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Transacylation. Biomimetic Synthesis of Esters of Acetic Acid

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ABSTRACT: *By mixing of β-hydroxypropyl phosphate and acetic acid in ethanol solution, ethyl acetate is produced. As found, acetyl phosphate is first formed, then it reacts with the solvent to give the final ethyl acetate product. By similar procedures, acetates of methanol, n-propanol, and n-butanol are also produced. Propylene oxide serves as a condensing agent.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:350–352, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20216

INTRODUCTION

Chemical interactions that imitate the type or the results of biochemical reactions are called biomimetic ones [1]. Many biochemical reactions proceed with the participation of a phosphate group. The typical process involves the transfer of a phosphate onto the substrate, the formation of a new chemical bond, and the liberation of the phosphate. Let us take as an example the formation of acetyl phosphate (AcP) from acetic acid (AcOH) and adenosine triphosphate (ATP), a process of phosphorylation of acetic acid (Scheme 1).

There are several methods of synthesis of AcP [2,3]. Acetyl phosphate is a macroergic compound which produces acetamides on reaction with amines and the respective esters on reaction with alcohols. However, AcP is difficult to prepare and unstable, so that it has not found any practical application in the synthesis of amides and esters.

The β-hydroxy esters of phosphoric acid may be used as phosphorylating agents [4,5]. In previous reports, we have shown how to phosphorylate D-glucose [6], deoxynucleosides [7], and glycine [8]. With an attempt to phosphorylate acetic acid with β-hydroxypropyl phosphate (β-HPP), we have found that β-hydroxypropyl acetate is also produced. The present report is the result of our studies of the reaction yielding acetyl phosphate and the subsequent interaction of the latter with the glycol present in the system to produce the respective acetic acid ester.

RESULTS AND DISCUSSION

The phosphorylation of AcOH with β-HPP was monitored by ^{1}H-NMR spectroscopy. A shift in the signal of the acetic acid methyl protons is observed from 1.91 to 1.84 with $J_{H,P}$ 1.7 Hz, which is the signal of the methyl protons of acetyl phosphate. On heating the reaction mixture for half an hour at 60°C, an NMR signal at 2.00, s, appears, which is characteristic of an ester. The reaction mixture was diluted in water, neutralized with sodium hydrogen carbonate, and extracted with ethyl ether. From the extract, β-hydroxypropyl acetate was isolated and identified by the gas chromatographic analysis using a standard sample. ^{1}H NMR (DMSO): 1.18, d, 6.3 Hz, 3H, C<u>H</u>$_3$—CH; 2.00, s, 3H, C<u>H</u>$_3$—C(O); 3.30–3.12, m, 2H, C<u>H</u>$_2$(O)CH(OH)CH$_3$; 3.6, m, 1H, CH$_2$(O)C<u>H</u>(OH)CH$_3$; CH$_3$C(O)OCH$_2$—CH(OH)CH$_3$; β-hydroxypropyl acetate.

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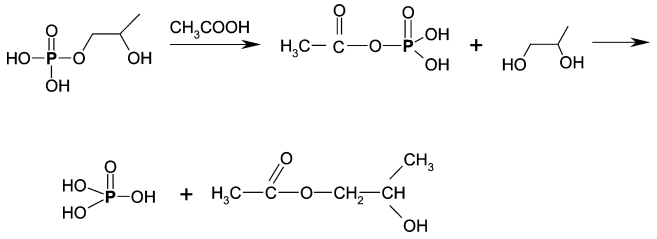
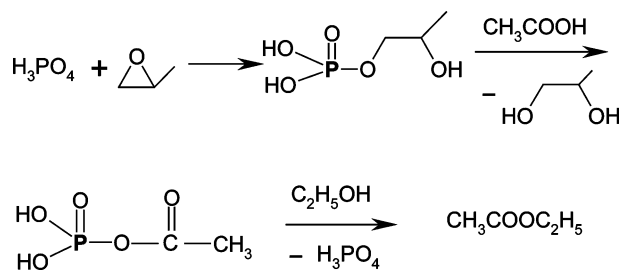


SCHEME 1 Synthesis of β-hydroxypropyl acetate.

The formation of β-hydroxypropyl acetate proceeds according to Scheme 1. This scheme suggests an idea of direct preparation of esters, without proceeding to isolation of acetyl phosphate. The procedure consists in mixing of phosphoric acid, acetic acid, and the respective alcohol, and the addition of propylene oxide. The changes in the reaction mixture were observed by gas chromatography, and the products were identified by the use of standard samples. A series of experiments with equimolar quantities of the reactants were performed. The reactions were carried out at room temperature. Propylene oxide that generates acetyl phosphate in situ via in situ generation of hydroxypropyl phosphate (Scheme 2) [6]. The Table 1 presents the reactants in the system, the duration of the reaction, and the reaction products in moles with respect to acetic acid.

