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Effect of *gem* 2,2′-disubstitution and base in the formation of spiro- and ansa-1,3-propandioxy derivatives of cyclotriphosphazenes

Aylin Uslu [a,*], Simon J. Coles [b], David B. Davies [c], Mükremin Esen [a], Michael B. Hursthouse [b], Adem Kılıç [a]

[a] Department of Chemistry, Gebze Institute of Technology, Kocaeli, Turkey
[b] Department of Chemistry, University of Southampton, Southampton SO17 1BG, UK
[c] School of Biological and Chemical Sciences, Birkbeck College, University of London, Malet Street, London WC1E 7HX, UK

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ABSTRACT

The *gem*-dialkyl effect has been investigated in the reactions of cyclotriphosphazene, $N_3P_3Cl_6$ **1**, with various 2,2′-derivatives of 1,3-propandiol, $CXY(CH_2OH)_2$, in either THF or DCM to form spiro (6-membered) and ansa (8-membered ring) derivatives. The reactions were made with a number of symmetrically-substituted (X = Y, methyl, ethyl, *n*-butyl and a malonate ester) and unsymmetrically-substituted (X ≠ Y, methyl/H, phenyl/H, methyl/*n*-propyl, ethyl/*n*-butyl and Br/NO_2) 1,3-propandiols. The products were analysed by ^{1}H and ^{31}P NMR spectroscopy and some of the spiro and ansa derivatives were also characterized by X-ray crystallography. Reactions of **1** with unsymmetrically-substituted 1,3-propandiols results in the formation of two structural isomers of ansa-substituted compounds, both isomers (endo and exo) have been structurally-characterized by X-ray crystallography for the ethyl/*n*-butyl derivative. It is found that the regioselectivity of the reaction is changed when the base is changed. The relative proportions of spiro and ansa compounds formed under different reaction conditions were quantified by ^{31}P NMR measurements of the reaction mixtures. The results were rationalised mainly in terms of the electronic effect of the substituents, whereas the steric effect has a secondary role in the formation of both spiro and ansa compounds.

1. Introduction

Cyclization reactions are frequently critical components of natural product synthesis, where the nature of the target molecule often requires the formation of thermodynamically-unfavourable medium-sized rings. To overcome the problem of formation of seven-, eight or nine-membered rings, advantage has been taken of the accelerated rate of cyclization resulting from a *gem*-dialkyl moiety in the acyclic carbon backbone [1]. The *gem*-dialkyl effect (originally described as the Thorpe–Ingold effect [2–4]) is defined by an increase in both rate and equilibrium constants of cyclization reactions resulting from the introduction of substituents in the linking chain [1–6]. Whilst the *gem*-dialkyl effect has been frequently employed in organic chemistry, there are considerably fewer examples of its application in inorganic or organometallic systems [7–10].

In this work we have investigated the *gem*-dialkyl effect on the cyclization reactions of cyclotriphosphazene, $N_3P_3Cl_6$ **1**, an inorganic heterocyclic compound, with a series of 1,3-propanediol derivatives. The reactions of **1** with difunctional reagents such as diols can give rise to two types of cyclic derivatives: spiro (in which the two P–O bonds are formed to the same P-atom) and ansa (in which the two P–O bonds are formed to different P-atoms) [11–14]. Previous work on the cyclization reactions of **1** with different diols (Table 1) shows that using pyridine as base (to neutralize the HCl formed in the reaction) spiro derivatives are overwhelmingly formed in a range of solvents [15–21], whereas significant amounts of ansa derivatives are also formed using the strong base NaH in THF [15,22,23]. It is difficult to rationalise all the results in Table 1 because the reactions have been done with different bases, different solvents and even at different temperatures. For example, although the reactions of **1** with various 1,3-propandiol derivatives, which might provide some insight into the *gem*-dialkyl effect, have been done with the same base, pyridine, they have been carried out in three different solvents, *viz.* Et_2O for 1,3-propanediol [15], dioxane for 2,2-dimethylpropane-1,3-diol [16] and THF for diethyl bis(hydroxymethyl)malonate [17,18], bromoneopentyl glycol [20] and at different temperatures.

In order to provide some insight into the importance of the *gem*-dialkyl effect in reactions of **1** with diols, it is necessary to investigate the reactions in a systematic manner and to use the same method(s) for quantifying the relative proportions of the products. It has recently been shown that ^{31}P NMR spectroscopy of reaction

* Corresponding author. Address: Department of Chemistry, Gebze Institute of Technology, P.O. Box 141 41400, Kocaeli, Turkey. Tel.: +90 262 6053129; fax: +90 262 6053101.
E-mail address: aylin@gyte.edu.tr (A. Uslu).

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Table 1
The results of cyclization reactions of **1** with some diols.

Reaction	Yield %		Solvent	Base	Temp	Ref.
	Sp.[a]	An. [a]				
1,3-propanediol	41	4	Et_2O	pyridine	Room temperature	[15]
2,2-dimethylpropane-1,3-diol	29	-	dioxane	pyridine	Room temperature	[16]
diethyl bis(hydroxymethyl)malonate	52	-	THF	pyridine	reflux	[17,18]
3-hydroxy-2-(hydroxymethyl)-2-methylpropyl)methacrylate	17	-	Et_2O	4-dimethylaminopyridine	Room temperature	[19]
bromoneopentyl glycol	53	-	THF	pyridine	reflux	[20]
1,3-butanediol	56	-	benzene	triethylamine	reflux	[21]

[a] Sp. = Spiro, An. = Ansa.

mixtures is a reliable way of quantifying the relative proportions of spiro and ansa derivatives [24] and these results may be compared with those for isolation of the compounds. In this work, as summarized in Scheme 1, the reactions of cyclotriphosphazene, $N_3P_3Cl_6$, **1**, with various 1,3-propandiols, $CXY(CH_2OH)_2$, will be investigated quantitatively under different solutions conditions in order to provide greater understanding of the effects of substituents (X = Y and X ≠ Y) on the formation of both of spiro and ansa derivatives.

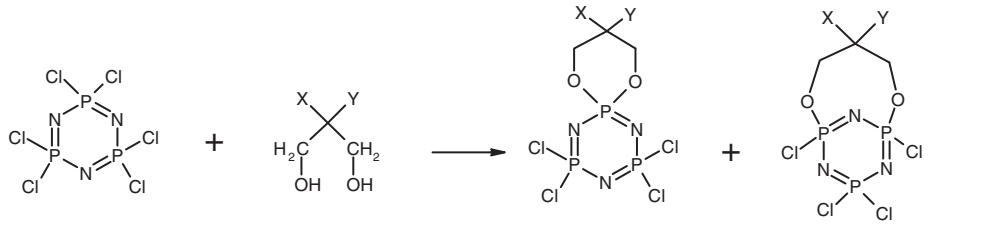
2. Experimental

2.1. Materials

Hexachlorocyclotriphosphazene (Shin Nisso Kako Co. Ltd.) was purified by fractional crystallisation from hexane. The following chemicals were obtained from Merck; 1,3-propanediol (>98%), 2,2-dimethylpropandiol (>98%), silica gel 60, tetrahydrofuran (≥99.0%), dichloromethane (≥99.0%) ethyl acetate (≥99.0%), *n*-hexane (>96%), sodium hydride (>60%), and from Aldrich; diethylbis(hydroxymethyl)malonate (>97%), 2-butyl-2-ethyl-1,3-propandiol (>99%), 2,2-diethyl-1,3-propandiol (>99%), 2-methyl-2-propyl-1,3-propandiol (>98%), 2,2-dibutyl-1,3-propandiol (>97%), 2-bromo-2-nitro-1,3-propandiol (>98%), 2-phenyl-1,3-propandiol (>98%), 2-methyl-1,3-propandiol (>99%). The deuteriated solvent ($CDCl_3$) for NMR spectroscopy was obtained from Apollo Scientific.

