Crystallographic Proof of Double Walden Inversion in Nucleophilic Substitution Reactions of Macrocyclic Cyclotriphosphazene Derivatives

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Using X-ray crystallography it is demonstrated unambiguously that a double Walden inversion reaction occurs for successive nucleophilic substitution of the mono-spiropropanoxyamino derivative of the *cis*-ansa-macrocyclic cyclophosphazene compound $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]Cl_2$ (**3**). The spiropropanoxyamino moiety enables groups above and below the plane of the N_3P_3 ring to be distinguished. The first nucleophilic substitution of compound **3** with X^- (e.g., X = 2-naphthoxy) gives $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]XCl$ (**4a**), which has a *trans*-ansa-macrocyclic ring as a result of the inversion reaction, and then subsequent reaction of **4a** with the same nucleophile gives $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]X_2$ (**5a**), in which the macrocyclic ring is *cis*-ansa again, but it is now on the *opposite side* of the N_3P_3 ring from that of the starting material **3** as a result of the second inversion reaction. Structures stereochemically analogous to compound **5a** were also obtained upon reaction with other monofunctional nucleophiles, such as phenol, pyrrolidine and aniline, to give compounds **5b**, **5c** and **5d**, respectively, and with the difunctional nucleophile 2,2,3,3-tetrafluorobutanediol to give the di-ansa derivative **6**. Compound **3** was also sequentially treated with two different mononucleophiles – phenol and aniline – to give the unsymmetrically disubstituted compound **7**, in which the macrocyclic ring is also *cis*-ansa again and on the *opposite side* of the N_3P_3 ring from that of the starting material, as a result of the double Walden inversion reactions.

Introduction

The Walden inversion[1] has played an important part in the study of reaction mechanisms in organic chemistry.[2] For S_N2 reactions involving four-coordinate carbon atoms, attack by a nucleophile leads to an inversion of configuration, which is usually confirmed by starting with an optically active compound so that the product has the opposite optical rotation.[3] A similar approach has been taken for reactions involving four-coordinate phosphorus atoms; unless pseudorotation or steric constraints intervene, nucleophilic attack generally leads to inversion of configuration, if the reaction is associative, via either a five-coordinate transition state $S_N2(P)$ or intermediate.[4,5] Pentacoordinate intermediates with fluoride ions have been reported for $(NPF_2)_n$ (n = 4, 5 and 6) and crystallographically characterised as the $(N_4P_4F_9)^-$ and $(N_6P_6F_{13})^-$ anions.[6]

Instead of using changes in optical rotation to investigate reaction mechanisms involving inversion of configuration, we have used a different approach involving reactions of *meso* compounds to give racemates, which can react further to give either another *meso* compound or another racemate depending on the second substituent.[7,8] In recent years macrocyclic derivatives of cyclotriphosphazene have been isolated and X-ray crystallographic investigations of the initial products with polyether macrocyclic rings in the ansa configuration have been found, so far without exception, to have *cis*-ansa structures.[9,10] In macrocyclic cyclophosphazene compounds such as **1** (Scheme 1), the two P atoms carrying the macrocyclic ring, P(Om)Cl (where Om = macrocyclic residue), are stereogenic and, because compound **1** is symmetrically substituted, it is the *meso* form.[7] The first reaction of compound **1** with a nucleophile (X^-) takes place at either of the two P(Om)Cl groups to give the P(Om)X moiety, in which the macrocyclic ring now exists in a *trans*-ansa configuration and the molecule is racemic.[7,8] Further reaction with the same nucleophile X^- then converts the second P(Om)Cl group into another P(Om)X moiety and the resulting derivative has regained a *cis*-ansa structure and is *meso* again.[7] On the other hand, reaction of **1** with

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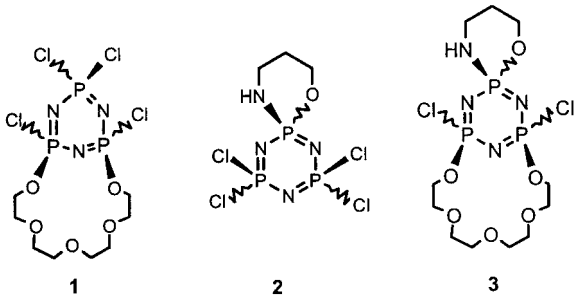
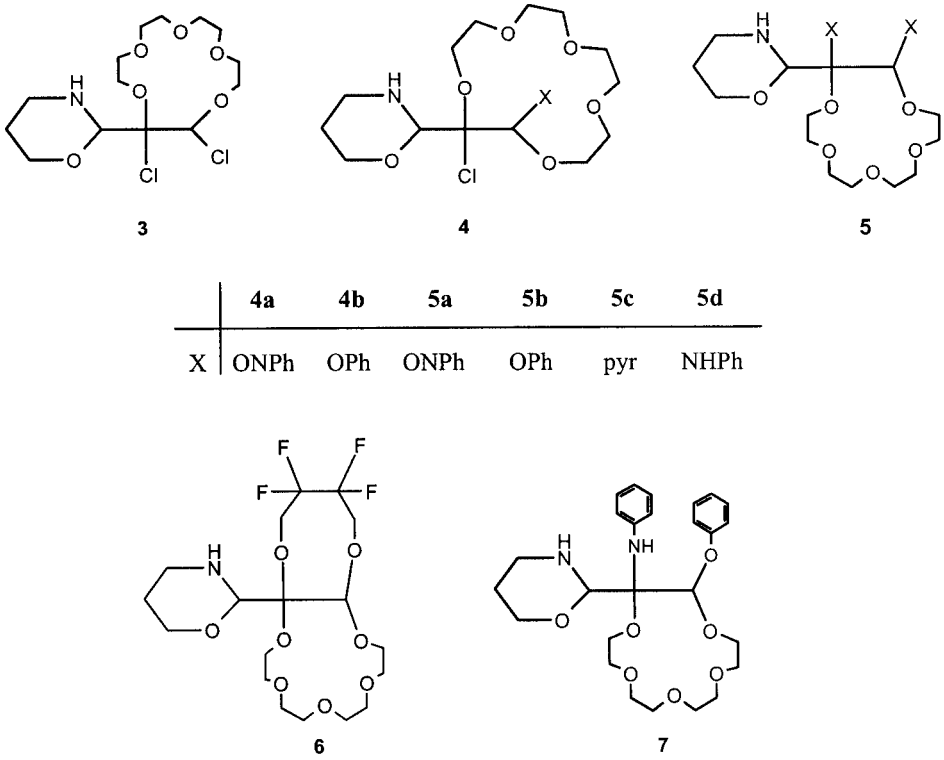
the first nucleophile X^- and then further reaction with a different nucleophile Y^- converts the second P(Om)Cl group into a P(Om)Y moiety and the resulting derivative has regained a *cis*-ansa structure, but is now racemic.[8] These structures have been confirmed crystallographically for single-bridged and double-bridged macrocyclic cyclophosphazene compounds, thus supporting the postulate of Walden inversions for both steps of the reaction.[7] However, only the first step was proven crystallographically; the second was assumed by analogy based mainly on ^{31}P NMR measurements.[7,8]



