Planarity of the Intermediate in Phosphoramidothioate Hydrolysis

By A. F. GERRARD and N. K. HAMER
(*University Chemical Laboratory, Cambridge*)

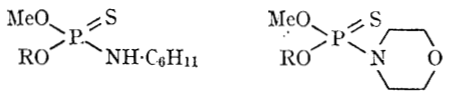
THE intervention of unimolecular metaphosphate intermediates has been postulated on several occasions to account for kinetic measurements and product distributions observed in the reaction of nucleophiles with certain partially esterified derivatives of phosphoric acid[1-3] but hitherto a direct demonstration of their existence was lacking. We present stereochemical evidence to indicate that a symmetrical intermediate, analogous to a monomeric metaphosphate, is formed in the basic solvolysis of methyl *p*-nitrophenyl *N*-cyclohexylphosphoramidothioate (I).

Treatment of the silver salt of methyl *p*-nitrophenyl hydrogen phosphorothioate[4] with phosphorus pentachloride followed (without isolation of the phosphorochloridothioate) by cyclohexylamine gave (I) (racemate m.p. 83—83·5°) in good yield. When the (+)-enantiomer[4] of the acid was used there was obtained, after several recrystallisations, the (+)-enantiomer of (I) (m.p. 58—58·5° $[\phi]_D$ + 60°). An analogous procedure gave the corresponding phosphoromorpholidothioate ester (II) (racemate m.p. 82—83°) but the enantiomers of this have not yet been obtained optically pure.

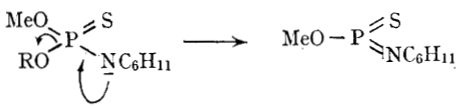
Both (I) and (II) were hydrolysed quantitatively by sodium hydroxide to *p*-nitrophenol and the corresponding methyl hydrogen phosphoramidothioates (III)[5] and (IV). In dioxan–water (4 : 6) at 39° (ionic strength 0·10) the first-order rate constants for the hydrolysis of both (I) and (II) showed an approximate linear dependence on sodium hydroxide concentration, those for (I) being a factor of 10^2 greater than those for (II). With sodium methoxide in methanol the amounts of *p*-nitrophenol liberated from (I) and (II) were 1·00 and 0·94 moles respectively [small amounts, *ca.*

5% of *p*-nitroanisole and (IV) were also formed from (II)] which indicates that both compounds undergo substitution predominantly at phosphorus rather than on the aryl nucleus.[6] When the (+)-enantiomer of (I) was hydrolysed with sodium hydroxide it was found that although the product (III) was racemic neither (I) itself nor (III) [(+)-form] underwent racemisation under the conditions of the hydrolysis. In contrast a specimen of (II) (m.p. 69—72°, $[\phi]_D$ + 19°) under similar conditions gave (IV) ($[\phi]_D$ −9° isolated as potassium salt).

It seems clear that, during the hydrolysis of (I), a symmetrical intermediate is formed and thus both the stereochemistry and rate variation with hydroxide ion are explicable in terms of a mechanism analogous to that proposed by Traylor and Westheimer[3] from studies on phosphordiamidic halides. This supposes that the rate-determining step is the liberation of *p*-nitrophenate ion from the anion of (I) to give (V) which is analogous to a monomeric metaphosphate—a species expected to be planar. The hydrolysis of (II) on the other hand would appear to involve a direct displacement on phosphorus by the nucleophile and while the difference in rate between (I) and (II) is rather smaller than that observed between comparable phosphoramidic halides[3,7] (a factor of 10^2 as against 10^3—10^6), this may, in part, be attributed to the fact that *p*-nitrophenate ion is a poorer leaving group than halide ion. This rather small difference in solvolysis rates emphasises that, even with compounds of the type (I), the kinetic advantage of the "metaphosphate" reaction over the direct S_N2 (P) attack by OH^- is by no means overwhelming. Hence the present results need not conflict with those of Coult and Green[8] who have shown that *NN'*-disubstituted *p*-nitrophenyl phosphorodiamidates undergo reaction with HO_2^- (a much more powerful nucleophile for phosphorus than OH^-) by an S_N2 (P) mechanism.



(I) R = *p*-NO_2·C_6H_4 (II) R = *p*-NO_2·C_6H_4
(III) R = H (IV) R = H



(V)

All new compounds gave satisfactory elemental analyses and had spectra (i.r. and n.m.r.) consistent with the proposed structures. Rotations were determined in methanol (*c* = 0·02).

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