2.2. Methods

Elemental analyses were obtained using a Carlo Erba 1106 Instrument. Mass spectrometric measurements were made on a



(1) **(2a-11a)** **(5b, 7b-10b, 7c-10c)**

R^1, R^2	Spiro	Ansa
i) Symmetrical substitution : X = Y		
H	**2a**	**2b**
CH_3	**3a**	**3b**
C_2H_5	**4a**	**4b**
C_4H_9	**5a**	**5b**
$C(O)OC_2H_5$	**6a**	a
ii) Unsymmetrical substitution : X ≠ Y		
CH_3, H	**7a**	**7b**, **7c**
Ph, H	**8a**	**8b**, **8c**
C_3H_7, CH_3	**9a**	**9b**, **9c**
C_4H_9, C_2H_5	**10a**	**10b**, **10c**
Br, NO_2	**11a**	a

a. Ansa isomer not observed

Scheme 1. Formation of spiro and ansa derivatives in the reactions of cyclophosphazene (**1**) with 2,2′-substituted 1,3-propanediols.

HP G1800A GC–MS spectrometer using the HP-5 column and a Bruker MicrOTOF LC–MS spectrometer with electrospray ionization (ESI) method; ^{35}Cl values were used for calculated masses. Analytical Thin Layer Chromatography (TLC) was performed on Merck Silica gel plates (Merck, Kieselgel 60, 0.25 mm thickness) with F_{254} indicator. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh; for 3 g crude mixture, 100 g silica gel was used in a column of 3 cm in diameter and 60 cm in length). ^1H and ^{31}P NMR spectra were recorded in $CDCl_3$ solutions on a Varian INOVA 500 MHz spectrometer using 85% H_3PO_4 as an external reference for ^{31}P and TMS as internal reference for ^1H NMR. In order to assign the ^{31}P NMR signals of some compounds both proton-coupled and proton-decoupled ^{31}P NMR spectra were recorded.

2.3. Synthesis

2.3.1. General procedure used for reaction of diols with cyclotriphosphazene (*1*) in the presence of pyridine in THF solution

1,3-Propanediol (0.4 g, 1.29 mmol) in 5 mL of THF was added dropwise to a stirred solution of compound **1** (0.5 g, 1.44 mmol) dissolved in 5 mL of THF under an argon atmosphere and then pyridine (0.204 g, 2.58 mmol) in 5 mL of dry THF was added dropwise. The reaction mixture was stirred for a further 3 days at room temperature and the reaction was followed by TLC indicating the presence of a number of products. The precipitated salt (pyridinium hydrochloride) was then filtered off and solvent was removed under reduced pressure.

2.3.2. General procedure used for reaction of diols with cyclophosphazene (*1*) in the presence of NaH in THF solution

1,3-Propanediol (0.4 g, 1.29 mmol) in 5 mL of dry THF was added dropwise to a stirred solution of compound **1** (0.5 g, 1.44 mmol) dissolved in 5 mL of dry THF under an argon atmosphere, then sodium hydride (0.062 g, 2.58 mmol) in 5 mL of dry THF was added dropwise. The reaction mixture was stirred for a further 3 days at room temperature and the reaction was followed by TLC indicating the presence of a number of products. The precipitated salt (NaCl) was then filtered off and the solvent was removed under reduced pressure.

2.3.3. General procedure used for work-up of the products of the reaction of each diol with *1*

The products were isolated from the combined crude reaction mixture by column chromatography. Crystals of pure spiro and ansa derivatives were obtained using DCM:*n*-hexane (5:1) and analysed by microanalysis and mass spectrometry and the results are summarized in Table S1. Each product was also characterized by ^1H and ^{31}P NMR spectroscopy and the ^{31}P NMR parameters are given in Table 2 and the ^1H NMR parameters are given in Table S2 in the Supplementary material. Crystals suitable for X-ray crystallography were found for spiro compounds **4a**, **7a**, **8a**, 11a and for ansa compounds **3b**–**5b**, **7b**, 10b and **10c**. Some compounds (**5a**, **6a**, **9a**, **10a**, **8b**, **9b**, **7c**, 8c and **9c**) remained as oily products.

2.3.4. General procedure used to estimate the relative proportions of products of the reaction of diols with cyclophosphazene (*1*) by ^{31}P NMR spectroscopy

A small portion of each filtered and solvent-free crude reaction mixture was dissolved in $CDCl_3$ and the relative ratios of the starting material **1**, spiro and ansa derivatives and any other products were estimated from the proton-decoupled ^{31}P NMR spectra performed under pulsing conditions (Π/3 pulse, overall repetition time of 3.6 s) that allowed for relaxation times of the ^{31}P nuclei of up to 6 s in spiro- and ansa-substituted cyclophosphazene derivatives [25].

Table 2
^{31}P NMR parameters of compounds **2a**–**11a**, **2b**–**10b** and **7c**, **10c** [a,b].

Cpd	>P(OCH$_2$)	>PCl$_2$	>PCl$_2$	>C(X,Y)		^2J(PP)/Hz		
	1	2	3	X	Y	1, 2	1, 3	2, 3
(i) Symmetrically-substituted Spiro compounds: X = Y								
2a	3.07	23.90		H	H	69.1		
3a	2.83	24.14		CH_3	CH_3	68.7		
4a	4.14	24.53		C_2H_5	C_2H_5	68.6		
5a	4.22	24.42		C_4H_9	C_4H_9	68.6		
6a	4.24	24.98		CO_2Et	CO_2Et	70.7		
(ii) Unsymmetrically-substituted Spiro compounds: X ≠ Y								
7a	3.31	23.42	25.50	H	CH_3	61.7	76.1	61.5
8a	3.43	23.10	26.16	H	Ph	59.5	79.7	60.6
9a	3.74	24.39	24.65	C_3H_7	CH_3	67.7	69.4	61.0
10a	4.19	24.31	24.72	C_4H_9	C_2H_5	67.8	69.4	61.3
11a	3.75	23.86	27.11	Br	NO_2	57.7	85.5	58.4
(iii) Symmetrically-substituted Ansa compounds: X = Y								
2b	26.63	25.78		H	H	59.2		
3b	27.46	26.17		CH_3	CH_3	57.5		
4b	28.05	26.61		C_2H_5	C_2H_5	56.4		
5b	27.82	26.27		C_4H_9	C_4H_9	57.2		
(iv) Unsymmetrically-substituted Ansa compounds: X ≠ Y								
7b	27.87	26.99		H	CH_3	57.3		
7c	27.01	25.52		H	CH_3	58.4		
8b	28.15	26.88		H	Ph	57.8		
8c	28.38	27.39		H	Ph	58.2		
9b	28.12	26.85		C_3H_7	CH_3	56.5		
9c	27.66	26.18		C_3H_7	CH_3	58.1		
10b	28.02	26.57		C_4H_9	C_2H_5	56.8		
10c	27.90	26.39		C_4H_9	C_2H_5	57.2		

[a] 202.38 MHz ^{31}P NMR measurements in $CDCl_3$ solutions at 298 K in this work, chemical shifts referenced to external H_3PO_4.

