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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

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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 ($X \neq Y$, methyl/H, phenyl/H, methyl/*n*-propyl, ethyl/*n*-butyl and Br/NO_2) 1,3-propandiols. The products were analysed by ^1H 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

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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.

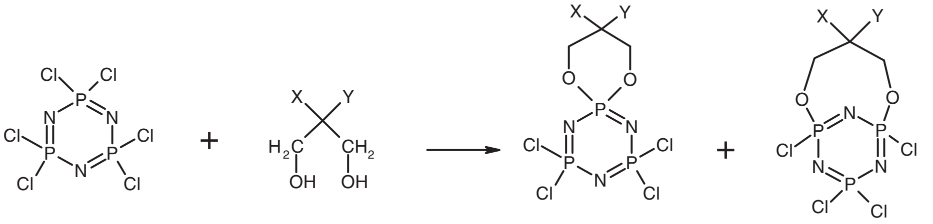
2. Experimental

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.