Acyl (Phosphoryl) Transfer by Use of *gem*-Dihalides

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gem-Dihalides are capable of promoting acyl transfer; for example, *sym*-diesters of pyrophosphoric acid are formed when 4-methoxybenzylidene dichloride is heated with a monoester of orthophosphoric acid. In the presence of an alcohol, ester formation occurs. Analogous acylations by use of carboxylic acids can be observed.

TREATMENT of an α-dichloro-ether with a carboxylic acid leads initially to the formation of the unstable orthoformyl chloride (I); further reaction can give rise to the diacyloxymethyl ether (II).[1,2] On pyrolysis (I)

$$R^1O{\cdot}CHCl(O{\cdot}COR^1) \quad \text{(I)} \qquad R^1O{\cdot}CH(O{\cdot}COR^2)_2 \quad \text{(II)}$$

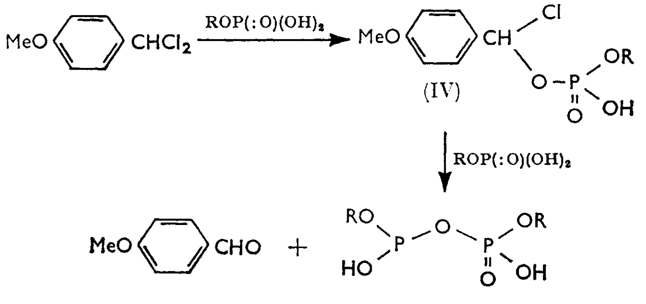
$$R^1R^2CCl_2 \quad \text{(III)}$$

decomposes[2] to the acyl chloride $R^2CO{\cdot}Cl$, and the formate ester, HCO_2R^1. Under similar conditions (II) yields the acid anhydride together with the same formate ester.[3] These reactions have been utilised in the synthesis of both acid anhydrides and peptides.[4,5]

Recently we reported that suitably reactive *gem*-dihalides were capable of promoting phosphoryl transfer.[6] The rate constant for S_N1 solvolysis of 4-methoxybenzylidene dichloride (III; $R^1 = H, R^2 = 4\text{-MeO}{\cdot}C_6H_4$) is considerably greater than that of 4-methoxybenzyl chloride,[7] owing, presumably, to the stabilisation of the cation by incorporation of the *p*-electrons of the chlorine atom into the delocalised π-system. The possibility of the formation of a stable carbonium ion suggested[6] that (III; $R^1 = H, R^2 = 4\text{-MeO}{\cdot}C_6H_4$) should be capable of promoting phosphoryl transfer and this has been subsequently confirmed by use of (III; $R^1 = R^2 = Ph$).[8]

In our hands (III; $R^1 = H, R^2 = 4\text{-MeO}{\cdot}C_6H_4$) together with a monoester of phosphoric acid, when heated under reflux in benzene solution, gives the corresponding P^1P^2-diester of pyrophosphoric acid in almost quantitative yield. Copious fumes of hydrogen chloride are evolved; the only other identifiable product is 4-methoxybenzaldehyde. Similar promotion of phosphoryl transfer is observed with (III; $R^1 = H, R^2 = 2\text{-MeO}{\cdot}C_6H_4$) and (III; $R^1 = H, R^2 = MeO$); however, (III; $R^1 = H, R^2 = Ph$) and (III; $R^1 = H, R^2 = 3\text{-NO}_2{\cdot}C_6H_4$) give virtually no pyrophosphate under the same conditions.

The reaction presumably proceeds *via* the formation of (IV) which is a P–XYZ phosphorylating system.[9] Pyrophosphate formation can occur by direct attack of another molecule of the phosphate ester on (IV) (see Scheme) with expulsion of chloride ion. However, attack by chloride at the phosphoryl centre of (IV) to give a phosphorochloridate cannot be ruled out, nor can the cyclic rearrangement of (V). Electrophoretic investigation of the reaction after a few min. did not reveal the presence of polyphosphate esters, and we conclude that a trimetaphosphate is not involved in the



SCHEME

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[2] A. Rieche and H. Gross, *Chem. Ber.*, 1959, **92**, 83.

[3] H. Gross and A. Rieche, *Chem. Ber.*, 1961, **94**, 538.

[4] H. Gross and E. Hoft, *Z. Chem.*, 1964, **4**, 401.

[5] K. Poduška and H. Gross, *Chem. Ber.*, 1961, **94**, 527.

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[7] J. Hine and R. J. Rosscup, *J. Amer. Chem. Soc.*, 1960, **82**, 6115.