[b] The ^{31}P NMR spectra of symmetrically-substituted spiro compounds **2a**–**6a** were analysed as A_2X spectra, those for unsymmetrically-substituted spiro compounds **7a**–**11a** as ABX spectra and those for ansa compounds **2b**–**5b**, **7b**–**10b**, **7c**–**10c** were analysed as A_2B spectra.

2.3.5. X-ray crystallography

X-ray structure determination and crystallographic data were collected by means of combined phi and omega scans on a Bruker-Nonius Kappa CCD area detector situated at the window of a rotating anode (λMo Kα = 0.71073 Å). The structures were solved by direct methods, SHELXS-97 and refined using SHELXL-97 [26]. The data were corrected for absorption effects using SADABS [27], The X-ray crystallographic data are summarized in Table 3 and full details of data collection and structure determination have been deposited with the Cambridge Crystallographic Data Centre and assigned deposition numbers.

3. Results and discussion

The aim of the present work is to investigate the *gem*-dialkyl effect on the formation of spiro and ansa derivatives of cyclotriphosphazene, **1**, with various 2,2′-substituted 1,3-propandiols using the same solvents (THF or DCM) but under different conditions that are known to favour ansa compounds using the alkoxide [28] or favour spiro compounds with pyridine as the hydrogen halide acceptor [29,30]. The results of the reactions using DCM or THF as solvent are almost the same and so only those in THF have been described in detail. In the 1,3-propandiols, HO(CH_2)CXY(CH_2)OH, the X and Y groups may be the same (X = Y) or different (X ≠ Y) (Scheme 1); in most of the substituted 1,3-propandiols, X or Y are alkyl groups thus making the alkoxide CH_2–O^- group slightly more electron-rich whereas, for comparison purposes, two of the diols [with two $COOC_2H_5$ or NO_2/Br groups] contain electron-withdrawing groups making the CH_2–O^- group slightly less electron-rich.

Table 3
X-ray data and molecular parameters for spiro (**4a**, **7a**, **8a**, **11a)** and ansa (**3b**, **4b**, **5b**, **7b**, **10b**, **10c)** compound.

	4a	**7a**[a]	**8a**	**11a**	**3b**	**4b**	**5b**	**7b**	**10b**	**10c**
(i) X-ray data										
Empirical formula	$C_7H_{14}Cl_4N_3O_2P_3$	$C_4H_8Cl_4N_3O_2P_3$	$C_9H_{10}Cl_4N_3O_2P_3$	$C_3H_4BrCl_4N_4O_4P_3$	$C_5H_{10}Cl_4N_3O_2P_3$	$C_7H_{14}Cl_4N_3O_2P_3$	$C_{11}H_{22}Cl_4N_3O_2P_3$	$C_4H_8Cl_4N_3O_2P_3$	$C_9H_{18}Cl_4N_3O_2P_3$	$C_9H_{18}Cl_4N_3O_2P_3$
Formula weight	406.92	364.84	426.91	474.72	378.87	406.92	463.03	364.84	434.97	434.97
Crystal system	Triclinic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic	Triclinic	Orthorhombic
Space group	$P\bar{1}$	*Cc*	$Pna2_1$	*Pbca*	*Pnnm*	$P2_1/c$	$P2_1/c$	*Pbca*	$P\bar{1}$	*Pbca*
a (Å)	8.03340(10)	14.8296(9)	23.2125(7)	13.0288(4)	11.5390(9)	15.9483(5)	10.6315(2)	13.3334(2)	8.20120(10)	11.4593(2)
b (Å)	10.0791(2)	6.0926(3)	9.1684(2)	12.2797(4)	12.4271(8)	12.1905(3)	12.0869(2)	12.3344(4)	9.06650(10)	16.8538(2)
c (Å)	11.1829(3)	15.4113(12)	7.6006(2)	18.0331(5)	9.9748(5)	16.5233(4)	15.6257(3)	15.9953(4)	12.81310(10)	19.0612(2)
α (°)	97.4510(10)	90	90	90	90	90	90	90	83.3440(10)	90
β (°)	111.0060(10)	109.500(3)	90	90	90	99.189(2)	101.5850(10)	90	84.0130(10	90
γ (°)	103.9920(10)	90	90	90	90	90	90	90	72.5300(10)	90
Volume ($Å^3$)	796.48(3)	1312.56(14)	1617.57(7)	2885.11(15)	1430.35(16)	3171.20(15)	1967.03(6)	2630.58(11)	900.230(16)	3681.34(9)
Z	2	4	4	8	4	8	4	8	2	8
D_{calc} (mg/m^3)	1.697	1.846	1.753	2.186	1.759	1.705	1.564	1.842	1.605	1.570
Absorption coefficient (mm^{-1})	1.043	1.255	1.033	3.934	1.155	1.048	0.855	1.252	0.929	0.908
F(0 0 0)	412	728	856	1840	760	1648	952	1456	444	1776
Crystal size (mm)	0.38 × 0.20 × 0.05	0.40 × 0.20 × 0.20	0.24 × 0.20 × 0.02	0.50 × 0.25 × 0.10	0.60 × 0.15 × 0.13	0.35 × 0.20 × 0.20	0.60 × 0.15 × 0.15	0.50 × 0.14 × 0.02	0.18 × 0.10 × 0.05	0.12 × 0.10 × 0.02
θ_{max} (°)	27.49	27.50	27.49	27.50	27.50	27.50	27.50	27.49	2.96–27.50	3.03–27.48
Reflections collected	16270	2043	15068	23902	13938	41102	25240	19829	37334	57233
Independent reflections	3645	1519	3611	3290	1723	7260	4512	3013	4131	4213
R_{int}	0.0254	0.0445	0.0443	0.0570	0.0267	0.0477	0.0403	0.0447	0.0350	0.0494
Final *R* indices	$R_1 = 0.0262$,	$R_1 = 0.0658$,	$R_1 = 0.0309$,	$R_1 = 0.0384$,	$R_1 = 0.0232$,	$R_1 = 0.0347$,	$R_1 = 0.0284$,	$R_1 = 0.0316$,	$R_1 = 0.0235$,	$R_1 = 0.0310$,
$F^2 > 2\sigma F^2$	$wR_2 = 0.0648$	$wR_2 = 0.1561$	$wR_2 = 0.0657$	$wR_2 = 0.0902$	$wR_2 = 0.0663$	$wR_2 = 0.0766$	$wR_2 = 0.0667$	$wR_2 = 0.0690$	$wR_2 = 0.0614$	$wR_2 = 0.0779$
$\Delta\rho$ max/min ($e Å^{-3}$)	0.287 and −0.490	0.792 and −0.866	0.322 and −0.295	2.351 and −0.851	0.273 and −0.435	0.364 and −0.503	0.361 and −0.420	0.366 and −0.538	0.327 and −0.389	0.363 and −0.375
(ii) Cyclophosphazene ring										
Maximum deviation (Å)	0.084	0.077	0.051	0.085	0.272	0.263; 0.227	0.273	0.294	0.301	0.290
Minimum P···P distance (Å)	2.744	2.741	2.740	2.744	2.644	2.638; 2.673	2.643	2.635	2.634	2.638
(iii) Exocyclic ring pucker (Q)			Spiro				Ansa			
Mean	0.5521	0.558	0.547 0.549 (±0.006)	0.538	1.1902	1.1974	1.2023 1.201 (±0.013)	1.175	1.2268	1.2131