With the reaction of acetic acid and ethanol, a minimum quantity of ethyl acetate is produced, which is in equilibrium with the reactants. The presence of water does not actually affect the yield of acetyl acetate (Experiments 1 and 2). No esterification occurs with acetic acid and propylene oxide, while a small amount of propylene glycol is formed due to the presence of water in the system (Experiments 3 and 4). The addition of ethanol to systems 3 and 4 favors the formation of insignificant quantities of propylene glycol and ethyl acetate (Experiments 5 and 6). By mixing of acetic acid, ethanol, and phosphoric acid, ethyl acetate is produced (Experiment 7). The reaction is a typical case of acid catalysis of carbonic acid esterification. The interaction proceeds slowly; the equilibrium quantity of the product being firmly established at 34% (Experiment 7). Acetic acid, phosphoric acid, and propylene oxide were produced by mixing β-hydroxypropyl acetate. The reaction is fast; the yield is about 40% and is not remarkably influenced by the presence of water in the system (Experiments 8 and 9). The formation of β-hydroxypropyl acetate is shown in Scheme 1.



SCHEME 2 Synthesis of ethyl acetate.

This interaction may be regarded as a transacylation reaction. The forming β-hydroxypropyl phosphate condenses with acetic acid to yield acetyl phosphate. The latter reacts with the released propylene glycol, and β-hydroxypropyl acetate is obtained as the final product, with simultaneous release of the initial phosphoric acid. This kind of interaction is observed for the first time.

By Experiments 10 and 11, the products of the reaction of acetic acid, phosphoric acid, ethanol, and propylene oxide are studied. By this reaction, β-hydroxypropyl acetate is isolated as a side-product. These interactions are represented in Scheme 2.

The formation of ethyl acetate proceeds with several steps. Phosphoric acid and propylene oxide react to produce β-hydroxypropyl phosphate. The reaction of the latter with acetic acid yields acetyl

TABLE 1 Relationship of yield of products vs. initial reactants

Reactants	*Duration of Reaction*	*Reaction Products (moles/mole AcOH)*
1. AcOH, EtOH	7 days	EtOAc, 0.08
2. AcOH, EtOH, H_2O	7 days	EtOAc, 0.09
3. AcOH, P.O.	7 days	–
4. AcOH, P.O., H_2O	7 days	P.G., 0.15
5. AcOH, EtOH, P.O.	7 days	EtOAc, 0.09
6. AcOH, EtOH, P.O., H_2O	7 days	EtOAc, 0.16 P.G., 0.09
7. AcOH, EtOH, H_3PO_4	1 day	EtOAc, 0.04
	7 days	EtOAc, 0.34
	14 days	EtOAc, 0.34
8. AcOH, P.O., H_3PO_4	60 min	HPAc, 0.45
9. AcOH, P.O., H_3PO_4, H_2O	60 min	HPAc, 0.41
10. AcOH, EtOH, H_3PO_4, P.O.	60 min	EtOAc, 0.76 P.G., 0.62 HPAc, 0.12
11. AcOH, EtOH, H_3PO_4, H_2O, P.O.	60 min	EtOAc, 0.72 P.G., 0.60 HPAc, 0.10

AcOH: Acetic acid, P.O.: propylene oxide, EtOH: ethanol, P.G.: propylene glycol, EtOAc: ethyl acetate, HPAc: β-hydroxypropyl acetate.

phosphate with the release of propylene glycol. Acetyl phosphate reacts with ethanol to give ethyl acetate as the final product. This stepwise interaction may be accomplished in the presence of water too. Experiments 11 and 12 show that the isolation of β-hydroxypropyl acetate may be avoided by the introduction of another alcohol which to be acetylated in the system. For this purpose, experiments were carried out with other hydroxyl compounds. Methanol, *n*-propanol, and *n*-butanol produced methyl acetate, propyl acetate, and butyl acetate, respectively. The reaction pattern of the formation of ethyl acetate is observed in these cases. However, the attempt to synthesize phenyl acetate was unsuccessful, leaving the added phenol unchanged. This is an indirect evidence of the intermediate participation of acetyl phosphate in the presented scheme, as the nucleophile attack may proceed only on the apically oriented substituents of the phosphoryl group. In the case of phenol, the reaction cannot take place due to the steric requirements of the benzene ring.

MATERIALS AND METHODS

All reagents and materials were commercial products of Fluka and were used without preliminary treatment. NMR-spectrometer Bruker DRX-250, IR-spectrometer "IFS 113v," and gas chromatograph Carlo Erba 4100 with HP-5 column were used.

EXPERIMENTAL

General Method of Preparation of Esters

A flask, equipped with a magnetic stirrer and a reflux condenser, was filled with 11.53 g of 85% aqueous solution of phosphoric acid, 18 g (0.3 mol) of acetic acid, 0.4 mol of the chosen alcohol (methanol, ethanol, *n*-propanol, or *n*-butanol) and stepwise mixed with 29 g (34.4 mL, 0.5 mol) of propylene oxide, at the initial temperature of 20°C. During the interaction of propylene oxide and phosphoric acid, the temperature was gradually raised up to 40°C for 1 h. The reflux condenser was then replaced by a Vigreux rectification column and a condenser, and the reaction mixture was heated to the appropriate temperature for distillation of the respective acetate. By this procedure, the following products were obtained: methyl acetate 18 g, 81%; ethyl acetate 22 g, 84%; *n*-propyl acetate 24 g, 78%; *n*-butyl acetate 28 g, 80%.

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