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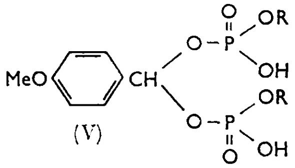
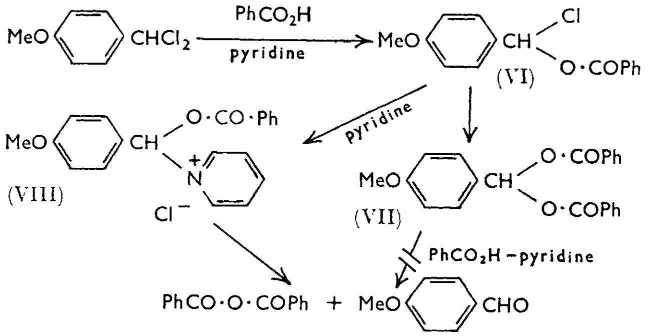
phosphorylation reaction (*cf.* ref. 10). P^1P^2-Diesters of pyrophosphoric acid, however, can be activated by *gem*-dihalides. Addition of an alcohol and a further amount of (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) to the mixture obtained on reaction of phenyl dihydrogen phosphate with (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) after pyrophosphate formation is complete, gives rise to phosphodiesters. Good yields of such phosphodiesters (70—80%) are obtained when alcohols are included in the reaction mixture from the outset. Phosphodiesters are probably formed by attack of the alcohol either on (IV) or on its pyrophosphate analogue. No reaction can be detected between a diester of phosphoric acid and (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) in benzene solution.



(V)

Acyl transfer is also observed when benzoic acid and (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) are used in pyridine solution. In contrast, 4-methoxybenzylidene dibenzoate (VII) is formed when benzoic acid is heated with (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) under reflux in benzene; (VII) is unchanged when heated in pyridine with or without added benzoic acid but is completely converted into benzoic anhydride on pyrolysis at 220°. This suggests that the intermediates (VI) or (VIII) are attacked by benzoate ion at the carbonyl centre rather than at the benzylic carbon atom.



Attempts to prepare esters of benzoic acid by the above reaction gave low yields (*ca.* 15%) presumably owing to competitive attack by the alcohol on (III).

The reaction between (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) and phenyl dihydrogen phosphate is not greatly affected in rate or in product composition when pyridine is used as solvent. However, trimetaphosphate (80%), unaccompanied by pyrophosphate, is formed when a solution of the trianion of orthophosphoric acid is heated in pyridine with (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$); in dioxan, only slow formation of pyrophosphate can be detected.

The trimetaphosphate appears to arise from a disproportionation of linear tetraphosphate, since the tetra-anion of pyrophosphoric acid is converted into trimetaphosphate (75%) and orthophosphate (25%) by the action of (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) in pyridine. The disproportionation reaction does not take place when dioxan is used as solvent. Pyridine-catalysed dismutation reactions of adenosine polyphosphates are known to take place quite readily,[11] but cyclic trimetaphosphate esters have not been detected, presumably because of their high lability.

Neither diphenyl phosphoric acid nor its tetra-n-butylammonium or pyridinium salts when treated with (III; $R^1 = R^2 = 4\text{-MeO}\cdot C_6H_4$) in benzene or pyridine solution gives any tetraphenyl pyrophosphate or 4-methoxybenzaldehyde under conditions in which the monoester undergoes complete conversion into the pyrophosphate diester.

EXPERIMENTAL

Paper chromatography was carried out with Whatman No. 30 paper [solvent propan-2-ol–ammonia–water (8 : 1 : 1)]. Phosphates were detected by the method of Hanes and Isherwood [12] and their relative amounts were determined by the method of Usher.[13] In all reactions, particular attention was paid to the exclusion of moisture.

P^1P^2-*Diphenyl Pyrophosphate.*—4-Methoxybenzylidene dichloride [14] (0·76 g., 0·4 mmole) was added to a solution of phenyl dihydrogen phosphate (0·07 g., 0·4 mmole) in benzene (5 ml.) and the mixture was heated under reflux for 2 hr., during which time gaseous hydrogen chloride was evolved and the solution turned deep red. When the mixture was cool, the benzene was removed under reduced pressure to leave a gum which was taken up in acetone (50 ml.) containing cyclohexylamine (2 ml.). The solution was set aside at 0° until precipitation of chromatographically pure dicyclohexylammonium P^1P^2-diphenyl pyrophosphate (0·094 g., 90%; m.p. 252—254°) was complete. P^1P^2-Bis-4-chlorophenyl pyrophosphate (90%; m.p. 272—275°) was obtained in similar manner from 4-chlorophenyl dihydrogen phosphate (1 mmole) and (III; $R^1 = H$, $R^2 = 4\text{-MeO}\cdot C_6H_4$) (1 mmole). There was no discernible reaction with diphenyl hydrogen phosphate nor with its tetra-n-butylammonium salt under these conditions.