[a] Chiral space group.

3.1. Characterization of products by ^{31}P NMR spectroscopy

The isolated spiro and ansa derivatives were characterized by mass spectrometry, microanalysis and ^{1}H NMR and ^{31}P NMR spectroscopy. The chemical shifts and phosphorus–phosphorus coupling constants are summarized in Table 2 and the other analytical information is summarized in the Supplementary material.

The proton-decoupled ^{31}P NMR spectra of spiro compounds resulting from symmetrically-disubstituted 1,3-propandiols (compounds **2a**–**6a**) were observed as simple AX_2 spin systems with very similar spin-coupling constants between the $>P(OCH_2)$ and $>PCl_2$ [^{2}J(PP) 68.6–70.7 Hz], whereas those resulting from unsymmetrically-disubstituted 1,3-propandiols (compounds **7a**–**11a**) were observed as ABX spin systems, in which the PCl_2 groups exhibit anisochronism; the latter phenomenon has been observed and explained previously in terms of the two PCl_2 groups being in non-equivalent relationships to the other two different geminal groups [28,31]. The two sets of ^{2}J(PP) between the $>P(OCH_2)$ and $>PCl_2$ groups in the unsymmetrically-substituted spiro compounds are different and depend on the substituents (ranging from 57.7–67.8 to 69.4–85.5 Hz) though the average ^{2}J(PP) for each compound is in the same range (68.6–71.6 Hz) as for the symmetrically-substituted spiro compounds.

The proton-decoupled ^{31}P NMR spectra of the ansa compounds resulting from symmetrically-disubstituted 1,3-propandiols (compounds **2b**–**5b**) are observed as A_2B spin systems, in which the

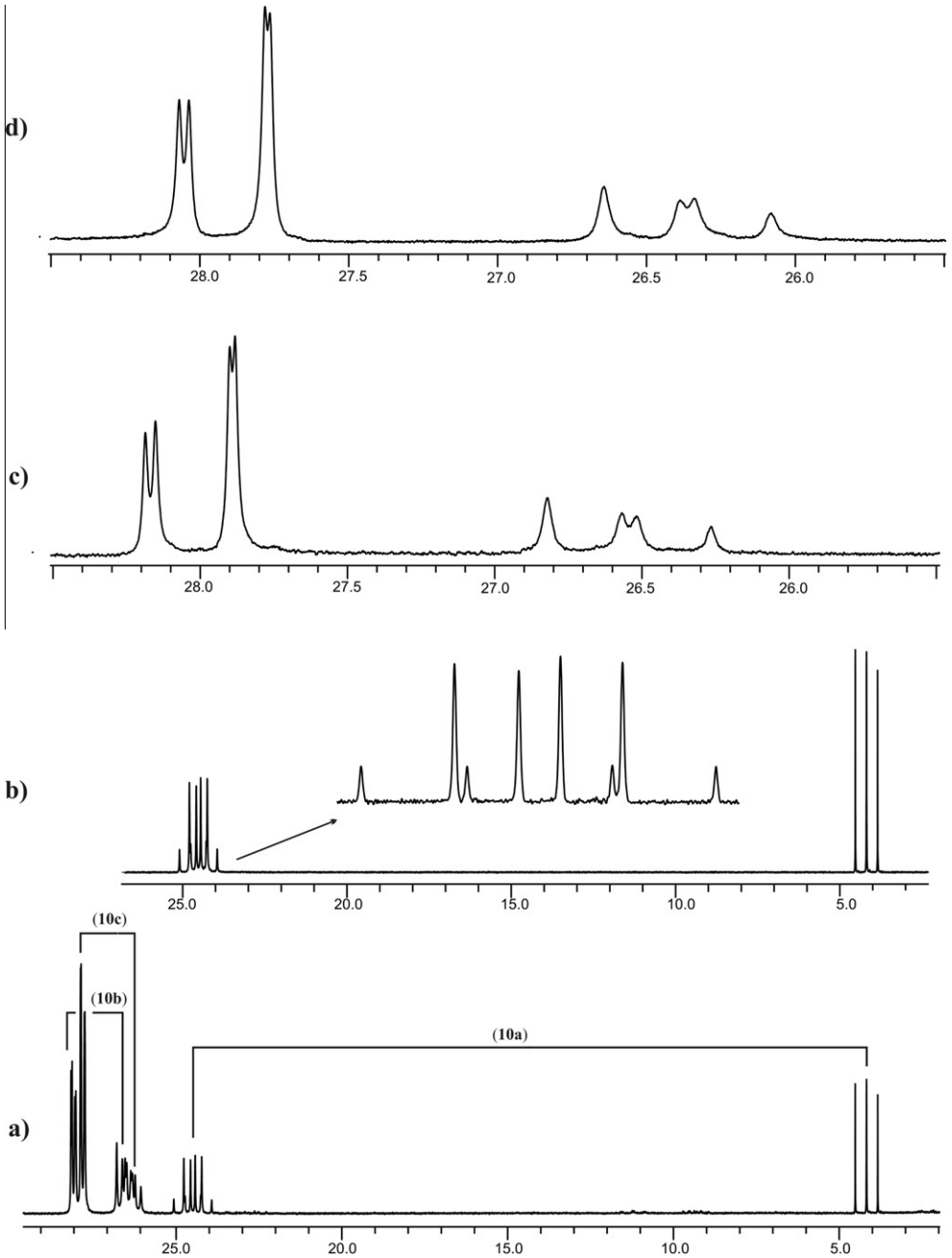


Fig. 1. (a) Proton-decoupled ^{31}P NMR spectrum of the reaction mixture of the reaction of cyclophosphazene, (**1**), with 2-butyl-2-ethyl-1,3-propandiol (after filtration, evaporation of solvent and dissolving in $CDCl_3$ solution). (b) Superposition of the proton-decoupled ^{31}P NMR ABX spin system of the spiro compound **10a** together with expansion of the AB part of the spectrum, (c) expansion of the proton-decoupled ^{31}P NMR A_2B spectra of the ansa compounds **10b** and (d) **10c** on the same chemical shift scales.

