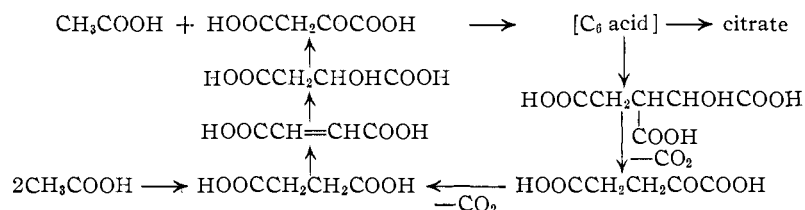


in connection with the Thunberg-Knoop oxidation scheme described above; and has recently been suggested by Slade and Werkman to account for the formation of isotopic succinate from C^{13} tagged acetate during glucose fermentation by *Aerobacter*.¹⁹ The occurrence of this reaction to a small extent simultaneous with the reactions of the tricarboxylic acid cycle would account very well for the presence of 57% C^{13} in the carboxyl carbons of the C_4 acids.

Over-all Scheme for Acetate Oxidation in Yeast.—The conclusions derived from these experiments are summarized in the following outline which may be considered to represent the "steady state" of acetate oxidation in yeast.



The chemical form in which acetate enters the cycle is still in doubt as is the identity of the C_6 condensation product. Various possibilities have already been discussed.^{3,4}

The remarkable similarity to the analogous processes of animal tissues is immediately apparent. One feature, constituting one of the principal modifications of the original Krebs cycle, is the intermediary formation of an unsymmetrical C_6 acid rather than citrate. This was already deduced for animal tissues from the key observations: (a) the presence of isotopic carbon in the carboxyl adjacent to the keto group of α -ketoglutarate formed during the oxidation of pyruvate by

(19) Slade and Werkman, *Arch. Biochem.*, **2**, 97 (1943).

pigeon liver in the presence of isotopic bicarbonate^{2,3}; (b) the presence of isotopic carbon mainly in the δ position of α -ketoglutarate formed during the oxidation of isotopic acetate²⁰ and acetoacetate²¹ by kidney. The fact that this conclusion was derived for yeast entirely independently of the data on animal tissues emphasizes not only the broad scope of the tricarboxylic acid cycle but also the correctness of this oxidative mechanism.

Acknowledgment.—We acknowledge with thanks the support and interest of the Sun Oil Company in this work.

Summary

The oxidation of carboxyl- C^{13} -tagged magnesium and barium acetate by bakers' yeast led to the accumulation of citrate and carbon dioxide, whose C^{13} content and distribution were in accord with the conception that the tricarboxylic acid cycle is a major oxidative process in yeast. The data indicate, first, that an unsymmetrical C_6 acid rather than citrate is the direct participant in the cycle; second, that not all of the C_4 acids are formed from the cycle, but that another independent mechanism exists for their formation from acetate; third, that under the conditions of these experiments intermediates in the conversion of acetate to citrate are not in rapid equilibrium with carbon dioxide or bicarbonate.

The rapid synthesis of cellular lipids from acetate was confirmed.

(20) Weinhouse, Medes and Floyd, *J. Biol. Chem.*, **161**, 745 (1945).

(21) Buchanan, Sakami, Gurin and Wilson, *ibid.*, **159**, 695 (1945). PHILADELPHIA, PENNA.

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[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Acylation Studies in the Thiophene and Furan Series. IV. Strong Inorganic Oxyacids as Catalysts

By HOWARD D. HARTOUGH AND ALVIN I. KOSAK¹

The authors reported previously that iodine and hydriodic acid,² zinc chloride³ and silicate compositions such as montmorillonite clays and synthetic silica-metal oxide gels⁴ promote the acylation of thiophene and furan with anhydrides and acyl halides.

Strong inorganic oxyacids such as phosphoric acids, sulfuric acid, and fluo-acids of phosphorus, sulfur and boron have now been found to catalyze

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(2) Hartough and Kosak, *THIS JOURNAL*, **68**, 2639 (1946).

