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PHOSPHORYLATION BY ACYL PHOSPHATES

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Acyl phosphates - mixed anhydrides of orthophosphoric acid, its mono or diesters, and carboxylic acids - have been demonstrated to be acylating agents(1). These anhydrides possess two reactive centres, one each being common to pyrophosphates and carboxylic-carboxylic anhydrides respectively. These centres are chemically very dissimilar, as is apparent when the reactions of pyrophosphates and carboxylic-carboxylic anhydrides with nucleophiles are compared. There is a fundamental difference in the reaction mechanisms which is most obviously revealed by the nature of their ionic products. Thus the stronger acid moiety of the pyrophosphate molecule appears as the anion. By contrast, and in the absence of steric hindrance at a carbonyl group, the weaker of the two constituent acids of a carboxylic-carboxylic anhydride becomes the anion.

When phosphoric and carboxylic acid residues are united in the acyl phosphate molecule there are two possible contrasting mechanisms by which it may react with a nucleophile. One will resemble the be-

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haviour of pyrophosphates the other carboxylic-carboxylic anhydrides. Since in practice it is found that the products are the acylated nucleophile and the phosphate anion, the latter being the stronger acid moiety in all recorded examples, the mechanism resembles that of the pyrophosphates.

Lord Todd(2) has discussed this difference between the two classes of anhydride. He suggests that it stems from the ability of the carbonyl group to form intermediate addition compounds whereas no such intermediates are formed in the parallel reactions at the phosphoryl group. In the latter case synchronous bond formation and fission occur and under these conditions the reaction that liberates the stronger ion will be energetically the more favourable. He suggested that in the case of trifluoracetyl dialkyl phosphates the disparity in acid strength of the two components might be sufficient to out-weigh the effect of the carbonyl so that these compounds might act as phosphorylating agents. This suggestion has been tested by the writer using trifluoracetyl diethyl phosphate; it was found that despite the strength of trifluoracetic acid the compound is essentially an acylating agent rather than a phosphorylating agent.

Gold(3) has shown that the position of nucleophilic attack on mixed carboxylic-carboxylic anhydrides can be influenced by steric hindrance at one of the carbonyl groups. It was thought that by a judicial choice of carboxylic acids, acyl phosphates could be prepared with hindered carbonyl groups such that the nucleophile was prevented from reacting with them. These compounds should then phosphorylate.

A series of acyl diethyl phosphates was prepared and is listed in Table I.

TABLE I

Physical Properties of Acyl Diethyl Phosphates I: $(EtO)_2P(O).O.C(O)R$

	R	m.p.	b.p./m.m.	n_D^{25}
a	- CF_3	-10°	30°/0.01	-
b	- C_6Cl_5	72-4°	-	-
c	- C_6HCl_4	76-8°	-	-
d	- $C_6H_2Cl_3$	-	81°/0.004	1.5139
e	- CPh_3	71-2°	-	-
f	- CMe_3	-	64°/0.05	1.4144
g	- COEt	-	89°/0.02	1.4106

Satisfactory analytical results and infra-red spectra were obtained for these compounds. The general method of preparation was by reaction between an acid chloride and a sodium salt in an inert solvent, usually ether. It was found to be important that the ionic reactant should be the salt of the stronger acid of the components of the anhydride. Thus sodium trifluoracetate was allowed to react with diethyl phosphorochloridate to yield trifluoracetyl diethyl phosphate (Ia). On the other hand sodium diethyl phosphate and ethyl chloroformate reacted to give ethoxy-carbonyl diethylphosphate (Ig) in good yield. After removal of the sodium chloride and ether the anhydrides were purified by distillation or crystallisation. Trifluoracetyl diethyl phosphate was collected on a cold finger at -70°. It was very unstable, about half of it disproportionating to trifluoracetic anhydride and tetraethyl pyrophosphate in 24 hours at room temperature. Ethoxycarbonyl diethyl phosphate was the most stable of the series, little change being noted after six months at room temperature. The disproportionation could be followed conveniently by changes in the infra-red spectrum. The characteristic doublet of the carboxylic-carboxylic anhydrides in the carbonyl region appeared, accompanied by a band at 940cm^{-1} typical of the P-O-P system.

Ethereal solutions of the acyl phosphates were allowed to react with aniline in ether at temperatures ranging from O° for trifluoracetyl diethyl phosphate (Ia), to 35° for pentachlorobenzoyl diethyl phosphate (Ib). Trimethylacetyl, trifluoracetyl and ethoxycarbonyl diethyl phosphates (If, Ia and Ig) were exclusively or substantially acylating agents. Triphenylacetyl diethyl phosphate (Ie) yielded 29% N-phenyl diethylphosphoramidate and 57% triphenylacetanilide in this reaction. However 2, 3, 6-trichlorobenzoyl, 2, 3, 5, 6-tetrachlorobenzoyl and pentachlorobenzoyl diethyl phosphates (Id, Ic and Ig) were essentially phosphorylating agents. In these cases the yields of phosphoramidate obtained ranged from 83 to 100%. This work will be reported in greater detail later.

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