When the reaction with phenyl dihydrogen phosphate was interrupted after 25 min. and examined by electrophoresis at pH 8·3, only phenyl phosphate and P^1P^2-diphenyl pyrophosphate could be detected. The addition of a two-fold molar excess of water reduced the pyrophosphate yield to 30%; a five-fold molar excess of water inhibited the reaction completely.

4-*Methoxybenzaldehyde.*—From a reaction similar to that outlined above, 4-methoxybenzaldehyde was isolated by preparative t.l.c. The aldehyde had i.r. and n.m.r. spectra identical with those of an authentic sample. The yield (70%) was conveniently estimated from the n.m.r. spectrum

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[11] W. E. Wehrli and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 3760.

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[14] H. Schmidt, *Ber.*, 1908, **41**, 2331.

of the reaction mixture by comparison of the signal due to the aldehydic proton with that of the methoxy-protons.

Phosphoryl Transfer with Other gem-*Dihalides.*—The phosphorylation reactions described above were carried out with equal success with (III; R^1 = H, R^2 = 2-MeO·C_6H_4); 2-methoxybenzaldehyde was isolated by preparative t.l.c. on alumina. When (III; R^1 = H, R^2 = MeO) was used, P^1P^2-diphenyl pyrophosphate was formed (70%) together with methyl formate (33%). The latter, which was the only volatile product, was collected by preparative g.l.c., (Wilkens Autoprep, 20 ft. × 3/8 in., 30% S.E. 30 column, 82°) and its i.r. and n.m.r. spectra were compared with those of an authentic sample.

Phosphorylation of Alcohols.—(a) 4-*Nitrobenzyl phenyl phosphate.* 2-Methoxybenzylidene dichloride (0·91 g., 4·7 mmoles) was added to 4-nitrobenzyl alcohol (0·316 g., 2·1 mmoles) and phenyl dihydrogen phosphate (0·070 g., 0·4 mmole) in benzene (5 ml.), and the mixture was heated under reflux for 3 hr. The solvent was removed under reduced pressure and the residue was partitioned between ether and water. The ethereal layer was separated and dried (K_2CO_3). Cyclohexylamine (2 ml.) was added and the solution was evaporated to dryness. The residue (147 mg.) was dissolved in acetone (5 ml.) containing a few drops of methanol. Addition of light petroleum (b.p. 60—80°) precipitated a product which was recrystallised from chloroform–light petroleum to give cyclohexylammonium 4-nitrobenzyl phenyl phosphate (0·118 g., 72%; m.p. 188—190°) (Found: N, 6·9; P, 7·7. Calc. for $C_{19}H_{25}N_2O_6P$: N, 6·9; P, 7·6%). In similar experiments with ethyl and benzyl alcohols, paper chromatographic examination indicated good yields of ethyl phenyl phosphate and benzyl phenyl phosphate, respectively.

TABLE 1

Phosphate	Yield (%) inorganic phosphates Ortho	Pyro	Alkyl ester *
H_3PO_4	40	60	
$(Bu_4N)H_2PO_4$	78	13	9
$(Bu_4N)_2HPO_4$	77	8	15
$(Bu_4N)_3PO_4$	53	47	
$(Bu_4N)_4P_2O_7$	25	75	

* The alkyl ester was not identified but was probably a diester, as indicated by its behaviour on electrophoresis at pH 8·3 and paper chromatography in alkaline solvents.

TABLE 2

Phosphate (moles)		(III) (moles)		Product yield (%) Ortho	Pyro	Trimeta	Phenyl phosphate	Diphenyl pyrophosphate
$(Bu_4N)_3PO_4$	(1)	None		80	20			
$(Bu_4N)_3PO_4$	(1)	(R^1 = H, R^2 = 4-MeO·C_6H_4	(2)	20		80	0	0
$(Bu_4N)_4P_2O_7$	(3)	(R^1 = H, R^2 = 4-MeO·C_6H_4)	(1)	25		75		
PhOP(:O)$(OH)_2$*	(1)	(R^1 = H, R^2 = 4-MeO·C_6H_4)	(1)				20	80
PhOP(:O)$(OH)_2$*	(1)	None					75	12
PhOP(:O)$(OH)_2$*	(1)	(R^1 = H, R^2 = MeO)	(2)				50	50

* After 2 hr., products analysed by chromatography in propan-2-ol–ammonia–water.

