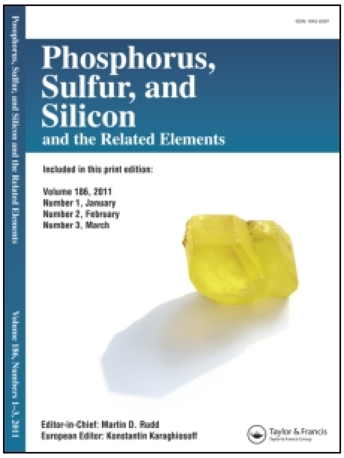


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE EFFECT OF ADDED LITHIUM CATIONS ON THE STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT PHOSPHORUS

C. Richard Hall[a]; Thomas D. Inch[a]; Colin Pottage[a]
[a] Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, England

To cite this Article Hall, C. Richard , Inch, Thomas D. and Pottage, Colin(1981) 'THE EFFECT OF ADDED LITHIUM CATIONS ON THE STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT PHOSPHORUS', Phosphorus, Sulfur, and Silicon and the Related Elements, 10: 2, 229 — 232

To link to this Article: DOI: 10.1080/03086648108077510

URL: http://dx.doi.org/10.1080/03086648108077510

Phosphorus and Sulfur, 1981, Vol. 10, pp. 229–232
0308-664X/81/1002-0229$06.50/0

THE EFFECT OF ADDED LITHIUM CATIONS ON THE STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT PHOSPHORUS

C. RICHARD HALL, THOMAS D. INCH and COLIN POTTAGE

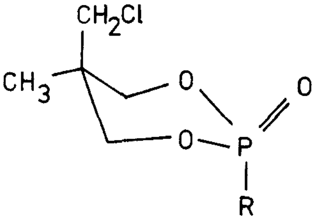
Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, SP4 OJQ, England

(*Received October 20, 1980*)

Added lithium cation has no effect on the stereochemical outcome of the displacement of chloride or *p*-nitrophenoxide from phosphorus in acyclic and some cyclic molecules. In other cyclic systems the preponderant stereochemistry can be biased from inversion to retention of configuration.

INTRODUCTION

The stereochemistry of displacement reactions at phosphorus in some 1,3,2-dioxaphosphorinan-2-ones has been reported to be influenced by added cations; lithium ion in particular has a significant effect.[1,2] For example, the *p*-nitrophenyl derivative **1**, on treatment with one equivalent of potassium *p*-methylphenoxide in dimethylformamide, afforded a 1 : 1 mixture of the retention product **3** and the inversion product **4** whereas under similar conditions, but in the presence of two equivalents of lithium perchlorate, the ratio favouring the retention product **3** was 10:1. Also, the chloridate **5** on treatment with *p*-methoxyphenol-triethylamine in acetonitrile afforded preponderantly (91%) the inverson product **6** in the absence of added cations but gave preponderantly (96%) the retention product **7** when two equivalents of lithium perchlorate were added to the reaction mixture.[2]



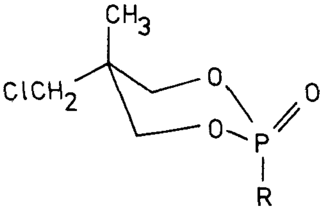
R

1 $OC_6H_4NO_2$ (p)

3 OC_6H_4Me (p)

5 Cl

7 OC_6H_4OMe (p)



R

2 $OC_6H_4NO_2$ (p)

