

The Reaction of Lead Tetraacetate with Unsymmetrical Ketones

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2-Butanone, when treated with lead tetraacetate (LTA) in acetic acid, gave 1-acetoxy-2-butanone as the major product. Similarly, 3-methyl-2-butanone and 2-octanone gave 1-acetoxy-3-methyl-2-butanone and 1-acetoxy-2-octanone as the major products. Phenylacetone, however, gave 1-acetoxy-1-phenyl-2-propanone as the major product. Similar results were obtained in propionic acid, propionoxy ketones being the major products, although minor amounts of acetoxy ketones were obtained. In trifluoroacetic acid, trifluoroacetoxy ketones were obtained, and the major products were 3-trifluoroacetoxy-3-methyl-2-butanone, 3-trifluoroacetoxy-2-octanone, and 1-trifluoroacetoxy-2-propanone. Deuterium exchange results indicate that the rates of substitution for the less and the more highly substituted positions for 2-octanone and isopropyl methyl ketone are about equal, while the rates of substitution for the more highly substituted position is favored in 2-butanone and phenylacetone. Enol acetates, when treated with LTA, yield acetoxy ketones, and the position of the acetoxy group is dependent upon the position of the double bond in the parent enol acetate.

The treatment of carbonyl compounds with lead tetraacetate (LTA) is a well-known method for producing α -acetoxy ketones and aldehydes. Fuson¹ observed that carbonyl compounds, which exist primarily in their enol form, react with LTA with unusual ease.

The rapid reaction of enols seems to suggest a mechanism similar to that proposed for the oxidation of monohydric phenols²⁻⁴ where the reaction is believed to proceed through a lead ester.

Evidence to support the intermediacy of the enol in the reaction comes from several sources. Ichikawa⁵ observed that the rate of the reaction is dependent only upon the concentration of the ketone and not on that of LTA. Henbest and coworkers⁶ observed that the rate of oxidation of ketones by LTA is strongly accelerated by BF_3 . The rate enhancement is explained as a catalysis due to BF_3 , which accelerates the formation of the enol. Recently Ellis⁷ observed that the formation of the acetoxy derivative takes place at a position α to a carbonyl group even when other positions are available. He also presented evidence supporting the enolate anion as an intermediate for the acetoxy ketone.^{7b}

In the course of studying this reaction with unsymmetrical ketones rather than with symmetrical ketones,⁸⁻¹⁰ it became apparent that the orientation of the acetoxy group on the ketone is not the same as that reported for the acid-catalyzed bromination of unsymmetrical ketones.^{11,12}

The orientation of the acetoxy group in the reaction of LTA with ketones favors the less substituted carbon rather than the more substituted carbon. This result motivated us to do a further study of this reaction.

Results

The ketones were treated with LTA in a 1:1 molar ratio in acetic acid or propionic acid at $100 \pm 2^\circ$ for 2 hr and in refluxing trifluoroacetic acid for 2 hr. The products were isolated by gas chromatography and analyzed by ir and nmr spectroscopy. The results are summarized in Table I. The reaction proceeded more rapidly in acetic acid than in benzene, and in neither case were any dimers found even though dimers have been reported in some cases.^{10,13} After 2-octanone (1) was refluxed with LTA in benzene for 2 hr, 99% of the starting material was recovered and less than 1% of 1-acetoxy-2-octanone (5) was obtained.

2-Adamantanone, which cannot enolize, was treated with LTA. It was recovered unchanged, suggesting that an enol is a required intermediate in the formation of acetoxy ketones.

Since enols are clearly involved in the reaction, it seemed desirable to study the rates and orientation of enolization under our reaction conditions. If enolization is indeed the rate-controlling factor, this should be reflected in deuterium exchange studies. Nmr spectroscopy proved to be the best technique for studying the rates of enolization at these two positions for these ketones.

Several studies of the rates of substitution at enolic sites in ketones using nmr spectroscopy have already been reported.^{12,14-17} In deuterated HCl, Rappe¹² found that the methylene group in methyl ketones is deuterated faster than the methyl group. However, certain methyne groups do exchange their protons more slowly than do the methyl groups. The effect is attributed to the steric hindrance from the branches on the methyne group.

