S1; doubling of both sets of signals occurs with small additions of CSA to a 0.3:1 mol ratio and further addition of CSA clearly shows the two sets of signals for the r_1 and r_2 isomers by a 1:1 mol ratio (and up to an ca. 3:1 mol ratio, not shown).

In each case the chiral properties of compounds **7**, **9**, and **10** are manifested for additions of CSR up to an ca. 0.3:1 mol ratio and up to an ca. 3:1 mol ratio for additions of CSA to compounds **7**, **8**, **9**, and **10** in line with results from many molecules.[5−7]

Confirmation by ^{31}P NMR Spectroscopy of the Reaction Mechanism of the Sequence of Compounds in Scheme 2. The chiral configurational analysis of the reactions in Scheme 2 is based on inversion of configuration in each step of the reaction for substitution of a P−Cl by an aryloxy/amino group. Although the structures of some of the symmetrically substituted bridged compounds (**4**, **6**) have been confirmed by X-ray crystallography,[2] it is not feasible to check the configuration of each new compound in any reaction sequence by this technique and it is helpful to use a routine NMR method to distinguish between cis and trans configurations of the macrocyclic rings. Previous work has shown that the magnitudes of the P−O−CH_2(macrocyclic ring) coupling constants observed in proton-coupled ^{31}P NMR spectra of macrocyclic-phosphazene compounds are diagnostic for the cis and trans configurations of the ansa-substituted macrocyclic-cyclophosphazenes.[2] The proton-coupled ^{31}P NMR signals of >P(O-macrocycle)Z groups (Z = Cl, OAr, etc.) are usually observed as triplets resulting from P−O−CH_2 coupling and it has been found for compounds with authenticated trans configurations of the cyclophosphazene-macrocyclic ring (e.g. the bino compound **4**) that the sum of vicinal P−O−CH_2 coupling constants for >P(OR)Cl groups is $\sum J$ >30 Hz, whereas for compounds with authenticated cis configurations of the cyclophosphazene-macrocyclic ring (e.g., the bis-bino compound **6**) that the sum of vicinal P−O−CH_2 coupling constants for >P(OR)Z groups is much smaller, $\sum J$ < 20 Hz and often 10−15 Hz;[2] the latter magnitude is difficult to determine due to multiple coupling paths in compound **6** but has been confirmed to be $\sum J$ = ca. 15 Hz for compounds having nonsymmetrically substituted macrocyclic rings in the cis configuration, e.g. pernaphthoxy derivatives of compound **6** (Z = OAr).[11] A clear example is shown for the proton-coupled ^{31}P NMR spectrum of compound **9** in Figure 1b, where the expanded signal of the >P(OR)Cl group gives $\sum J$(P−O−CH_2) = 36.1 Hz and that for the >P(OR)(OAr) group gives a $\sum J$(P−O−CH_2) = 16.1 Hz.

Using the magnitude of $\sum J$(P−O−CH_2) as the criterion of cis and trans configurations of the macrocyclic rings,[2] the results in Table 1 confirm that there is inversion of configuration at each substitution step of the reactions of compound **1**, as summarized in Scheme 2, i.e. the cis configuration of the macrocyclic ring of **1** is converted to the trans configuration for monosubstitution, as in compound **7** ($\sum J$ = 34.8 Hz), and back to the cis configuration for disubstitution as in compound **8** ($\sum J$ = 15.2 Hz). When two phosphazene-macrocycles are involved, the configuration of the two macrocyclic rings is cis−trans for the mono-2-naphthoxy-bino compound **9** ($\sum J$ = 16.1 and 36.1 Hz)**,** which is a model for the "intermediate" compound **5** in Scheme 1, and cis−cis for the per-substituted bino compound **10** ($\sum J$ = 10.8 and 13.5 Hz). These results confirm that there is inversion of configuration at each step of the reaction in Scheme 2, which is also consistent with both chiral compounds **7** and **8** being formed as racemic mixtures and both chiral compounds **9** and **10** being diastereoisomers consisting of two different racemic mixtures.