4 OC_6H_4Me (p)

6 OC_6H_4OMe (p)

19 OPh

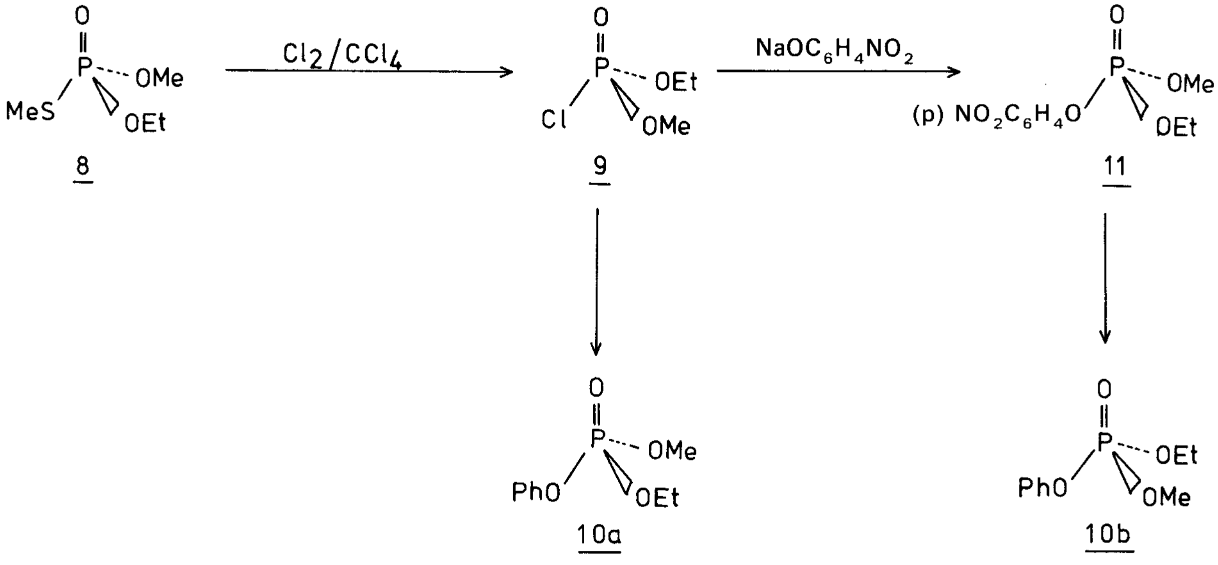
In this paper we report studies to determine whether or not lithium ions have similar effects on displacements at phosphorus in acyclic and other cyclic systems.

RESULTS

Acyclic Systems

Ethyl methyl phosphorochloridate **9**, prepared by treating the phosphorothioate **8** with chlorine in carbon tetrachloride, was enantiomerically pure before distillation but a 4:1 mixture of S:R enantiomers when distilled.[3] The enantiomer purity of **9** and all derived products was determined by a ^1H n.m.r. procedure using the chiral shift reagent $Eu(hfc)_3$.[4] All experiments used the 4:1 S:R mixture of **9** and the stereochemistry of the reactions with respect to the major isomers is shown in Scheme 1, (provided that previous assumptions for configurational assignment are correct).[3]

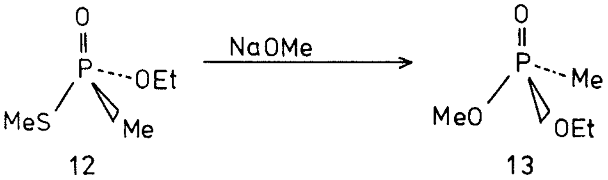
The chloridate **9** in acetonitrile with (a) sodium phenoxide, (b) phenol and triethylamine and (c)



Scheme I

phenol, triethylamine and two equivalents of lithium perchlorate afforded **10a** as the same 4:1 mixture of R:S enantiomers in each case. Similarly, the nitrophenyl derivative **11** was converted into **10b** on treatment with potassium phenoxide in DMF; the stereochemical outcome was unaffected by the addition of four equivalents of lithium perchlorate.

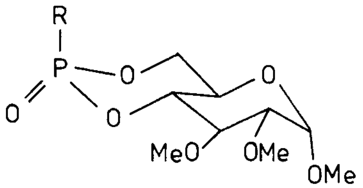
The displacement of alkylthio groups by sodium alkoxides from phosphonothioates, e.g. **12** to **13**, usually proceeds with 80–90% inversion of configuration depending on the reaction conditions and nature of substituents.[5] Although the rate of reaction was reduced by the addition of up to six equivalents of lithium perchlorate the stereochemistry of the reaction of **12** with sodium methoxide in methanol or acetonitrile was unaffected.