Scheme 1. Wedge-based structure representation of compounds **1**–**3** in order to emphasise that the macrocyclic ring of compound **3** is in the *cis-ansa* configuration with respect to the cyclophosphazene ring and is *cis* to the NH group of the spirocyclic ring.

Although there is good evidence of inversion of configuration at each step of the reaction, we could not prove by X-ray crystallography that the second Walden inversion led to a *cis*-ansa structure in which the macrocyclic ring was now on the *opposite side* of the N_3P_3 ring to that of the starting material. In order to distinguish groups that are above and below the plane of the N_3P_3 ring, a marker is needed having non-identical substituents on the third phosphorus atom, i.e. the one not involved in the ansa segment. This was achieved by using the mono-spiro derivative $N_3P_3Cl_4[O(CH_2)_3NH]$ (**2**; Scheme 1), whose synthesis[11,12] and crystal structure[12] have been reported previously. The spiropropanoxyamino group is approximately perpendicular to the cyclophosphazene ring[12] and, because it is linked by two different groups (O and NH) to the N_3P_3 ring, a distinction can be be made between the two sides (above and below) of the planar cyclophosphazene ring. Reaction of **2** with the sodium derivative of tetraethylene glycol, $NaO(CH_2CH_2O)_4Na$, gives $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]Cl_2$ (**3**), which is a suitable starting material for further nucleophilic substitution reactions of the two remaining P–Cl bonds in a *cis*-ansa relationship. Compound **3** (Scheme 1) was chosen as an easily accessible starting material with no more than two P–Cl bonds in the molecule (to avoid side-reactions) and because the two P–Cl bonds had to exist in a definite *cis* relationship; suitably substituted *cis*-ansa compounds provide such a juxtaposition of bonds.



	4a	4b	5a	5b	5c	5d
X	ONPh	OPh	ONPh	OPh	pyr	NHPh

Scheme 2. Diagrammatic representation of the structure of compound **3** showing the macrocyclic ring in the *cis-ansa* configuration with respect to the cyclophosphazene ring and *cis* to the NH group of the spirocyclic ring. The structure of compound **4** shows the macrocyclic ring in the *trans-ansa* configuration with respect to the cyclophosphazene ring, resulting from one inversion reaction of compound **3** with a mono(nucleophile). The structure of compounds **5**–**7** shows the macrocyclic ring in the *cis-ansa* configuration with respect to the cyclophosphazene ring but it is now *trans* to the NH group of the spirocyclic ring as a result of double inversion reactions.

However, if the length of the *cis*-ansa chain is too short, reaction could lead to retention of configuration, as recently observed in two systems containing nine-membered ansa rings.[13] Previous work has shown that the sixteen-membered ring of the *cis*-ansa macrocyclic cyclophosphazene derivative **1** is sufficiently large and flexible to take up both *cis* and *trans* configurations as a result of nucleophilic substitution reactions,[7,8] and so this same macrocyclic ring was incorporated into compound **3**. Reaction of compound **3** with a range of mononucleophiles (2-naphthol, phenol, pyrrolidine and aniline) with different steric demands and different nucleophilicities gave examples of the monosubstituted compound **4** (**4a**, X = 2-naphthoxy; **4b**, X = phenoxy) and of the disubstituted compounds **5a**, **5b**, **5c** and **5d**, respectively. Compound **3** was also treated with the difunctional nucleophile 2,2,3,3-tetrafluorobutanediol, to give the diansa derivative **6**, and also treated sequentially with two different mononucleophiles − phenol and aniline − to give the unsymmetrically disubstituted compound **7**. The products (**3**, **4a**, **5a**, **5b**, **5c**, **6** and **7**, summarised in diagrammatic form in Scheme 2) were characterised by X-ray crystallography to show that double Walden inversion reactions had taken place.