(3) Hartough and Kosak, *ibid.*, **69**, 1012 (1947).

(4) Hartough, Kosak and Sardella, *ibid.*, **69**, 1014 (1947).

the acylation of thiophene and furan with acyl anhydrides and halides. Orthophosphoric acid is the most efficient catalyst and produced the least side reactions of any of the acids used. It was chosen, therefore, for the bulk of this work and was used exclusively in the examples described in the experimental part. However, all the inorganic oxyacids containing fluorine, sulfur, or phosphorus tested, having at least one ionizable hydrogen and an ionization constant greater than 1×10^{-2} for the first hydrogen ion are effective catalysts for the acylation of thiophene and furan. Phosphorous acid (50%), pyrophosphoric acid, fluo-

phosphoric acid, fluophosphoric acid monohydrate, sulfuric acid, fluosulfonic acid, *p*-toluenesulfonic acid monohydrate and dihydroxyfluoroboric acid have all produced acylation of thiophene and furan with acetic anhydride (see Table I). Polymerized metaphosphoric acid, $(\text{HPO}_3)_x$,

TABLE I
ACYLATION OF THIOPHENE AND FURAN WITH ACETIC ANHYDRIDE WITH STRONG OXYACIDS^a

Heterocyclic used per mole of acetic anhydride ^b	Catalyst used Formula	g.	Reaction conditions Temp., °C.	Time, hr.	Yield of 2-acetylthiophene, %
Thiophene					
1	H ₂ SO ₄	5	100-125	3	46
1	H ₂ SO ₄	5	55	5	54
0.5	H ₂ SO ₄	4	122-127	3	43
1	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H·H ₂ O	4	100-125	4.7	62
1	(CH ₃) ₂ SO ₄	3	84-96	1	0
1	HSO ₃ F	10	84-115	2	41
1	H ₂ PO ₃ F·H ₂ O	10	95-115	3	81
1.5	H ₂ PO ₃ F·H ₂ O	3	93-104	2	71
1	H ₃ BO ₃ F ₂	10	110-116	2	51
1	(H ₃ PO ₃) ₃ ·BF ₃	10	115-124	2	63
1	H ₃ PO ₃	4	94-108	2	38
2	H ₄ P ₂ O ₇	2	97	4	37
Furan					
2	H ₂ SO ₄	2	0-20	1.2	42
0.85	H ₂ BO ₃ F	3	25	3	48
0.5	<i>p</i> -CH ₃ C ₆ H ₄ SO ₃ H·H ₂ O	2	56-64	2.5	45
1.6 ^c	H ₂ PO ₃ F	2	25-26	6	0.9

^a For results with orthophosphoric acid see Table II.

^b One hundred and seven g. of 95% acetic anhydride used.

^c Seventy-eight g. of acetyl chloride used *in lieu* of acetic anhydride.

does not promote the acylation of thiophene or furan. Other acids falling in the ionization constant range but failing to catalyze the reaction are picric acid, chloroacetic acid, trichloroacetic acid, hydrogen fluoride, hydrogen chloride and hydrogen bromide. Boric acid failed to promote acylation. If the hydroxyl groups are blocked, as in dimethyl sulfate, no acylation of thiophene or furan could be obtained. Catalytic quantities of hydrogen fluoride failed to promote acylation of thiophene with acetic anhydride, but when the concentration of hydrogen fluoride was increased to 50 to 60% by weight of the reaction mixture, a 44% yield of 2-acetylthiophene was obtained. No acylation could be detected with glacial acetic acid and thiophene with as much as 70% by weight of anhydrous hydrogen fluoride.

It was convenient to use commercial sirupy orthophosphoric acid (85%). Since organic acid anhydrides react rapidly with water in the presence of acid, orthophosphoric acid is converted to the anhydrous form. Therefore the decomposed anhydride was compensated for in some cases by addition of an excess of anhydride when a molar excess of the heterocyclic was used.