Conclusions

1. In this work the chiral configurational properties of derivatives of unsymmetrically substituted cyclotriphosphazatriene rings with two (one N_3P_3 unit) or four (two N_3P_3 units) stereogenic centers have been elucidated by investigation of the sequence of reactions in Scheme 2 using four different reactants. ^{31}P NMR spectroscopic studies on addition of a chiral shift reagent (CSR) and/or chiral solvating agent (CSA) found that compounds **7** and **8** are racemates and that compounds **9** and **10** are diastereoisomeric, each of the latter existing as two different racemic mixtures.

2. The mechanism of the reaction sequence in Scheme 2 also has been confirmed by ^{31}P NMR investigations of the

(11) Bartsch, R. A.; Lee, E. K.; Chun, S. I.; Elkarim, N.; Brandt, K.; Porwolik-Czomperlik, I.; Siwy, M.; Lach, D.; Silberring, J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 442−448.

configurational properties of the macrocyclic ring, showing that there is inversion of configuration at each step of the reaction of >P(OR)Cl with nucleophile Z (e.g., Z = naphthoxy, piperazino, pyrrolidino) to form >P(OR)Z derivatives.

Experimental Section

Materials. Hexachlorocyclotriphosphazatriene, obtained as a gift from the Otsuka Chemical Co. Ltd., was purified by fractional crystallization from hexane. 2-Naphthol (98%, Aldrich Chemical Co) was crystallized from $CHCl_3$/hexane (2:1). Piperazine and pyrrolidine were used as received from Aldrich Chemical Co. The chiral shift reagent (CSR) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), Eu(tfc)$_3$, was obtained from Fluka and the chiral solvating agent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (CSA), was obtained from Sigma Chemical Co. Deuterated solvents for NMR spectroscopy were obtained from Apollo Scientific ($CDCl_3$) and Goss Scientific (toluene-d_8). Silica gel 60 (230−400 mesh, Merck) was used for column chromatography.

Methods. TLC analyses were performed on Merck precoated silica gel 60 plates. Flash chromatography was carried out with silica gel (100−200 mesh, Merck), eluted with hexane−THF (3:1). Silica gel 60 was used for column chromatography and elutions were carried out with a variety of solvent mixtures, but mainly acetone−light petroleum in different volume ratios. Mass spectra (ESI-MS) were recorded on a Finnigan LCQ ion trap spectrometer (Finnigan, San Jose, CA). The ESI source was operated at 4.25 kV, the capillary heater was set to 200 °C, and the experiments were performed in positive ion mode. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DRX 500-MHz NMR spectrometer, using solutions ($CDCl_3$ or toluene-d_8) with TMS as the internal reference for ^{1}H and ^{13}C and 85% H_3PO_4 as an external reference for ^{31}P. In ^{31}P NMR measurements both proton-coupled and proton-decoupled 200-MHz spectra were recorded, whereas only proton-decoupled 125-MHz spectra were recorded for ^{13}C NMR measurements. The chiral properties of molecules were investigated by ^{31}P NMR measurements of compounds on titration with CSR and/or CSA. Owing to differential broadening effects on ^{31}P NMR signals from added CSR, it was found that observation of the separation of chiral signals occurred over a relatively small range of CSR concentrations, so Eu(tfc)$_3$ in solution was added stepwise to solutions of compounds in the same solvent up to a mole ratio of CSR−compound of ca. 0.3:1 and the ^{31}P NMR spectrum recorded at each addition. The chemical shift effect of addition of CSA is smaller than that with CSR, though line broadening was less of a problem, and CSA was added stepwise up to a mole ratio of CSA−compound of ca. 3:1.

Synthesis of the 2-Naphthoxy Derivative of the bino(pip) Compound 9 (Scheme 2). Cis-ansa 2,4-oxy(tetraethylenoxy)-2,4,6,6-tetrachlorocyclotriphosphazatriene, compound **1**, was synthesized as previously reported[12] and separated from the crude reaction mixture by column chromatography on silica gel eluted with hexane−THF (2:1).