^2J(PP) between the >P(OCH$_2$) and >PCl$_2$ groups are similar to each other (56.4–59.2 Hz) but significantly smaller than those observed in analogous spiro compounds (**2a**–**6a**). Similar differences between ^2J(PP) in spiro- and ansa-substituted 1,3-propanedioxy derivatives have been observed for both spirane-bridged [25] and spermine-bridged compounds [32], which must reflect the strain in the cyclotriphosphazene ring of the ansa-compounds compared to the spiro-substituted derivatives.

The proton-decoupled ^{31}P NMR spectra of the ansa compounds resulting from unsymmetrically-disubstituted 1,3-propandiols (compounds **7**–**10**) are observed as two sets of A$_2$B spin systems having slightly different chemical shifts and coupling constants. There are two structural isomers of unsymmetrically-substituted ansa compounds, in which substituent groups can be described as endo or exo with respect to a common structural feature, as reported by Elias and co-workers [11,33] for a pair of ansa-substituted fluorophosphazenes. The two sets of ansa compounds **7**–**10** were separated by column chromatography and the ^{31}P NMR parameters are summarized in Table 2, such that the isomer with the smaller coupling constant is denoted **7b**–**10b** and with the larger coupling constant as **7c**–**10c**. Examples of the ^{31}P NMR spectra of spiro and ansa derivatives formed from an unsymmetrically-disubstituted 1,3-propandiol are shown in Fig. 1a for the reaction mixture of cyclophosphazene, **1**, with 2-butyl-2-ethyl-1,3-propandiol together with the superposition of the proton-decoupled ^{31}P NMR ABX spin system of the isolated spiro compound **10a** (Fig. 1b), and with expansion of the proton-decoupled ^{31}P NMR A$_2$B spectra of the two isolated ansa compounds **10b** (Fig. 1c) and **10c** (Fig. 1d) on the same chemical shift scales.

3.2. Characterization of products by X-ray crystallography

Compounds **2a** [34,35], **2b** [25] and **3a** [36] have been characterized previously by X-ray crystallography, whereas the molecular structures of spiro (**4a**, **7a**, **8a**, **11a**) (Fig. 2a–d) and ansa compounds (**3b**, **4b**, **5b**, **7b**) (Fig. 3a–d) and the isomeric pair (**10b** and **10c**) (Fig. 4a and b) were characterized in this work. The X-ray diffraction data of all compounds are given in Table 3. Other isolated compounds (**5a**, **6a**, **9a**, **10a**, **8b**, **9b**, **7c**, 8c and **9c**) remained as oily products. The structures of the pair of unsymmetrically-disubstituted 1,3-propandiol derivatives **10b** and **10c** are shown in Fig. 4 with the ethyl and butyl groups either endo or exo to the plane of the cyclophosphazene ring. Following the notation used by Elias and co-workers [11,37,38] for the pair of ansa-substituted fluorophosphazenes, where the relationship to the plane of the cyclophosphazene ring of the larger substituent in the ansa ring defines the endo/exo designations, the structure of **10b** is designated exo and **10c** is endo. Comparison of the geminal P–P coupling constants for these two compounds indicates that ^2J(PP) for **10c** (endo) is slightly larger than for **10b** (exo), an observation that might tentatively be used to assign the endo and exo isomers of the other unsymmetrically-disubstituted 1,3-propandiol derivatives of compounds **7**–**9**. Unfortunately the hypothesis cannot be tested using analogous data for the pair of ansa-substituted fluorophosphazenes, because that data was not recorded by Elias and co-workers [33]. However, the hypothesis is shown to be consistent with the results for compound **7b**, whose crystal structure (Fig. 3d) shows that it is the exo isomer (i.e. H/endo–CH$_3$/exo) and whose ^2J(PP) is slightly smaller than that of the other ansa isomer, **7c**. Using the NMR data in Table 2, it is assumed by analogy that compounds **8b**, 9b are also the exo isomers and compounds **8c**, 9c are the endo isomers.

The cyclotriphosphazene rings of spiro 1,3-propandioxy derivatives are essentially strain-free and planar, in which the deviation of individual atoms from the N$_3$P$_3$ plane in all the compounds reported here (**4a**, **7a**, **8a**, **11a**) is less than 0.1 Å (Table 3), similar to that observed previously for **2a** [34,35] and **3a** [36] and a number of other 1,3-propandioxy-spiro derivatives of both spirane-bridged [25] and spermine-bridged compounds [32]. On the other hand, the eight-membered *cis*-ansa ring of such 1,3-propanedioxy cyclophosphazene derivatives causes strain in the cyclophosphazene ring, which is relieved by being non-planar. It is found for all the ansa compounds (**3b**, **4b**, **5b**, **7b**, 10b and **10c**) in this work that the nitrogen atom between the phosphorus atoms carrying