The best yield (94%) of 2-acetylthiophene was obtained from three moles of thiophene and one mole of acetic anhydride catalyzed by 10 g. of 85% orthophosphoric acid. Due to higher yields,

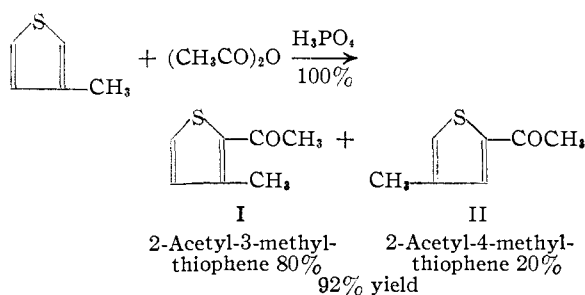
the acid anhydrides are preferred over acyl halides. Benzoyl chloride was the single exception and gave yields comparable to the anhydrides. These observations are consistent with prior work.^{2,3,4}

The phosphoric acids are preferred for the acylation of furan since excessive ring rupture or polymerization is not encountered. The acyl halides are not preferred with furan because the evolved hydrogen chloride in the presence of the catalyst caused excessive decomposition and little, if any, yield of acylated furan is obtained.

With the exception of the phosphoric and fluophosphoric acids, all the acids tested caused polymerization or ring rupture of thiophene with the evolution of hydrogen sulfide at temperatures near 100°. With sulfuric acid the yield can be improved from 46 to 54% by lowering the temperature from that of reflux to 55° and the decomposition products are markedly reduced. After the reaction had been carried out at the reflux temperature, no thiophene could be recovered; when the temperature was not allowed to exceed 55° about 90% of the unreacted thiophene could be isolated. The degradation tendencies of sulfuric acid are not exhibited by *p*-toluenesulfonic acid and somewhat improved yields are obtained.

The method of addition of the acid catalyst to the reaction mixture is important. The addition should be made at 60 to 80°. A 20% solution of orthophosphoric acid in acetic anhydride was prepared and allowed to stand overnight. When added to a mixture of three moles of thiophene and one mole of acetic anhydride, 10 g. of this solution (2.0 g. of 100% orthophosphoric acid) failed to produce acetylation of the thiophene after two hours at 90°. In an otherwise similar experiment, the 85% orthophosphoric acid (2.3 g.) was added at room temperature and after two hours at 90°, a 41% yield of 2-acetylthiophene was obtained. The addition procedure was reversed and the acetic anhydride was added to the thiophene and 85% orthophosphoric acid and after similar treatment, a yield of 55% was obtained. However, addition of the acid to the thiophene and acetic anhydride at 80° gave a yield of 74%.

Acetylation studies with 3-methylthiophene by previous workers^{5,6} using aluminum chloride catalyst do not mention the formation of isomers.



(5) Demuth, *Ber.*, **18**, 3026 (1885).

(6) Gerlach, *Ann.*, **267**, 153 (1892).