Results and Discussion

Macrocyclic cyclophosphazene derivatives are difficult to crystallise and, even when they do, often give rise to disordered structures. Many mono- and disubstituted derivatives (such as **4** and **5**, respectively) remained stubbornly as oils, even though they were shown to be pure by chromatography, elemental analyses, mass spectrometry and ^{31}P NMR spectroscopy. Other derivatives gave solids that were unsuitable for crystallography. The most probable cause of these difficulties is the conformational flexibility of the macrocyclic ring. In particular, the monosubstituted macrocyclic cyclophosphazene derivatives caused major experimental problems, though we eventually succeeded in obtaining a good crystalline product for one compound $\{N_3P_3Cl[O(CH_2CH_2O)_4][NH(CH_2)_3O]X$ (**4a**), X = 2-naphthoxy$\}$. We had more success in crystallisation of the symmetrically disubstituted derivatives $N_3P_3[O(CH_2CH_2O)_4][NH(CH_2)_3O]X_2$ [X = 2-naphthoxy (**5a**), X = phenoxy (**5b**),X = pyrrolidino (**5c**)],though not with X = anilino(**5d**). Crystal structures were also obtained for the symmetrically disubstituted derivative **6**, which is the diansa compound formed from reaction of compound **3** with thedifunctional nucleophile 2,2,3,3-tetrafluorobutanediol, and for the unsymmetrically disubstituted derivative **7**), formed from sequential reaction of compound **3** with phenol and aniline. The X-ray data for compounds **3**, **4a**, **5a**, **5b**, **5c**, **6** and **7** are summarised in the Exp. Sect. and the molecular crystal structures are given below.

Treament of compound **3** with the Na derivative of 2-naphthol gave, successively, the mono- (**4a**) and dinaphthoxy derivatives (**5a**). The same product (**5a**) was obtained in a one-pot reaction with 2 equiv. of thereagent**.** The crystal structure of the starting compound (**3**; Figure 1) shows that the *cis*-ansa macrocyclic ring is on the same side of the cyclophosphazene ring as the NH moiety of the spiropropanoxyamino ring, whereas that for the monosubstituted naphthoxy compound **4a** (Figure 2) shows that the macrocyclic ring is in a *trans*-ansa configuration as a result of a Walden inversion. The crystal structure of the disubstituted naphthoxy compound **5a** (Figure 3) shows that the macrocyclic ring again has a *cis*-ansa configuration as a result of a second Walden inversion, and that the macrocyclic ring is now on the opposite side of the cyclophosphazene ring to the NH moiety of the spiropropanoxyamino ring. These results prove conclusively that we are dealing in this reaction with two successive Walden inversions, which give rise to derivatives with a c*is*-ansa ring on the opposite side of the N_3P_3 ring to that of the starting material. It should be noted that the two P(OR)Cl groups in **3** have the opposite stereogenic configuration and the compound is therefore *meso* (Figure 1).Reaction of a mononucleophile with **3** can take place with equal probability at either P(OR)Cl group to form compound **4a**, which has been shown by X-ray crystallography to have a *trans*-ansa macrocyclic configuration (Figure 2) and exist as a racemate. Further reaction of **4a** with the same nucleophile gives the symmetrical compound **5a**, which has regained a *cis*-ansa structure and is *meso* (Figure 3).

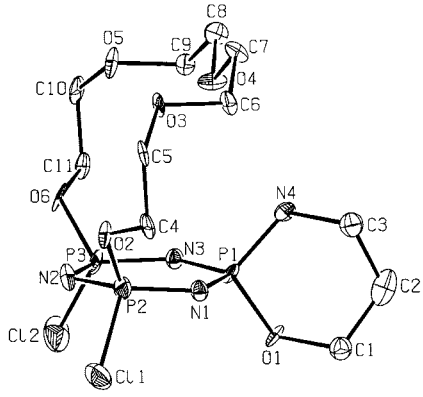


Figure 1. The molecular structure and atomic numbering scheme for one of the independent molecules of compound **3**, with hydrogen atoms (except for NH) and disorder omitted for clarity

In order to ensure that the double Walden inversion reaction does not depend on a bulky, anionic oxygen nucleophile (i.e. 2-naphthol), it was important to show the generality of the phenomenon with a variety of reagents with different steric demands and different nucleophilicities. Therefore we investigated the reaction of **3** with two smaller anionic analogues, phenol, to form the diphenoxide derivative **5b**, and the difunctional aliphatic nucleophile tetrafluorobutanediol, to give the diansa derivative **6**. The crystal structures of **5b** (Figure 4) and **6** (Figure 5) both demonstrate that double inversion has taken place because the macrocyclic ring is found to exist in the *cis*-ansa configuration that was *trans* to the NH group of the spiropropanoxy-

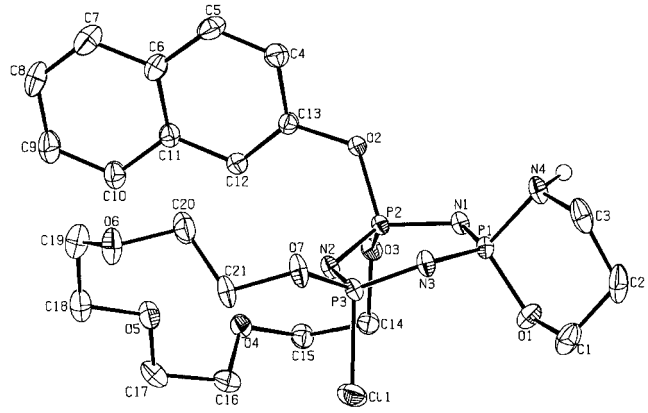


Figure 2. The molecular structure and atomic numbering scheme for compound **4a**, with hydrogen atoms (except for NH) and solvent omitted for clarity