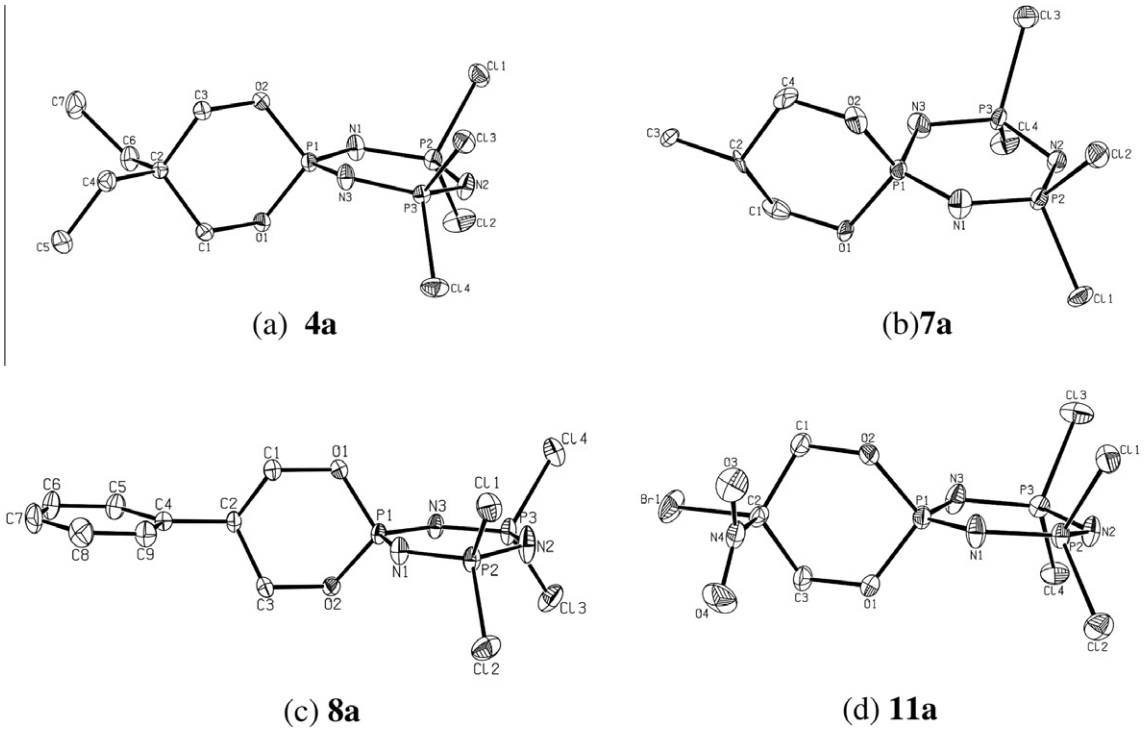


Fig. 2. X-ray crystal structures of the mono-spiro derivatives **4a**, **7a**, **8a** and **11a**.

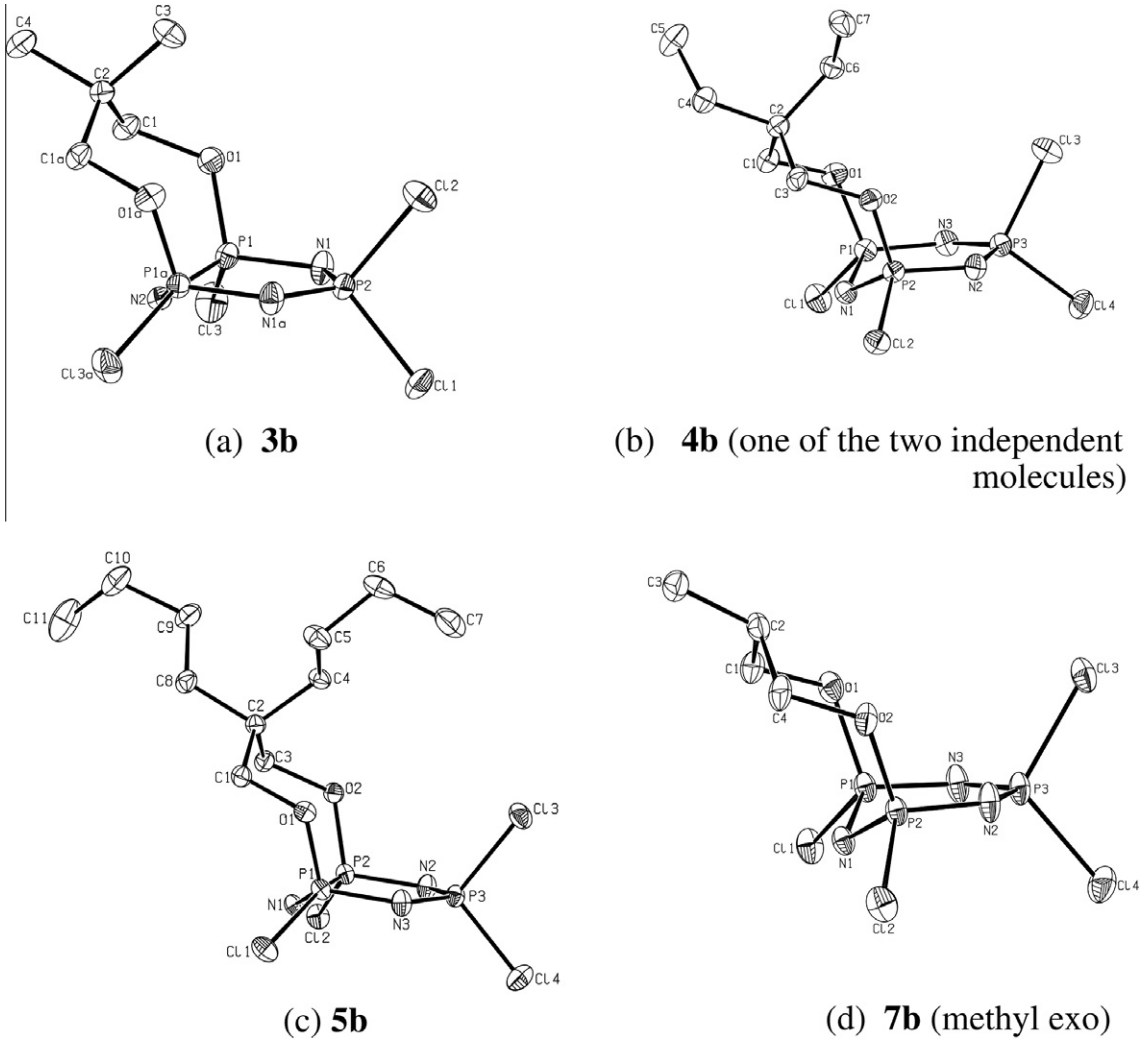


Fig. 3. X-ray crystal structures of the mono-ansa derivatives **3b**, **4b**, **5b** and **7b**.

the ansa moiety is furthest out-of-plane of the other atoms of the cyclophosphazene ring and that the deviation from the plane is greater than 0.2 Å (Table 3), similar to that found previously for analogous 1,3-propanedioxy cyclophosphazene derivatives **2b** [25,32]. Another indication of the non-planar cyclophosphazene ring is the significant shortening of the non-bonded P···P distance (*ca.* 2.6 Å) between the ansa-carrying atoms (Table 3), compared to the normal value of *ca.* 2.77 Å for planar cyclophosphazene rings [37,38] and *ca.* 2.74 Å for the approximately planar cyclophosphazene rings of the spiro derivatives in this work (Table 3), and a number of other 1,3-propandioxy-spiro derivatives of cyclophosphazene [25].

Puckering analysis [39] is a useful measure of ring conformation in which calculation of the mean plane and puckering parameters provides a unique quantitative descriptor, the total puckering amplitude (Q), for a ring conformation that can be applied to both spiro and ansa rings. The spiro rings in the six-membered $P(OCH_2C(XY)CH_2O)$ spiro-substituted structures (**4a**, **7a**, **8a**, **11a**) are all found to have similar chair conformations with a strictly alternating positive/negative torsion angle sequence around the ring and each ring component in a *gauche* conformation with respect to its neighbour. The puckering amplitude, Q, for each spiro ring (Table 3) is *ca.* 0.55, similar to that observed for other 1,3-propandioxy-spiro derivatives of cyclophosphazene [25]. Although the overall conformations of the eight-membered $NP–OCH_2C(XY)-CH_2O–P$ ansa rings of compounds characterized in this work (**3b**, **4b**, **5b**, **7b**, 10b and **10c**) work are similar, it is found (Table 3) that there is some dependence of the puckering amplitude, Q, on the size of the substituents X and Y; the value of Q for **7b** (1.175) having substituents Me/H is similar to the average value of 1.177 for a number of 1,3-propandioxy-spiro derivatives of cyclophosphazene (X = Y = H) [25], whereas increasing size of the substituents X/Y results in a small increase in the value of Q, *viz.* Me/Me (**3b**, 1.190), Et/Et (**4b**, 1.197), Bu/Bu (**5b**, 1.202) and for mixed substituents Et/Bu (**10b**, 1.227 and **10c**, 1.213).