TABLE II
 ACYLATION OF THIOPHENE AND FURAN WITH 85% ORTHOPHOSPHORIC ACID

Compound	Yield, %	B. p. °C.	mm.	n_D^{20}	M. p., °C.	M. p., °C.	Oxime derivative	
							Formula	Nitrogen analyses Calcd. Found
2-Acetylthiophene ^a	94	77 ^t	4	1.5666	10-11	112-113 ^t		
2-Acetyl-5-methylthiophene ^b	90	84.5	2	1.5622	27-28	124-125.5 ^u	C ₇ H ₉ NOS ^r	9.03 8.97
2-Acetyl-4-methylthiophene ^c	18	86	3	1.5600	132.5-134 ^m	C ₇ H ₉ NOS ^v	9.03 9.07
2-Acetyl-3-methylthiophene ^c	74	79	4	1.5618	84.5-86 ^{n,v}	C ₇ H ₉ NOS ^s	9.03 9.05
2-Acetyl-5-chlorothiophene ^d	70	88	4	46.5-47 ^o	159.5-160.5	C ₆ H ₆ ClNOS	7.84 7.84
2-Acetyl-5-chlorothiophene ^e	18	46.5-47 ^p	159.5-160.5 ^p		
2-Propanoylthiophene ^f	89	88	7	1.5539		^w		
2,5-Dipropanoylthiophene ^f	1.5	129-129.2			
2- <i>n</i> -Butanoylthiophene ^g	87	87-92	3	1.5413				
2-Benzoylthiophene ^h	81	120-121	2	56.5-57 ^q			
5-(2-Thenoyl)-pentanoic acid ⁱ	35	79-80 ^r			
2-Acetylfuran ^j	62	45-50	5	30-32 ^s			
2-Benzoylfuran ^k	70	140-150	3	43.5-44	121-122	C ₁₁ H ₉ NO ₂	7.48 7.29

^a 3:1 (see experimental for explanation of molar ratios of reactants). ^b 10:10. The H₃PO₄ (100 g.) was added at room temperature and the temperature controlled at 40-60° by means of an ice-bath before warming finally to 100-110°. ^c See footnote b. The products were separated by several fractionations and final purity of greater than 99% established by infrared absorption analysis. ^d 3:3.5. Unreacted 2-chlorothiophene (42 g.) recovered. Product recrystallized from dilute alcohol. ^e 1:2. Unreacted 2,5-dichlorothiophene (120 g.) recovered by steam distillation. Product purified by crystallizing three times from petroleum ether. ^f 5:6; 25 g. of 85% H₃PO₄; reaction temperature was 110-145°. 2,5-Dipropanoylthiophene received as a residue and purified by repeated crystallizations from ethyl acetate and petroleum ether. *Anal.* Calcd. for C₁₀H₁₂O₂S: S, 16.33. Found: S, 16.26. ^g 6.7:4.1; 24 g. of 85% H₃PO₄ at 113-122° for four hours. Semicarbazone, m. p. 175-176°. *Anal.* Calcd. for C₉H₁₁N₃OS: N, 19.90. Found: N, 19.82. ^h 20:10 (benzoyl chloride) product distilled as green crystalline mass. Color improved by recrystallization from ASTM naphtha. ⁱ 1:0.27 (adipyl chloride); 5 g. of 85% H₃PO₄ heated progressively from 50-80° for four hours. Purified by method described in ref. 4. Mixed m. p. with authentic sample, ref. 4, showed no depression. ^j 0.5:1; 5 g. of 85% H₃PO₄ at 35-60° for one hour. Mixed melting point with authentic sample 3 showed no depression. ^k 3:1; 3 g. of H₂PO₂F.H₂O at 40° for three hours. ^l The oxime, after six recrystallizations from dilute alcohol, melted at 124-125.5°, solidified at 126° and melted again at 128-129°; cooling, the product froze at 122°, melted again at 124.5-128°; recooling, the product froze at 100° and melted at 122-124°. Ref. 11 lists m. p. of 125°. ^m After similar purification as above ^l the oxime melted at 132.5-134°, solidified at 135° and melted again at 135.5-137°; cooling, it froze at 127° and melted the second time at 130-132°. ⁿ After purification as described in ^l product melted at 84.5-86° solidified at 87° and melted again at 88-89°; cooling it froze at 77.5° and remelted at 87.5-89°; recooling it froze at 77.5 and melted at 88-89°. It seems likely that heating causes rearrangement of one form to the other, either syn to anti or vice-versa, and only in the latter case has the oxime acquired the more stable form in contrast to those described in ^l and ^m. ^o Ref. 4 lists m. p. 46.5-47°. ^p Mixed m. p. with authentic sample^l gave no depression. ^q Ref. 3 lists m. p. 56.5-57°. ^r Mixed m. p. with authentic sample, ref. 3, gave no depression. ^s Mixed m. p. with authentic sample, ref. 3, gave no depression. ^t Mixed m. p. with authentic sample gave no depression. ^u Demuth, *Ber.*, 19, 1859 (1886), reports m. p. of 125°. ^v Ref. 8 reports m. p. of 85-86°. ^w Semicarbazone; m. p. 172-173°. Mixed m. p. with authentic sample, ref. 4, gave no depression. ^x Calcd.: S, 20.65. Found: S, 20.74. ^y Calcd.: S, 20.65. Found: S, 20.82. ^z Calcd.: S, 20.65. Found: S, 20.68.