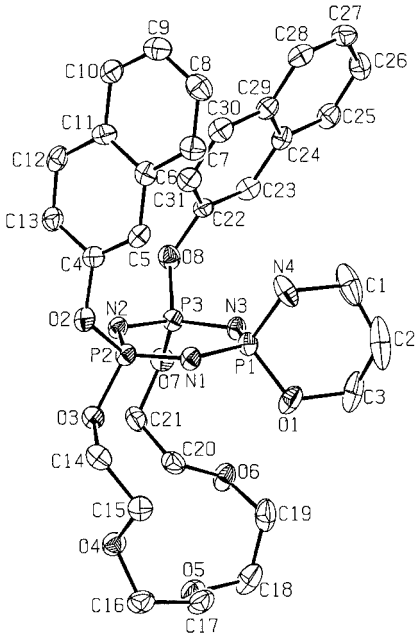


Figure 3. The molecular structure and atomic numbering scheme for one of the independent molecules of compound **5a**, with hydrogen atoms (except for NH) omitted for clarity

amino group. The investigation was then extended to test the inversion reaction with neutral nucleophiles. Reaction of **3** with the fairly strong nucleophilic secondary aliphatic amine pyrrolidine gave **5c**, whose crystal structure (Figure 6) again showsthat a double inversion has taken place as the macrocyclic ring is on the opposite side of the cyclophosphazene ring compared to the starting compound. It should be noted that reaction of primary amines with the P(OR)Cl group of **1**, which is analogous to **3**, takes place with inversion of configuration,although double inversion could not be conclusively proved in the absence of a stereochemical marker group.[7]

All of the symmetrically disubstituted compounds (**5a**–**c**, **6**; Scheme 2) have the ansa ring in a *cis* configuration and are *meso*. It therefore remained to synthesise an unsymmetrically disubstituted compound, which has a *cis*-ansa ring

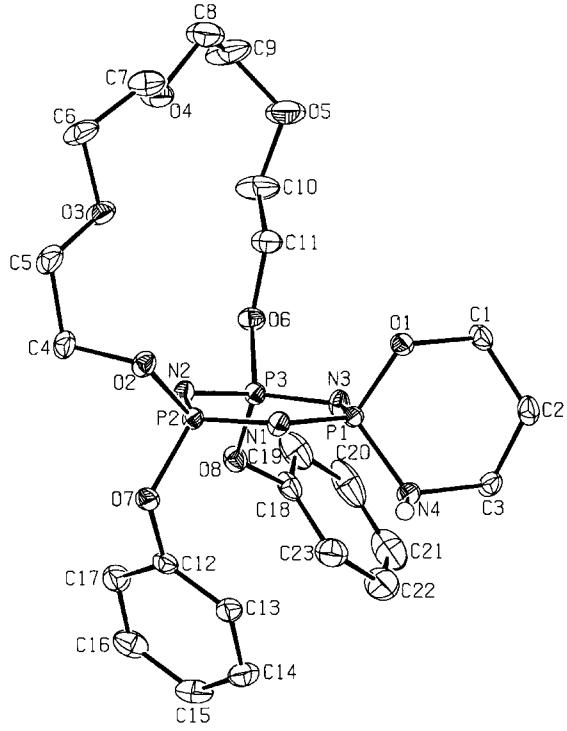


Figure 4. The molecular structure and atomic numbering scheme for compound **5b**, with hydrogen atoms (except for NH) omitted for clarity

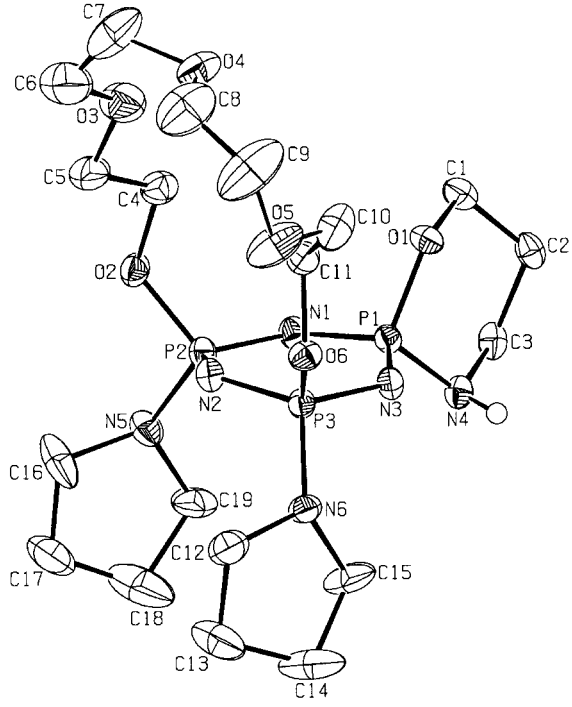


Figure 5. The molecular structure and atomic numbering scheme for one of the independent molecules of compound **6**, with hydrogen atoms (except for NH) and minor component disorder omitted for clarity

