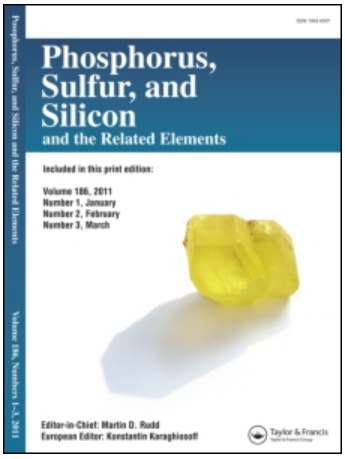

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PHOSPHORYL AND THIOPHOSPHORYL TRANSFER REACTIONS: STEREOCHEMICAL IMPERATIVES FOR METAPHOSPHATE AND THIOMETAPHOSPHATE

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Abstract The stereochemical courses of phosphoryl transfer reactions in aprotic solvents and thiophosphoryl transfer reactions in protic solvent have been determined. The extensive racemisation observed in both instances is discussed in terms of metaphosphate and thiometaphosphate intermediates of significant life-times.

INTRODUCTION

Enzyme catalysed phosphoryl transfer reactions are ubiquitous in metabolism. Studies on model reactions of phosphate monoesters have suggested a dissociative mechanism involving monomeric metaphosphate.[1,2] However, stereochemical investigations of a large number of enzyme catalysed phosphoryl transfer reactions[3] and of the solvolysis of aryl phosphates in aqueous solutions[4] have shown these to proceed with clean inversion of configuration, which would apparently rule out a "free" metaphosphate. We report here some of the first stereochemical studies of phosphoryl transfer reactions in aprotic solvents that proceed with substantial racemisation of configuration.[5,6] We also report methods for the synthesis and configurational analysis of chiral [$^{16}O,^{18}O$]thiophosphate monoesters. Using these methods we have determined the stereochemical course of the first simple thiophosphoryl transfer reaction.

RESULTS AND DISCUSSION

It has been shown that adenosine 5'-diphosphate trianion will phosphorylate even hindered alcohols such as ^{t}BuOH at appreciable rates particularly in acetonitrile solvent. We have studied the stereochemistry of this reaction using [β-$^{16}O,^{17}O,^{18}O$]ADP, Figure 1.[6] The synthesis[7] and configurational analysis[8] were achieved

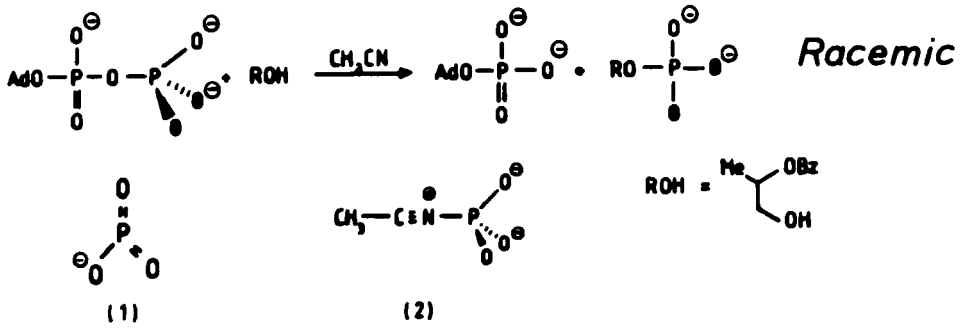


FIGURE 1 Stereochemistry of Phosphoryl Transfer from ADP.

by the published methods and the results of this study have indicated that the phosphoryl transfer is accompanied by almost complete racemisation of configuration. This result would accord with a "free" metaphosphate intermediate (1). However, there is an alternative explanation namely that a solvent coordinated zwitterion such as (2) is involved and that the racemisation of configuration arises because of multiple phosphoryl transfer reactions.

P^1,P^1-Disubstituted pyrophosphate dianions are unique in their reactivity amongst pyrophosphates in that they spontaneously decompose to phosphate diester and a species that shows many of the properties expected of monomeric metaphosphate. In order to study the stereochemistry of such phosphoryl transfer reactions P^1-O-ethyl-P^1-thio-P^2[^{16}O,^{17}O,^{18}O] pyrophosphate has been synthesised by the literature procedures.[5,7] Upon methylation with a variety of methylating agents, the P^1,P^1-disubstituted pyrophosphate is generated in situ, and as the dianion, spontaneously decomposes. In the presence of an alcohol, the corresponding phosphate ester and O-ethyl-S-methyl thiophosphate are obtained in good yield. Using 2-O-benzyl-(*S*)-propane-1,2-diol the phosphate ester was obtained, Figure 2, and the isotopic configurational analysis was achieved by the literature procedure[8] using high field ^{31}P NMR spectroscopy.