Steinkopf and Jacob⁷ reported that 2-benzoyl-3-methylthiophene and 2-benzoyl-4-methylthiophene were formed from 3-methylthiophene and benzoyl chloride with aluminum chloride catalyst. The relative amounts of isomers were not determined. The present work indicates that substitution in the 2-position predominates with about 20% of the substitution taking place in the 5-position.

Acetylation of 2-chlorothiophene gave a 70% yield of 2-acetyl-5-chlorothiophene. Acetylation of 2,5-dichlorothiophene under similar conditions gave an 18% yield of 2-acetyl-5-chlorothiophene.

The replacement of bromine and iodine by a CH₃CO-group in acetylation of 2,5-bromo- and 2,5-iodothiophene was reported by Gattermann and Romer.⁸ Later work confirmed the formation of 2-acetyl-5-bromothiophene along with the formation of 2,5-dibromo-3-acetylthiophene from the action of acetyl chloride on 2,5-dibromothio-

phene with aluminum chloride catalyst.⁹ Steinkopf and Kohler¹⁰ reported that 2,5-dichlorothiophene undergoes normal substitution in the 3-position with aluminum chloride catalyst.

It was previously reported that diacetylation took place in low yields when acetic anhydride reacted with 2-acetylthiophene with zinc chloride catalyst.⁸ It has been found that when an excess of propanoic anhydride reacts with thiophene a small amount of 2,5-dipropanoylthiophene can be isolated along with good yields of 2-propanoylthiophene.

Experimental

The purity of samples of thiophene, 2- and 3-methylthiophenes, 2-chlorothiophene and 2,5-dichlorothiophene used in the following work were greater than 99.5% as determined by infrared absorption analysis.

General Acylation Procedure.—A well-stirred equimolar mixture of the acid anhydride and thiophene was warmed to 60°, the heat removed, and 10 g. of 85% ortho-

(7) Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).

(8) Gattermann and Romer, *Ber.*, **19**, 688-695 (1889).

(9) Steinkopf and Jacob, *Ann.*, **515**, 282 (1935).

(10) Steinkopf and Kohler, *ibid.*, **532**, 265 (1937).

(11) Demuth, *Ber.*, **19**, 1859(1886).

phosphoric acid per mole of acid anhydride was added slowly with cooling to maintain the temperature below 90°. The mixture is then warmed to 100–110° (or at the reflux temperature when excess thiophene is used) for two to three hours. The reaction mixture was cooled, 200 ml. of water per mole of acid anhydride added, the mixture thoroughly washed, and finally washed with 10% sodium carbonate solution. The liquid products were rectified through a 12-plate fractionating column. Crystalline products were distilled in suitable apparatus and recrystallized.

With acyl halides the completed reaction mixture was washed with 10% sodium hydroxide solution.

Since the boiling point of furan will not allow the high temperatures used with thiophene the reaction temperature was normally that of the reflux, 40–60°. It was found preferable to cool the completed mixture below 20° before addition of the water.

In general, when an excess of the anhydride was not used, the yields are calculated on the basis that the water in the 85% orthophosphoric acid decomposes a corresponding amount of anhydride.