Cyclohexylammonium 4-nitrobenzyl phenyl phosphate (45%) was obtained in analogous fashion when 4-nitrobenzyl alcohol reacted with a mixture of phenyl dihydrogen phosphate and (III; R^1 = H, R^2 = 4-MeO·C_6H_4). The cyclohexylammonium salts of benzyl phenyl phosphoric acid (32%; m.p. 149—150°) and 4-*nitrobenzyl* 4-*chlorophenyl phosphoric acid* (33%; m.p. 183—185°) (Found: C, 51·3; H, 5·9; Cl, 8·2; N, 6·4. $C_{19}H_{24}ClN_2O_6P$ requires C, 51·5; H, 5·4; Cl, 8·0; N, 6·3%) were obtained in similar fashion.

When methanol replaced benzene as the solvent, no phosphoryl transfer to solvent could be detected: phenyl dihydrogen phosphate was recovered from the reaction.

Reactions of Orthophosphate.—The dichloride (III; R^1 = H, R^2 = 4-MeO·C_6H_4) (1 mmole) and orthophosphate (1 mmole) were heated under reflux in dioxan for 5 hr. and the mixture was analysed by chromatography in the system propan-2-ol–water–trichloroacetic acid–ammonia (*d* 0·880) (75 ml. : 25 ml. : 5 g. : 0·25 ml.) (see Table 1).

When pyridine was used as solvent in the phosphorylation reaction, chromatographic analysis indicated the product ratios shown in Table 2.

Acyl Transfer from Carboxylic Acids.—(a) *In an inert solvent.* Tetramethylammonium benzoate (1·95 g., 10 mmoles) was suspended in dioxan (40 ml.) and (III; R^1 = H, R^2 = 4-MeO·C_6H_4) (0·95 g., 5 mmoles) was added; the mixture was heated under reflux for 3 hr., cooled to 20°, and filtered to remove tetramethylammonium chloride. Solvent was removed under reduced pressure and the residue was partitioned between water (40 ml.) and ether (40 ml.). The ethereal layer was separated, dried, and evaporated to leave a gum which slowly crystallised. Recrystallisation from ethanol gave 4-*methoxybenzylidene dibenzoate,* m.p. 99—100° (1·34 g., 63%) (Found: C, 73·1; H, 5·1. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%). When the dibenzoate was heated at 220° in a sealed tube, decomposition to benzoic anhydride and 4-methoxybenzaldehyde was complete within 2 hr. When the dibenzoate was heated with an excess of *p*-toluidine in a sealed tube at 220° for several hours, only a trace of 4′-methylbenzanilide was formed.

4-Methoxybenzylidene diacetate (50%; m.p. 64—65°) was also prepared by the method outlined above. In contrast to the dibenzoate, the diacetate was unstable in the presence of atmospheric moisture; it decomposed rapidly into acetic acid and 4-methoxybenzaldehyde. Complete conversion into acetic anhydride and 4-methoxybenzaldehyde occurred when the diacetate was heated in a sealed tube at 320°. When the diacetate was heated with an equimolar amount of *p*-toluidine in benzene under reflux, 4′-methylacetanilide (25%), m.p. 150—151° was obtained.

(b) *In pyridine.* Benzoic acid (0·20 g., 1·6 mmole) was dissolved in pyridine (5 ml.) and (III; R^1 = H, R^2 = 4-MeO·C_6H_4) (0·31 g., 1·6 mmole) was added. The mixture was maintained at reflux temperature for 2 hr. and then cooled. Piperidine (0·20 g., 2·35 mmoles) was added and the mixture was examined by g.l.c. (Wilkens Autoprep, 20 ft. × 3/8 in., 15% L.A.C. on Celite column, 250°). 4-Methoxybenzaldehyde (70%; 2,4-dinitrophenylhydrazone, m.p. 255—256°), benzoic acid, and *N*-benzoylpiperidine (94%; m.p. 46—47°) were present. When a solution of 4-methoxybenzylidene dibenzoate in pyridine was heated under reflux for 2 hr., the ester was recovered unchanged. Repetition in the presence of an equimolar amount of benzoic acid did not produce any benzoic anhydride.

Esterification of Benzoic Acid.—Benzoic acid (0·122 g., 1 mmole) was added to a solution of (III; $R^1 = H$, $R^2 =$ 2-MeO·C_6H_4)(0·955 g., 5 mmoles) and ethanol (0·184 g., 4 mmoles) in pyridine (5 ml.) and the mixture was heated under reflux for 2 hr. G.l.c. analysis (Wilkens Autoprep, 20 ft. × 3/8 in., 15% L.A.C. on Celite column, 200°) showed the presence of ethyl benzoate (15%) and 2-methoxybenzaldehyde. These compounds were collected and identified by comparison of their i.r. spectra with those of authentic samples. When ethanol was replaced by n-butanol, n-butyl benzoate (15%) was produced.

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