The conclusion from the above experiments is that added lithium ions have no effect on the stereochemistry of displacements at phosphorus in acyclic systems, even where as with **12**-methoxide, there is competition between inversion sion and retention mechanisms in the un-doped case.

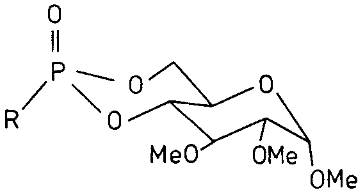
Cyclic Systems

Most experiments were carried out with the two well characterised nitrophenyl derivatives **14** and **15**.[6] Isomer **14** is thermodynamically stable and is formed rapidly by treating **15** with excess of sodium *p*-nitrophenoxide. Experiments were carried out in dimethylformamide and were monitored by ^{31}P FT n.m.r. using a JEOL JNM-FX60Q spectrometer with proton decoupling. Single phosphorus signals for **14**, **15** and product isomers were well separated.



	R
14	$OC_6H_4NO_2(p)$
17	OPh
18	Cl

On treatment with potassium phenoxide alone, or in the presence of lithium perchlorate, the more stable *p*-nitrophenyl derivative **14** underwent substitution with inversion of configuration affording



	R
15	$OC_6H_4NO_2$ (p)
16	OPh

16 and a trace of **17**, i.e. added lithium ions had no significant effect. [A similar result was obtained when the chloridate **18** was treated with phenol-triethylamine, with or without lithium perchlorate.]

The situation was not so clear for reactions of the equatorial nitrophenyl derivative **15** where there is a tendency for nitrophenoxide, displaced by phenoxide, to equilibriate **15** to **14** giving stereochemical results that are the consequence of double displacements with inversion of configuration. Thus when 1.2 equivalents of sodium phenoxide was added slowly to **15** a preponderance of the product **16** was obtained through the clear intermediacy of **14**. When mixing of **15** and sodium phenoxide was rapid, the product **17** was preponderant. Against this background it was difficult to determine the effects of added lithium perchlorate. However for one reaction in which the product ratio of **16**:**17** was unity the indications were, from observations of the relative concentrations **14**, **15**, **16** and **17** present throughout the reaction, that some **16** must result directly from **15** and not be formed just from **14**, i.e. lithium ions were promoting a mechanism leading to retention of configuration.

The above results, which showed only a small effect for added lithium ions, promoted a further (^{31}P n.m.r. monitored) investigation of the reaction of **1** and **2**. For **2**, with one equivalent of potassium phenoxide in dimethylformamide, displacement occurred with an inversion: retantion ratio of 8:1. Some conversion of **2** into **1** occurred during the reaction, but it is unlikely that total formation of **19** occurs through **1** because **2** reacts with phenoxide much more rapidly than **1** and the amount of **1** formed was insufficient to account for the retention product obtained. When the experiment was repeated in the presence of four equivalents of lithium perchlorate an inversion:retention ratio of unity was obtained. An additional experiment using lithium phenoxide as nucleophile gave an inversion:retention ratio of 2:1. Similar experiments with **1** also confirmed that lithium ions favoured the retention process although inversion:retention ratios as high as the 1:10 reported for a *p*-methylphenoxide nucleophile were not obtained.[1]

DISCUSSION

The results reported in this paper, that added lithium ions affect displacements in some ring systems but not in others, and apparently have no significant effect on the stereochemistry of reactions in acyclic molecules (although the rate of such reactions may be altered) parallels other results which show that the stereochemistry of displacements in 6-membered rings depends on nucleophile, solvent and leaving group in ways that are not apparent in acyclic systems. In 6-membered rings, it has been suggested[7] that reactions with inversion of configuration occur by direct attack at phosphorus opposite the leaving group, whereas reactions with retention occur by initial attack opposite a ring hetero-atom to form a trigonal bypyramidal intermediate which undergoes a single pseudorotation before the leaving group departs from an apical position. The inversion : retention product ratio depends on the initial direction of attack at phosphorus and on the relative rates of various bond forming, pseudorotation, and bond breaking processes. These are obviously delicately balanced, small changes having significant effect on product stereochemistry.