In preparing footnotes (a) to (k) in Table II the molar ratios of heterocyclic to anhydride used are listed numerically along with any significant departure from the amount of 85% orthophosphoric acid and the temperature or time of reaction.

Preparation of 2-Acetylthiophene Using Anhydrous Hydrogen Fluoride Catalyst.—To 100 g. of anhydrous hydrogen fluoride in a one-liter copper beaker cooled to 15° was added 107 g. (1 mole) of 95% acetic acid. Thiophene, 84 g. (1 mole), was added cautiously and the temperature maintained at 20°. After one hour the hydrogen fluoride was allowed to evaporate off on a steam-bath and the reaction products were processed and rectified as described above. The yield of 2-acetylthiophene was 55 g. (44%).

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carrying out some of the experiments, and Mr. Frank Hochgesang and Mr. John Ehlers for the infrared absorption analyses.

Summary

Strong inorganic oxyacids of fluorine, phosphorus and sulfur having at least one ionizable hydrogen and an ionization constant greater than 1×10^{-2} for the first hydrogen ion were found to be effective catalysts for the acylation of thiophene and furan.

Orthophosphoric acid was found to be the preferable catalyst since it caused little or no deteriorating effects on the heterocyclic nuclei.

Yields of 2-acetylthiophene and 2-acetylfuran as high as 94 and 62%, respectively, are reported. Yields of 2-benzoylthiophene and 2-benzoylfuran as high as 99 and 76%, respectively, are also reported.

3-Methylthiophene with acetic anhydride gave a 92% yield of acetylated product which was a mixture of 80% 2-acetyl-3-methylthiophene and 20% 2-acetyl-4-methylthiophene. 2-Methylthiophene with acetic anhydride gave a 90% yield of 2-acetyl-5-methylthiophene.

Acetylation of 2,5-dichlorothiophene with orthophosphoric acid catalyst gave an 18% yield of 2-acetyl-5-chlorothiophene rather than 3-acetyl-2,5-dichlorothiophene, the normal product obtained with aluminum chloride catalyst.

2,5-Dipropanoylthiophene was obtained from a reaction employing an excess of propanoic anhydride with thiophene.

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[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Acylation Studies in the Thiophene and Furan Series. V. Thiophene Carboxylic Acids and Semicarbazones Derived from Acetylthiophenes

BY HOWARD D. HARTOUGH AND LORETTA G. CONLEY

The availability of 2-acetylthiophene has led to a study of the possibility of oxidizing this, and substituted acetylthiophenes, to the corresponding thiophenecarboxylic acids by the haloform reaction. In order to characterize properly the acetylthiophenes their semicarbazones were prepared.

Eleven acetylthiophenes, three of which are reported for the first time, have been oxidized with sodium hypochlorite to the corresponding acids. The yields varied from 70 to 95% and appeared to depend upon the ring substituents. For example, 5-(2-pentyl)-2-acetylthiophene gave only a 52% yield of 5-(2-pentyl)-2-thiophenecarboxylic acid while 5-*t*-amyl-2-acetylthiophene gave an 89% yield of 5-*t*-amyl-2-thiophenecarboxylic acid. Products of indefinite structure and low sulfur contents were obtained from 2,5-di-*t*-butyl-3-acetyl

thiophene. Odors of butyric acid were noted and no 2,5-*t*-butyl-3-thiophenecarboxylic acid could be isolated. While this particular acetylthiophene did not give a semicarbazone and appeared to be a hindered ketone, 2,5-dichloro-3-acetylthiophene gave a semicarbazone and an 84% yield of 2,5-dichloro-3-thiophenecarboxylic acid and therefore appeared to be entirely free of steric hindrance.

The semicarbazones form easily in nearly quantitative yields but are somewhat unsuitable for identification purposes in that nearly all melt above 200° and most of them are extremely insoluble in most common solvents and are difficult to recrystallize. Despite recrystallization difficulties samples of high purity are obtained without recrystallization by digesting first with water and then with alcohol to remove impurities.