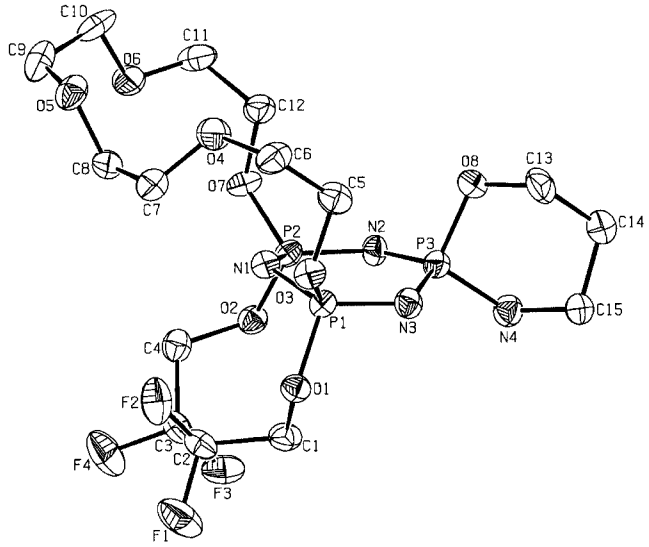


Figure 6. The molecular structure and atomic numbering scheme for compound **5c**, with hydrogen atoms (except for NH) and minor component disorder omitted for clarity

but exists as a racemate, by a double Walden inversion reaction. This was achieved by introducing two different substituents, viz. OPh and NHPh in compound **7**, whose molecular structure is shown in Figure 7 and diagrammatic representation in Scheme 2. This compound also confirms that the weak primary aromatic amine aniline reacts with the P(OR)Cl group with inversion of configuration, which could not be proved with the dianilino derivative **5d** because suitable crystals were not obtained.

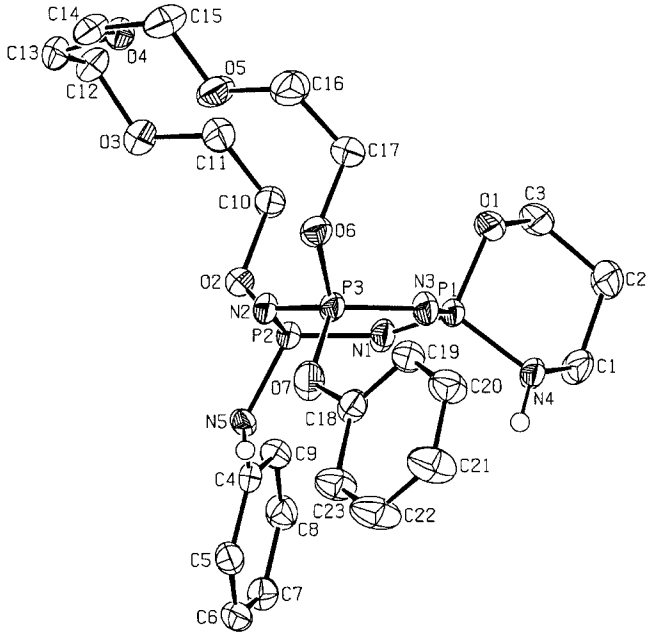


Figure 7. The molecular structure and atomic numbering scheme for compound **7**, with hydrogen atoms (except for NH) and the hydrogen-bonded water molecule omitted for clarity

Discussion of Crystal Structures

In all the crystal structures summarised in Figures 1–7, the bond lengths and bond angles of the N_3P_3 moieties are within the normal range found for cyclophosphazenes.[14] The shape of the cyclophosphazene ring varies from planar in compound **3**,through almost planar in **5b**, **5c** and **7**,to quite puckered in **4a**, **5a** and **6**. The really interesting features in this series of molecules are the hydrogen bonding and the conformation of the macrocyclic substituent with respect to the cyclophosphazene ring. Compound **3** is the only structure reported in this work that exhibits intramolecular hydrogen bonding; the other compounds exhibit intermolecular hydrogen bonding, except **5a**, which does not exhibit any significant hydrogen bonding at all. In compound **3** the macrocycle is pulled back over the N_3P_3 ring, probably because of the intramolecular hydrogen bonding of the NH group of the spiro ring to a central oxygen atom of the macrocycle. In compound **4a**, by contrast, the macrocycle is now pulled away from the N_3P_3 ring and the NH group is involved in intermolecular hydrogen bonding to the ring nitrogen atom of a second molecule to form discrete dimers. The sole 2-naphthoxy group adopts an edge-on conformation with respect to the N_3P_3 ring. A disordered Et_2O molecule is present in the crystal lattice. In the more symmetrical structure of compound **5a** the two 2-naphthoxy groups adopt quite different conformations with respect to the N_3P_3 ring, one being face-on and the other edge-on.The macrocycle is placed over the phosphazene ring, but here no hydrogen bonding is involved and, in fact, there are no close hydrogen bonds in this structure.In compound **5b** the macrocyclic moiety adopts an intermediate position, being neither pulled over or away from the phosphazene ring, even though, as in compound **4a**, the NH group is involved in intermolecular hydrogen bonding to the ring nitrogen atom of a second molecule to form discrete dimers. The structure of compound **5c** resembles that of **5b**,except that the macrocycle is pulled a bit further back from the N_3P_3 ring. In the diansa compound **6** the macrocycle is strongly pulled away from the N_3P_3 ring and the NH group is involved in intermolecular hydrogen bonding to one of the central oxygen atoms of the macrocycle of a second molecule to form infinite chains. In compound **7** the NH group hydrogen bonds intermolecularly to the oxygen atom of the macrocycle of another molecule to again form infinite chains. There is also a molecule of water present, which hydrogen bonds to a ring nitrogen atom and to an oxygen atom of the macrocycle.