3.3. Quantitation of products by ^{31}P NMR spectroscopy of reaction mixtures

The same experimental procedure was used to quantify the products of each reaction by ^{31}P NMR spectra of the reaction mixtures; each reaction was stirred for three days at room temperature, filtered, the solvent removed under reduced pressure and a portion of each crude sample dissolved in $CDCl_3$ and the proton-decoupled ^{31}P NMR measured using the same NMR conditions. The relative ratios of the starting material **1**, spiro and ansa derivatives and any other products (open chain, bridged or polymeric material) were estimated from the integrated spectrum and the proportions (%) of each component are summarized in Table 4. A good example is shown in Fig. 1 for the ^{31}P NMR spectrum of the

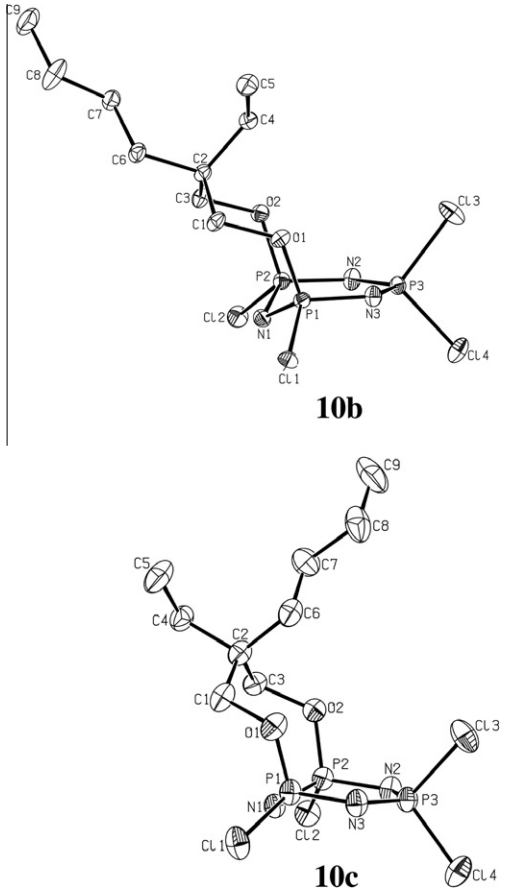


Fig. 4. The crystal structures of compounds **10b** (*n*-butyl exo) and **10c** (*n*-butyl endo).

reaction mixture of cyclotriphosphazene, **1**, with 2-butyl-2-ethyl-1,3-propandiol, which demonstrates the formation of the spiro (**10a**) and the two ansa derivatives (**10b**, **10c**) from this reaction. It should be noted that there is a slight preference for the exo-ansa compound (**10b**, 44%) over the endo-ansa compound (**10c**, 39%), which is consistent with a preference for the bulkier butyl moiety being exo in **10b** compared to the ethyl moiety being exo (and butyl endo) in **10c**. A similar effect is observed for the two ansa derivatives of compound **9** (relative proportions 49% and 36%), where it is likely that the bulkier propyl moiety is preferred exo (**9b**) rather than endo (**9c**) compared to the methyl group. The difference in relative proportions of endo and exo isomers is even more marked for compounds **7** and **8** because of the greater difference in bulk between the X/Y substituents, *viz.* CH_3/H in compounds **7** (ratio **7b**:**7c** *ca.* 2:1) and Ph/H in compounds **8** (ratio **8b**:**8c** *ca.* 4:1). It can be seen in Table 4 that reaction of the various 2,2′-substituted 1,3-propandiols with cyclotriphosphazene, **1**, using anhydrous pyridine as HCl receptor leads to formation of the spiro compounds (**2a**–**11a**) with only traces of ansa compounds, as found previously for reactions where **2a** [34,35] and **3a** [36] were synthesized. As expected, it is also found that the yield of spiro compounds (22–25%) with 2,2′-substituted 1,3-propandiols containing electron-withdrawing groups (compounds **6** and **11**) is significantly smaller than all the other derivatives with alkyl (or aryl) substituents (69–100%). It can also be seen in Table 4 that reaction of cyclophosphazene, **1**, with the alkoxide form of the various 2,2′-substituted 1,3-propandiols, *i.e.* in the presence of NaH, leads to formation of both spiro and ansa derivatives, except for 2,2′-substituted 1,3-propandiols containing electron-withdrawing groups (compounds **6** and **11**), where no spiro or ansa derivatives are formed. Compared to the reaction of **1** with 1,3-propandiols where the overall yield of compound **2** was only 30%, reaction of **1** with 2,2′-substituted 1,3-propandiols containing alkyl (or aryl) substituents gave significant overall yield of products for mono-substituted derivatives (84% for **7** and 90% for **8**) and even greater yields for di-substituted alkyl derivatives with bulkier groups (91% for **3**, Me/Me; 97% for **9**, **10**, mixed substituents; 98% for **4**, Et/Et; and 99% for **5**, Bu/Bu).

*3.4. Rationalisation of the effect of gem 2,2′-disubstitution in the formation of spiro- and ansa-1,3-propandioxy derivatives of cyclotriphosphazene, **1***

Previous work has shown that reaction of cyclophosphazene, **1**, with diols can give spiro and ansa cyclic products and, when pyridine is used as base to neutralise the hydrochloride formed, the major product is the spiro compound, because of the great thermodynamic stability of the five-, six-, or seven- membered spiro rings [40–44]. The preference for spiro over ansa 1,3-propanedioxy derivatives of cyclophosphazene is not surprising given that the spiro ring is a six-membered thermodynamically stable chair form, in contrast to the eight-membered strained ansa ring [15]. It has

Table 4
Estimation by ^{31}P NMR spectroscopy of the relative proportions of the spiro and ansa products from the reaction of **1** with various 1,3-propanediols under different solution conditions.