Our deuterium exchange study indicated that 2-butanone had a faster rate of enolization for the methylene position than for the methyl position. For 2-octanone and 3-methyl-2-butanone, the rates of enolization for both positions were about equal, while for phenylacetone, the rate of enolization for the methylene group was greater than for the methyl group (Table II).

Comparison of Table I and Table II indicates that the

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TABLE I
 PRODUCTS FROM THE OXIDATION OF KETONES WITH LTA

Ketone	In acetic acid ^a			In propionic acid			In trifluoroacetic acid		
	Total yield, ^b %	Ratio A ^c (acetoxy ketone)	1 ^d /K _{Br}	Yield, ^b %	Ratio A (acetoxy ketone)	Ratio A ^c (propionoxy ketone)	Total yield, ^b %	Ratio A ^c (acetoxy ketone)	Ratio A ^c (trifluoroacetoxy ketone ^e)
2-Butanone	64 ^h	1.68	0.37						
2-Octanone	81 ⁱ	2.00	<i>e</i>	73 ⁱ	2	1.6	36 ^h		0.145
3-Methyl-2-butanone	60 ⁱ	5.70	0.33 (0.91 ^j)	89 ^m	8	6.2	40 ⁿ	0.500	0.714
Phenylacetone	93 ^o	0.236		53 ^p	0.187	0.226	36 ^q		

^a At 100 ± 2° for 2 hr. ^b The total yields are based on the distilled products, and include the starting ketone recovered and diacetoxy ketones. ^c The ratio of the least substituted and the most substituted products (CH₃/CH₂ or CH). ^d Relative values obtained from Cardwell and Kilner¹¹ where K_{Br} = K_{CH₂}/K_{CH₃} or K_{CH}/K_{CH₃}. ^e No K_{Br} value has been reported for 2-octanone; however, K_{Br} for 2-heptanone has been reported to be 1.5. Therefore 1/K_{Br} for 2-heptanone is 0.67.¹¹ ^f Rappe and Sachs reported a value of K_{Br} = 1.1 for methyl isopropyl ketone; therefore 1/K_{Br} = 0.91. ^g Isolated as a mixture of trifluoroacetoxy ketone and hydroxy ketone. ^h 2-Butanone, 6%; 3-acetoxy-2-butanone, 12%; 1-acetoxy-2-butanone, 24%; diacetoxy ketone, 22%. ⁱ 2-Octanone, 29%; 3-acetoxy-2-octanone, 14%; 1-acetoxy-2-octanone, 28%; diacetoxy ketone, 10%. ^j 2-Octanone, 31%; 3-acetoxy-2-octanone, 2%; 3-propionoxy-2-octanone, 13%; 1-acetoxy-2-octanone, 4%; 1-propionoxy-2-octanone, 21%; diacetoxy ketone, 2%. ^k 2-Octanone, 13%; 3-trifluoroacetoxy-2-octanone, 15%; 1-hydroxy-2-octanone, 1%; 1-trifluoroacetoxy-2-octanone, 1%; 3-acetoxy-2-octanone, 5.5%. ^l 3-Methyl-2-butanone, 10%; 3-acetoxy-3-methyl-2-butanone, 6%; 1-acetoxy-3-methyl-2-butanone, 34%; diacetoxy ketone, 10%. ^m 3-Methyl-2-butanone, 58%; 3-acetoxy-3-methyl-2-butanone, 0.6%; 3-methyl-3-propionoxy-2-butanone, 3%; 1-acetoxy-3-methyl-2-butanone, 5%; 1-propionoxy-3-methyl-2-butanone, 17.5%; dipropionoxy ketone, 5%. ⁿ 3-Methyl-2-butanone, 6%; 3-methyl-3-trifluoroacetoxy-2-butanone, 14%; hydroxy ketone, 4%; 1-trifluoroacetoxy-3-methyl-2-butanone, 4%; 1-hydroxy-3-methyl-2-butanone, 6%; 3-acetoxy-3-methyl-2-butanone, 4%; 1-acetoxy-3-methyl-2-butanone, 2%. ^o Phenylacetone, 20%; 1-acetoxy-1-phenyl-2-propanone, 51%; 1-acetoxy-3-phenyl-2-propanone, 12%; diacetoxy ketone 10%. ^p Phenylacetone, 8.5%; 1-acetoxy-1-phenyl-2-propanone, 8.5%; 3-acetoxy-1-phenyl-2-propanone, 1.6%; 3-propionoxy-1-phenyl-2-propanone, 6.4%; 1-propionoxy-1-phenyl-2-propanone, 28%. ^q Phenylacetone, 26%; 1-acetoxy-1-phenylacetone, 15%; 3-acetoxy-1-phenylacetone, less than 0.5%; 1-trifluoroacetoxy-1-phenylacetone, 7%; 3-trifluoroacetoxy-1-phenylacetone, less than 0.5%.