Summary

It has been demonstrated by X-ray crystallography that all the nucleophilic reactions so far studied with the macrocyclic cyclophosphazene compound **3**, which contains a sixteen-membered tetraethylene glycol ansa moiety, give rise on monosubstitution, by a Walden inversion, to a racemic *trans*-ansa derivative, and on disubstitution, by a double Walden inversion, to *cis*-ansa compounds. The double

Walden inversion has been verified with a wide variety of nucleophiles (mono- and difunctional reagents with different steric demands and different nucleophilicities). It is also found that compound **3** is *meso*, the symmetrically disubstituted derivatives of **3** (viz. **5a**, **5b**, **5c** and **6**) are *meso* and the unsymmetrically substituted derivative of **3** (viz. **7**) is, as expected, a racemate.

In all nucleophilic substitution reactions studied in this work, inversion of configuration is the preferred mechanism of reaction, though the possibility cannot be excluded that under some conditions there might be a product with retention of configuration. It has now been demonstrated crystallographically that inversion of configuration takes place in nucleophilic substitution reactions of macrocyclic phosphazene compounds containing a sixteen-membered ansa ring system, whereas retention of configuration occurs in cyclophosphazenes containing nine-membered ansa rings.[13] We are currently investigating analogous *cis*-ansa cyclophosphazene compounds with ring sizes intermediate between nine and sixteen to determine at which point or in which range of ring sizes retention changes to inversion. The work will be greatly facilitated by using a marker, such as the spiro-propanoxyamino group, which can be used to distinguish above and below the plane of the cyclophosphazene ring, and hence to investigate retention versus inversion mechanisms.

Experimental Section

Materials: Hexachlorocyclotriphosphazene (a gift from Shin Nisso Kako Co. Ltd.) was purified by fractional crystallization from hexane. Sodium hydride (60% dispersion in mineral oil, Merck) was washed with dry heptane, followed by decantation, to remove the oil prior to use. 2-Naphthol, phenol, pyrrolidine and aniline were obtained from Merck. 2,2,3,3-Tetrafluorobutanediol was obtained from Aldrich. Tetraethylene glycol (Fluka) and 3-amino-1-propanol (Merck) were dried with molecular sieves (4 Å). All solvents used in this work were purified by conventional methods. THF was distilled from a sodium/potassium alloy under dry argon. All reactions were carried out under dry argon. Products were subjected to separation by column chromatography using silica gel (230–400 mesh, Merck). Deuterated $CDCl_3$ for NMR spectroscopy was obtained from Goss Scientific.

NMR Measurements: 200 MHz ^{31}P NMR spectra of all compounds were recorded at 25 °C in $CDCl_3$ solutions with a Bruker DRX 500 MHz spectrometer using 85% H_3PO_4 as an external reference. In some cases both proton-coupled and proton-decoupled ^{31}P NMR spectra were recorded to aid assignment of spectra.

Synthesis of 3: Compound **2** was synthesised by the reaction of hexachlorocyclophosphazene with 3-amino-1-propanol, as described in the literature.[11,12] Compound **2** (3.5 g, 10 mmol) and tetraethylene glycol (2.91g, 15 mmol) were dissolved in 650 mL of dry THF in a 1-L, three-necked, round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (1.2 g, 30 mmol) in 100 mL of dry THF was quickly added to the stirred solution under argon. The reaction mixture was stirred at room temperature for a further 2 h and was followed by TLC on silica gel plates with hexane/THF (1:1) as eluent. The reaction mixture was filtered to remove the sodium chloride formed, the solvent was removed under reduced pressure, and the resulting colourless oil was subjected to column chromatography with THF/hexane (2:1) as eluent. $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]Cl_2$ (**3**) was isolated as a colourless oil and crystallised from chloroform/hexane (1:2) to give white crystals, m.p. 137 °C (yield: 0.94 g, 20%). ^{31}P NMR (analysed as A_2X): δ = 13.8 [t, $^2J_{P,P}$ = 65 Hz, 1 P, P(spiro)], 23.4 [d, $^2J_{P,P}$ = 65 Hz, 2 P, P(OR)Cl] ppm. $C_{11}H_{23}Cl_2N_4O_6P_3$ (471): calcd. C 28.04, H 4.92, N 11.89; found C 28.04, H 4.88, N 12.5.

Reaction of 3 with 2-Naphthol To Give 4a: Compound **3** (0.47 g, 1 mmol) and 2-naphthol (0.216 g, 1.5 mmol) were dissolved in 50 mL of dry THF in a 100-mL, three-necked, round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (0.06 g, 1.5 mmol) in 25 mL of dry THF was quickly added to the stirred solution under argon. The reaction mixture was stirred at room temperature for a further 4 h and followed by TLC on silica gel plates with hexane/THF (1:1) as eluent. The reaction mixture was filtered to remove the sodium chloride formed, the solvent ws removed under reduced pressure, and the resulting colourless oil was subjected to column chromatography with THF/hexane (1:1) as eluent. $N_3P_3[O(CH_2)_3NH][O(CH_2CH_2O)_4]$(2-naphthoxy)Cl] (**4a**) was isolated as a colourless oil and crystallised from dichloromethane/light petroleum (boiling range 40–60°C) to give white crystals, m.p. 75°C (yield 1.13 g, 60%). ^{31}P NMR (analysed as AMX): δ = 12.8 [dd, 1 P, P(OR)(2-naphthoxy), A], 16.9 [dd, 1 P, P(spiro), M], 26.4 ppm [dd, 1 P, P(OR)Cl, X]; $^2J_{P,P}$ = 79.4 Hz, AM; $J_{P,P}$ = 71.8 Hz, AX; $J_{P,P}$ = 79.4 Hz, MX. $C_{21}H_{30}ClN_4O_7P_3$ (578.8): calcd. C 43.57, H 5.22, N 9.68; found C 43.60, H 5.20, N 9.70.