$CXY(CH_2OH)_2$		Yield of products (%)[a]									
		Pyridine, THF					NaH, THF				
X, Y	Compound	sp	an1	an2	Trimer	Other	sp	an1	an2	Trimer	Other
H, H	**2**	67	–	–	31	2	20	10	–	39	31
(i) mono-substituted											
CH_3, H	**7**	69	2	1	4	24	41	28	15	7	9
Ph, H	**8**	100	–	–	–	–	52	30	8	–	10
(ii) di-substituted (symmetrical)											
CH_3, CH_3	**3**	70	12	–	6	12	23	68	–	6	3
C_2H_5, C_2H_5	**4**	94	–	–	2	4	11	87	–	1	1
C_4H_9, C_4H_9	**5**	100	–	–	–	–	11	88	–	1	–
(iii) di-substituted (unsymmetrical)											
CH_3, C_3H_7	**9**	88	–	–	1	11	12	49	36	3	–
C_2H_5, C_4H_9	**10**	98	–	–	2	–	14	44	39	3	–
(iv) electron-withdrawing substituents											
CO_2Et	**6**	25	–	–	5	70	–	–	–	39	61
Br, NO_2	**11**	22	–	–	3	75	–	–	–	100	–

[a] Key: sp: spiro compound; an1 and an2: exo and endo-ansa compounds; trimer: starting compound **1**; other: other product.

been observed that the formation of ansa derivatives is promoted by using the more reactive sodium alkoxides (rather than the less reactive neutral propanediol and tertiary base) [24] which has been rationalised in terms of the co-coordination (cooperative binding) with the attacking oxy-nucleophile of the sodium counterion already present in an oxy-substituent [40,45]. These observations were investigated more systematically and quantitatively in this work in the reaction of **1** with substituted 1,3-propanediols, in which the central carbon atom in $CXY(CH_2OH)_2$ has various substituents X and Y (Scheme 1) and the relative ratios of spiro and ansa compounds in the crude reaction mixtures were estimated by ^{31}P NMR spectroscopy (Table 4).

Using pyridine as the base to neutralise the hydrochloride formed, the spiro derivative is formed virtually exclusively for all the diols and the yield depends mainly on the electronic properties of the substituents X and Y. This is shown clearly in Fig. 5a; the two diols containing electron-withdrawing groups [with either two $COOC_2H_5$ or NO_2/Br groups] make the $CH_2–O^-$ group slightly less electron-rich and only a small amount (*ca.* 25%) of spiro compound is formed; the diols containing two bulky alkyl groups, which make the $CH_2–O^-$ group slightly more electron-rich and significant amounts (>85%) of the spiro compound is formed; and 1,3-propanediol (X = Y = H) and the two diols containing one (X = H, Y = Me) or two Me groups (X = Y = Me) result in an intermediate amount of spiro compound (*ca.* 67–70%) being formed. In each of these three groups the size of the substituents X and Y has only a relatively small effect on the formation of spiro compounds (Fig. 5a), though there is a significant increase in the formation of spiro compounds from X = Y = Me (*ca.* 70%) to the other spiro compounds (>88%) with larger alkyl groups and then the expected small progressive increase in the formation of spiro compounds for increasing size of the alkyl group(s) as a result of the *gem*-dialkyl effect [6], or with 2-phenyl-1,3-propandiol, possibly due to the steric and mesomeric effect of the phenyl group under these neutral reaction conditions [46].

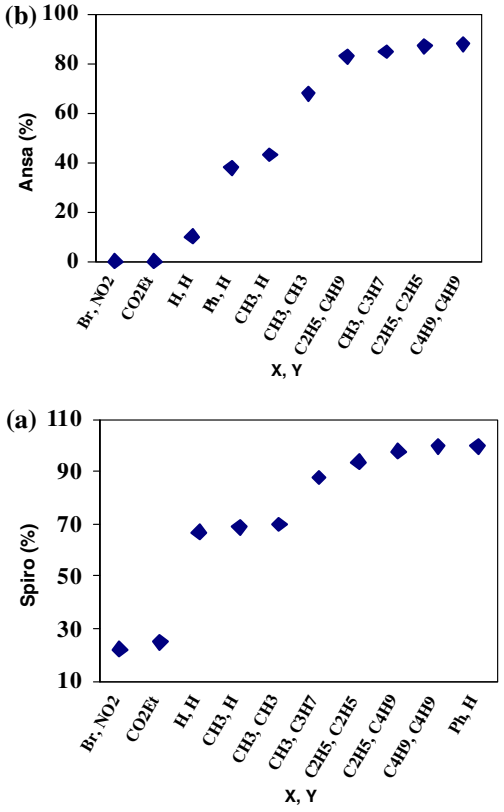


Fig. 5. (a) Yield (%) of spiro products for reactions using pyridine in THF; (b) total yield (%) of ansa products for reactions using NaH in THF.

In the reaction of **1** with the alkoxide form of the diols, both spiro and ansa derivatives may be formed (Table 4). Although no ansa (or spiro) compounds are found for the two diols containing electron-withdrawing groups [for either two $COOC_2H_5$ or NO_2/Br groups], significant amounts (>83%) of the ansa compounds are formed with the diols containing two bulky alkyl groups, and intermediate amounts of ansa compounds are produced from diols containing none (H/H, 10%), one (Me/H and Ph/H, *ca.* 40%) or two small substituents (Me/Me, *ca.* 70%). As two types of ansa compounds are formed when the substituents X and Y are different, it is necessary to compare the sum total of ansa compounds with the relative proportion formed when substituents X and Y are the same. It can be seen in Fig. 5b that the formation of ansa compounds mainly reflects the electronic properties of the substituents; all the diols with bulkier substituents have very similar relative proportions of total ansa compound(s) and so there appears to be a negligible steric effect under these very basic reaction conditions. The results using 2-phenyl-1,3-propandiol and 2-methyl-1,3-propandiol are very similar and in line with those that are intermediate between the extremes of electron-pulling and electron-pushing substituents, indicating that the very basic reaction conditions dominate over steric and any mesomeric effects.

4. Conclusions

Although the reactions of bidentate ligands (*e.g.* diols, diamines and polyamines) with cyclophosphazene, $N_3P_3Cl_6$ **1**, have been investigated and reviewed over the years, this is the first systematic investigation of the effect of substituents in a bidentate ligand on the formation of products. The reactions of **1** with various 2,2′-derivatives of 1,3-propandiol, $CXY(CH_2OH)_2$, give mainly spiro (6-membered ring) and/or ansa (8-membered ring) di-substituted derivatives, which have been characterized by NMR spectroscopy and, in some cases, by X-ray crystallography. Quantitation of the products in the reaction mixtures by ^{31}P NMR spectroscopy confirms that the spiro derivatives are overwhelmingly formed using pyridine as the base to neutralise the hydrochloride formed, with *ca.* 100% selectivity in some cases; it is found that the yield depends mainly on the electronic properties of the substituents X and Y, whereas the size of X and Y has only a relatively small effect on the formation of spiro compounds (Fig. 5a). On the other hand, although both spiro and ansa derivatives may be formed in the reaction of **1** with the alkoxide form of the diols, there are significant proportions of total ansa compounds for diols with alkyl (aryl) substituents, with *ca.* 90% selectivity in some cases; the relative proportions of ansa compounds also mainly reflect the electronic properties of the substituents X and Y (Fig. 5b) under these very basic reaction conditions. These results may also be used to aid the optimization of conditions for the selective formation of spiro or ansa derivatives of cyclophosphazenes.

Acknowledgments

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Appendix A. Supplementary data

CCDC 737153, 737154, 737155, 737156, 737157, 737158, 737159, 737160, 737161 and 737162 contains 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. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2010.07.005.

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