Lithium ion associates with alkoxides more strongly than other alkali metals, thereby reducing the nucleophilicity of the alkoxide.[8] The consequence of this may be steric, effectively changing the bulk of the solvated nucleophile and therefore its direction of attack. Alternatively, and perhaps more likely, the major effect may be on reaction rates. For example, if the rate determining step of the inversion mechanism is nucleophilic attack at phosphorus, but for the retention mechanism is either pseudorotation or loss of the leaving group, then addition of lithium ions, and hence reduction in nucleophilicity, may be expected to reduce the rate of the inversion mechanism relative to the retention mechanism.

EXPERIMENTAL

Displacement of Chloride from **9** *by Phenol and Triethylamine*

A solution of the chloridate **9**(0.3 g) [as a 4:1 mixture of S:R enantiomers][3,4] in acetonitrile (5 ml) was added to a solution of phenol (0.18 g) and triethylamine (0.26 ml) in acetonitrile (5 ml). After 24 h the mixture was poured into an excess of water, extracted with benzene, the benzene extract was washed with a dilute solution of sodium carbonate and with water. Concention and chromatography of the residue, eluting with 1:1 light petroleum:ether, gave the phosphate **10** (0.21 g, 53 %) as a 4:1 mixture of the R:S enantiomers. In the presence of Eu(hfc)$_3$ the P—OMe signal due to the R enantiomer resonates at high field relative to that of the S enantiomer.[4]

A similar procedure but including lithium chlorate (0.4 g) in the solution of the starting chloridate **9** yielded **10** as an 85:15 ratio of R:S enantiomers.

Displacement of Chloride from 9 *by Sodium p-Nitrophenate*

A solution of sodium *p*-nitrophenate (0.69 g) in acetonitrile (10 ml) was added to a solution of **9** (0.69 g; 4:1, S:R)[3] in benzene (50 ml). After 24 h the benzene solution was washed with dilute sodium bicarbonate and with water and was concentrated to give **11** (0.8 g, 71 %) as a light yellow oil. ^{1}H n.m.r. in the presence of Eu(hfc)$_3$ showed **11** was a 4:1 ratio of enantiomers. The P—OMe signal of the major enantiomer resonates at high field with respect to the minor enantiomer.

Displacement of p-Nitrophenate from 11 *by Potassium Phenoxide*

A solution of potassium phenate (0.1 g) in dimethyl formamide (5 ml) was added to a solution of **11** (0.2 g) in dimethyl formamide (5 ml). After 2 h the mixture was poured into dilute sodium carbonate solution and was extracted with ether, and the ether extract dried and concentrated. Chromatography of the residue, eluting with 1:1 light petroleum:ether, gave the phosphate **10** (0.14 g, 85 %) as a 4:1 ratio of the S:R enantiomers.

A similar result was obtained when lithium chlorate (0.32 g) was included in the initial solution of **11**.

Displacement Reactions from Cyclic Phosphates

Authentic samples of the cyclic phosphates involved were prepared as described in Refs. 1, 2, 6 and 7. Displacement reactions were constantly monitored by ^{31}P n.m.r. spectroscopy using a Jeol JNM-FX60Q instrument. Experimental procedure used is typified by that quoted above for the corresponding reactions of the acyclic analogues.

REFERENCES

1. M. Bauman and W. S. Wadsworth, *J. Amer. Chem. Soc.*, **100**, 6388 (1978).
2. W. S. Wadsworth, *J. Org. Chem.*, **38**, 2921 (1973).
3. C. R. Hall and T. D. Inch, *J.C.S. Perkin I*, 1104 (1979).
4. C. R. Hall and T. D. Inch, *Phosphorus and Sulphur*, **7**, 171 (1979).
5. D. B. Cooper, C. R. Hall, J. M. Harrison, and T. D. Inch, *J.C.S. Perkin I*, 1969 (1977).
6. J. M. Harrison, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1053 (1974).
7. C. R. Hall and T. D. Inch, *Tetrahedron*, **36**, 2059 (1980).
8. J. H. Exner and E. C. Steiner, *J. Amer. Chem. Soc.*, **96**, 1782 (1974).