Reaction of 3 with 2-Naphthol To Give 5a: Compound **3** (0.47 g, 1 mmol) and 2-naphthol (0.3 g, 2.1 mmol) were dissolved in 30 mL of dry THF in a 100-mL, three-necked, round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (0.084 g, 2.1 mmol) in 25 mL of dry THF was quickly added to the stirred solution under argon. The reaction mixture was stirred at room temperature for a further 18 h and followed by TLC on silica gel plates with hexane/THF (1:1) as eluent. The reaction mixture was filtered to remove the sodium chloride formed, the solvent was removed under reduced pressure, and the resulting colourless oil was subjected to column chromatography with THF/hexane (1:1) as eluent. $N_3P_3\{[O(CH_2)_3NH][O(CH_2CH_2O)_4](2\text{-Naphthoxy})_2\}$ (**5a**) was isolated as a colourless oil and crystallised from (1:1) chloroform/light petroleum (boiling range 40–60°C) to give white crystals, m.p. 116 °C (yield 0.3 g, 43%). ^{31}P NMR (analysed as A_2X): δ = 18.6 [t, 1 P, P(spiro)], 14.6 ppm [d, 2 P, P(OR)(2-naphthoxy)$_2$]; $^2J_{P,P}$ = 73.1 Hz. $C_{31}H_{37}N_4O_8P_3$ (686.94): calcd. C 54.23, H 5.43, N 8.16; found C 54.21, H 5.40, N 8.10.

Reaction of 3 with Monofunctional Nucleophiles To Give Symmetrically Disubstituted Compounds 5b–d: Compound **3** was treated with phenol, pyrollidine and aniline to give compounds **5b**, **5c** and **5d**, respectively. Experimental and analytical details are provided as Supporting Information.

Reaction of 3 with 2,2,3,3-Tetrafluorobutanediol To Give the Monospiro-diansa Compound 6: Compound **3** (0.95 g, 2 mmol) and 2,2,3,3-tetrafluorobutanediol (0.33 g, 2 mmol) were dissolved in 50 mL of dry THF in a 100-mL, three-necked, round-bottomed flask. NaH (1.2 g, 30 mmol) in 20 mL of dry THF was quickly added to the stirred solution under argon and the reaction mixture was stirred at room temperature for a further 5 d and followed by TLC on silica gel plates with THF as eluent. The reaction mixture was filtered to remove the sodium chloride formed, the solvent was removed under reduced pressure, and the resulting colourless oil was subjected to column chromatography with THF/hexane (3:1) as eluent. The solvent was removed under reduced pressure and the

Table 1. X-ray crystallographic data for compounds **3**, **4a**, **5a**, **5b**, **5c**, **6** and **7**

	3	**4a**	**5a**	**5b**	**5c**	**6**	**7**
Empirical formula	$C_{11}H_{23}Cl_2N_4O_6P_3$	$C_{22.50}H_{33.75}ClN_4O_{7.75}P_3$	$C_{31}H_{37}N_4O_8P_3$	$C_{23}H_{33}N_4O_8P_3$	$C_{19}H_{39}N_6O_6P_3$	$C_{15}H_{26}F_4N_4O_8P_3$	$C_{23}H_{36}N_5O_8P_3$
Formula weight	471.14	612.65	686.56	586.44	540.47	559.31	603.48
Crystal system	monoclinic	triclinic	monoclinic	triclinic	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1$	$P\bar{1}$	$C2/c$	$P2_12_12_1$	$P2_1/c$
a [Å]	15.846(3)	7.8459(2)	9.0346(14)	10.2889(3)	31.3856(10)	9.9411(3)	14.232(3)
b [Å]	14.991(3)	12.8968(3)	20.006(3)	12.4494(3)	9.3691(3)	17.6912(5)	19.571(4)
c [Å]	16.895(3)	14.6925(4)	17.882(3)	12.7523(3)	17.9477(6)	26.1432(7)	10.326(2)
α [°]	90	105.5030(10)	90	64.6480(10)	90	90	90
β [°]	97.73(3)	94.6410(10)	91.955(2)	75.2640(10)	99.322(2)	90	97.57(3)
γ [°]	90	95.7200(10)	90	71.6650(10)	90	90	90
V [Å^3]	3976.9(14)	1416.47(6)	3230.2(9)	1387.50(6)	5207.9(3)	4597.8()	2851.2(10)
Z	8	2	4	2	8	8	4
Density (calcd.) [Mg/m^3]	1.574	1.436	1.412	1.404	1.379	1.616	1.406
Crystal size [mm]	0.15×0.12×0.12	0.26×0.20×0.06	0.04×0.04×0.03	0.30×0.12×0.09	0.20×0.08×0.02	0.24×0.20×0.08	0.22×0.03×0.02
Independent reflections	4463	6256	11030	6254	5914	5344	6503
R(int)	0.0591	0.0212	0.0487	0.0862	0.1108	0.0636	0.0730
Final R indices	$R1$ = 0.0980	$R1$ = 0.0438	$R1$ = 0.0556	$R1$ = 0.0481	$R1$ = 0.0870	$R1$ = 0.0425	$R1$ = 0.0564
$F^2 > 2\sigma(F^2)$	$wR2$ (all) = 0.2497	$wR2$ (all) = 0.1220	$wR2$ = 0.1401	$wR2$ = 0.1311	$wR2$ = 0.1902	$wR2$ = 0.0992	$wR2$ = 0.1506
$\Delta\rho$(max/min) [e•Å^{-3}]	0.778/–2.065	0.906/–0.678	0.509/–0.5456	0.586/–0.636	0.852/–0.682	0.378/–0.281	1.256/–0.397