Step 1: (steps 1 and 2 were carried out in the same reaction vessel)**:** Compound **1** (0.469 g, 1 mmol) and 2-naphthol (0.147 g, 1 mmol) were dissolved in 60 mL of dry THF and placed in a 250-mL four-necked round-bottomed flask, supplied with a magnetic stirrer, reflux condenser, and argon inlet. NaH (60% oil suspension, 0.04 g, 1 mmol) was added and the reaction was carried out with stirring at room temperature for 1 h. The course of the reaction was monitored by TLC, using hexane−THF (1:1) as eluant and developing reagents, pyridine−*m*-toluidine (1:1) (for all chlorine-containing cyclophosphazene derivatives), and I_2 vapor (for multiple bond containing organic derivatives). When TLC analysis indicated full consumption of **1**, the sample of the reaction mixture was subjected to ^{31}P NMR analysis, which showed the overwhelming presence of an AMX spin system characteristic of 2,4-[oxytetraethylenoxy]-2-(2′-naphthoxy)-4,6,6-trichlorocyclotriphosphazatriene,[9] compound **7**.

Step 2: The flask containing the reaction mixture from step 1 was cooled in an ice bath to about 0 °C, then a solution of piperazine (0.348 g, 4 mmol; 100% excess) in 60 mL of hexane was added slowly over about 25 min under a dry argon atmosphere [this procedure was used to promote formation of the disubstituted product **8** and to avoid the possibility of reaction of the product with any residual **7**, because compound **8** still has one free NH group of the piperazine substituent available for reaction and **7** has one reactive >P(OR)Cl group]. Then the excess of piperazine was neutralized (the course of neutralization was followed by using indicator strips) with a previously prepared solution of concentrated HCl in THF kept over anhydrous Na_2SO_4. The reaction mixture was filtered to remove the salts (NaCl and piperazine hydrochloride) formed at the two steps of the reaction, the solvents were distilled off under reduced pressure, and the residue was dried in vacuo. The product (0.461 g, ∼70% yield) consisted of almost pure 2,4-[oxytetraethylenoxy]-2-(2′-naphthoxy)-4-(piperazinyl)-6,6-dichlorocyclotriphosphazatriene as the hydrochloride salt, **8**·*n*HCl, as inferred from the respective analytical data (Table 1, as well as Tables S1 and S2).

Step 3: Product **8**·*n*HCl, (0.461 g, 0.7 mmol) and compound **1** (0.328 g, 0.7 mmol) were dissolved in benzene (140 mL) and placed in a 250-mL four-necked round-bottomed flask. Sodium hydride (60% oil suspension, 0.112 g, 2.8 mmol) was added (enough to remove the HCl from the **8**·*n*HCl and to accept the HCl formed by the reaction of **1** and **8**) and the reaction was carried out with stirring at room temperature for 20 h under an atmosphere of dry argon and then quenched by adding a solution of concentrated HCl in THF. The precipitate formed was filtered off and benzene was removed in vacuo to leave a colorless oil. ESI-MS analysis and ^{31}P NMR spectra of the crude reaction mixture showed the presence of product **9** (∼75%) with small amounts of substrate **1** (∼10%) and some byproducts. (All relative abundances were inferred from ^{31}P NMR spectra by using the integrated signal area corresponding to a given compound to the overall peak intensity.) The normal procedure of selectively removing unreacted **1** by extraction with hexane was unsuccessful, therefore both the hexane-soluble and hexane-insoluble fractions were subjected to flash column chromatography on silica gel, using hexane−THF (3:1) as eluant. 50% of the pure product **9** was isolated from the hexane-soluble fraction (for analytical data see Table 1 and Tables S1 and S2), whereas only 35% of **9** was isolated from the hexane-insoluble fraction.

Step 4: A pure fraction of product **9** (0.065 g, 0.061 mmol, from the chromatographic separation of step 3) and excess pyrrolidine (0.088 g, 1.22 mmol) were dissolved in benzene (10 mL). The reaction mixture was refluxed for 24 h under an argon atmosphere and filtered and the solvent was distilled off in vacuo, leaving a colorless oil (0.057 g, 76% yield), which consisted of pure **10**, as

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(13) Allcock, H. R.; Kuharcik, S. E.; Visscher, K. B.; Ngo, D. C. *J. Chem. Soc., Dalton Trans.* **1995**, 2785−2795.

inferred from the analytical data (Table 1, as well as Tables S1 and S2).

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Supporting Information Available: Table S1, mass spectrometric (ESI-MS) and ^{1}H NMR data for compounds **7**−**10**; Table S2, ^{13}C NMR data for compounds **7**−**10**; Figure S1, 200 MHz ^{31}P NMR spectrum of diastereoisomeric compound **10** in toluene-d_8; and chiral configurational properties of the sequence of compounds in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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