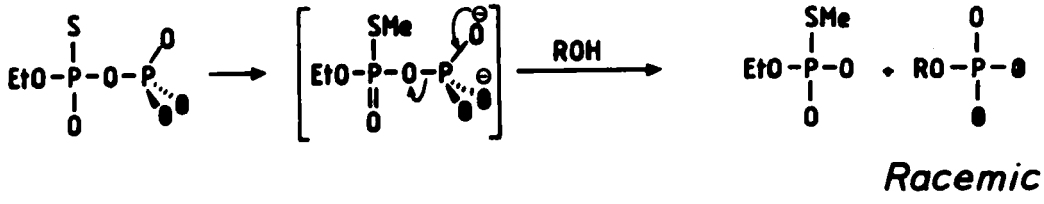


FIGURE 2 Phosphoryl Transfer from a P^1,P^1-Pyrophosphate Diester.

When the phosphoryl transfer reaction was conducted in dichloro-

methane the isolated product showed considerable racemisation of configuration at phosphorus with a small amount of excess inversion of configuration.[5] We have recently shown that the same reaction carried out in acetonitrile occurs with ***complete racemisation***.

Breslow[9] has reported that thiophosphates react more readily via a dissociative mechanism than the corresponding phosphates. We have sought to investigate the stereochemistry of a simple thiophosphoryl transfer reaction to compare with the results of the phosphoryl transfer reactions. We have synthesised O-ethyl S_p[^{16}O,^{18}O]thiophosphate (3) and O-p-nitrophenyl R_p[^{16}O,^{18}O]-thiophosphate (4) by variants of the general synthesis. Analysis of the absolute configuration of (3) and (4) has been achieved as shown in Figure 3. The position of the ^{18}O in (6a) and (6b) is located by the upfield shift on the ^{31}P NMR resonance. The ^{31}P NMR spectrum together with the assignments for the analysis of O-ethyl S_p[^{16}O,^{18}O]thiophosphate are shown in Figure 3.

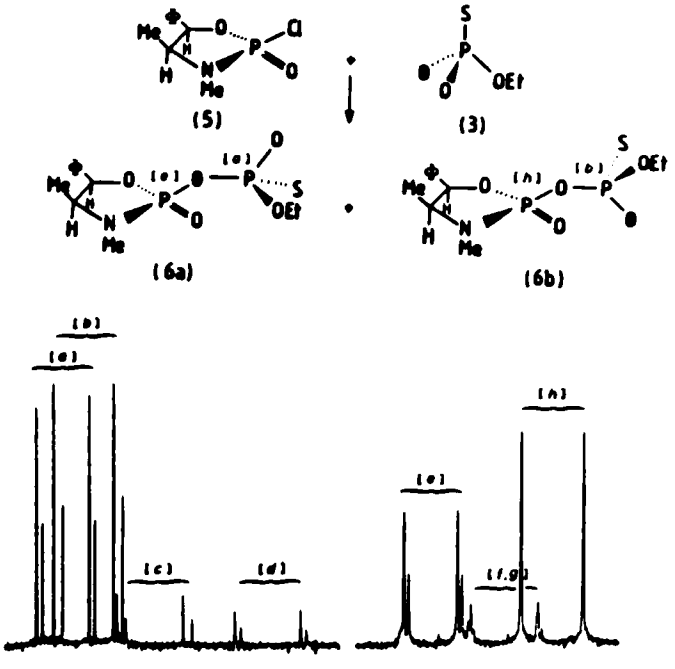
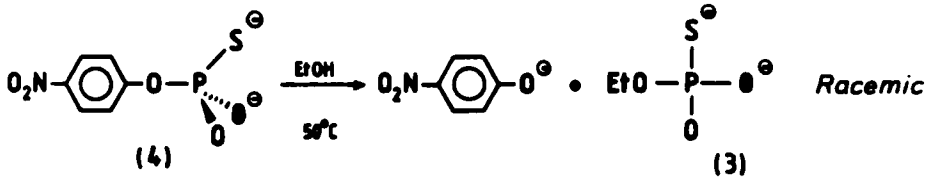


FIGURE 3 Configurational Analysis of Ethyl [^{16}O,^{18}O]thio-phosphate.

The stereochemical course of the solvolysis of R_p[^{16}O,^{18}O]p-nitrophenyl thiophosphate dianion in ethanol has been determined,

Figure 4. The resulting ethyl thiophosphate, *via* the above analysis (Figure 3), can be shown to be largely racemic. The appropriate controls confirmed that this racemisation arises during the thiophosphoryl transfer step.



(4) (3)

FIGURE 4 Solvolysis of p-Nitrophenyl [^{16}O,^{18}O]thiophosphate.

CONCLUSION

Stereochemical evidence would support a metaphosphate intermediate in phosphoryl transfer reactions conducted in aprotic solvents only. In contrast thiophosphoryl transfer reactions appear to proceed with a considerable loss of stereochemical integrity even in protic solvents which would suggest the involvement of a thiometaphosphate intermediate and that such an intermediate is a longer lived intermediate that the parent metaphosphate.

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