product crystallized from dichloromethane/hexane (1:1) to give **6** as white crystals, m.p. 110 °C (yield 0.13 g, 12%). ^{31}P NMR (analysed as A_2B): δ = 20.5 [1 P, P(spiro)], 21.2 ppm [2 P, P(OR)-($OCH_2CF_2CF_2CH_2O$)]; $^2J_{P,P}$ = 72.0 Hz. $C_{15}H_{27}F_4N_4O_8P_3$ (561.1): calcd. C 32.15, H 4.86, N 10.00; found C 32.11, H 4.87, N 9.97.

Sequential Reaction of 3 with Phenol and Aniline To Give the Unsymmetrically Disubstituted Compound 7. (i) Reaction of 3 with Phenol To Give 4b: Compound **3** (0.95 g, 2 mol) and phenol (0.188 g, 2 mmol) were dissolved in 50 mL of dry THF in a 100-mL, three-necked, round-bottomed flask. The reaction mixture was cooled in an ice-bath and NaH (0.08 g, 2 mmol) in 20 mL of dry THF was quickly added to the stirred solution under argon. The reaction mixture was stirred at room temperature for a further 4 h and followed by TLC on silica gel plates with hexane/THF (1:1) as eluent. The reaction mixture was filtered to remove the sodium chloride formed, the solvent was removed under reduced pressure, and the resulting colourless oil was subjected to column chromatography with THF/hexane (1:1) as eluent. $N_3P_3\{[O(CH_2)_3NH][O(CH_2CH_2O)_4](OPh)Cl\}$ (**4b**) was isolated as a colourless oil (yield 0.78 g, 74%). ^{31}P NMR (analysed as AMX): δ = 12.6 [dd, 1 P, P(OR)-(OPh), A], 16.9 [dd, 1 P, P(spiro), M], 26.4 ppm [dd, 1 P, P(OR)Cl, X]; $^2J_{P,P}$ = 79.1 Hz, AM; $J_{P,P}$ = 72.1 Hz, AX; $J_{P,P}$ = 69.3 Hz, MX. $C_{17}H_{28}ClN_4O_7P_3$ (529): calcd. C 38.61, H 5.34, N 10.59; found C 38.65, H 5.35, N 10.55. **(ii) Reaction of 4b with Aniline To Give 7:** Aniline (2.79g, 30mmol) was added dropwise from an addition funnel to a solution of **4b** (0.53 g, 1 mmol) in 15 mL of dry THF in a 50-mL, three-necked, round-bottomed flask. The reaction mixture was heated to reflux for 4 h and followed by TLC on silica gel plates with THF/hexane (2:1) as eluent. The reaction mixture was then cooled to room temperature, filtered and the solvent removed under reduced pressure. Distilled water (30 mL) was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was dried with anhydrous Na_2SO_4 and concentrated to 5 mL. The crude product was poured into 750 mL of hexane to give $N_3P_3\{[O(CH_2)_3NH][O(CH_2CH_2O)_4](OPh)(NHPh)\}$ (**7**) as white crystals, m.p. 76°C (yield 0.38 g 65%). ^{31}P NMR (analysed as ABX): δ = 14.7 [dd, 1 P, P(spiro), A], 14.0 [dd, 1 P, P(OR)(NPh), B], 18.1 ppm [t, 1 P, P(OR)(OPh), X]; $^2J_{P,P}$ = 72.3 Hz, AB; $J_{P,P}$ = 65.2 Hz, AX; $J_{P,P}$ = 65.4 Hz, BX. $C_{23}H_{34}N_5O_7P_3$ (586): calcd. C 47.18, H 5.85, N 11.96; found C 47.18, H 5.86, N 11.90.

X-ray Crystallography: Data were collected at low temperature with a Nonius KappaCCD area-detector diffractometer located at the window of a Nonius FR591 rotating anode X-ray generator, equipped with a molybdenum target (Mo-K_α, λ = 0.71073 Å). Structures were solved and refined using the SHELX-97 suite of programs.[15] Data were corrected for absorption effects by means of comparison of equivalent reflections using the program SORTAV.[16] Non-hydrogen atoms were refined anisotropically; NH hydrogen atoms were determined experimentally, whilst the other hydrogen atoms were generally fixed in idealised positions with their thermal parameters riding on the values of their parent atoms. Compound **3** exhibits 50:50 disorder at many sites in one of the two independent molecules, whilst **5c** and **6** show minor disorder in the macrocycle moiety and compound **4a** contains a disordered Et_2O solvent molecule. The absolute structure of **5a** was confirmed by refinement of the Flack parameter to a value of 0.01(9). The macrocycle moiety of **7** encapsulates a water molecule by means of hydrogen bonding. Details are given in Table 1. CCDC-189494 (**3**), -189495 (**4a**), -189496 (**5a**), -238735 (**5b**), -238736 (**5c**), -238737 (**6**) and-238738 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information: Details of the preparation and analytical data for compounds **5b**, **5c** and **5d** are provided as Supporting Information (see also footnote on the first page of this article).

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