TABLE II

 RATES OF DEUTERIUM EXCHANGE FOR UNSYMMETRICAL KETONES
 IN ACETIC ACID-d₄ AT 100 ± 2°

Ketone	CH ₃	CH ₂ or CH	K _R ^a	k _D ^b
	k × 10 ⁵ , sec ⁻¹	k × 10 ⁵ , sec ⁻¹		
2-Butanone	1.2	2.1	0.571	0.57
2-Octanone	1.7	1.8	0.944	0.69
3-Methyl-2-butanone	1.6	1.5	1.066	1.25
Phenylacetone	3.1	6.9	0.449	

^a K_R = k_{CH₃}/k_{CH₂} or k_{CH₃}/k_{CH}. ^b Relative values reported by Rappe¹² in deuterium chloride, deuterium oxide, and dioxane.

products ratio and the enolization rates do not correspond well. These results suggest that enolization may not be the rate-determining step in the formation of acetoxy ketones.

Enol acetates, on treatment with LTA, also yield acetoxy ketones as well as lead diacetate and acetic anhydride.^{18,19} In order to determine the relationship between the position of the double bond of the enol acetate and the acetoxy group in the product, isomerically pure enol acetates of ketones were prepared and treated with LTA in acetic acid at 100°. The results are summarized in Table III.

The results shown in Table III demonstrate that enol acetates lead rather specifically to just one or two possible products. These results might suggest that each acetoxy ketone comes from the appropriate enol acetate. However, enol acetates are eliminated as intermediates based on the fact that no enol acetates were found in the reaction mixture of LTA with ketones even though substantial amounts of enol acetates are recovered on treatment with LTA. Furthermore, the fact that just one of two possible acetoxy ketones was

obtained implies that acetoxy ketones are stable and do not isomerize under the reaction conditions.

Experimental Section²⁰

LTA Oxidations of Ketones.—The ketones (2–10 g) were heated at 100° for 2 hr with equimolar amounts of LTA in 50–100 ml of the acids (acetic, propionic, trifluoroacetic). Ethylene glycol (2–5 ml) was added, the mixtures were diluted with water (300 ml), and the organic materials were extracted with 2–3 portions of ether. The ether solutions were washed with 10% Na₂CO₃ until neutral and dried, and the product mixtures were separated by gc after distillation. Structural assignments of new compounds were made on the basis of spectral data, and the results are summarized in Table I.

Preparation of Enol Acetates.—The ketones (0.15–0.35 mol) were refluxed for 24 hr with isopropenyl acetate (0.3–0.5 mol) and *p*-toluenesulfonic acid (0.15–0.2 g). The mixtures were concentrated by distillation, cooled, and added to an ice-cold mixture of hexane (100 ml) and saturated NaHCO₃ (100 ml). The mixtures were stirred rapidly and the temperature was not allowed to rise above 10°. The hexane layers were separated and dried, and the products were isolated by gc after distillation. Structural assignments were made on the basis of spectral data.

Reactions of Enol Acetates with LTA.—The enol acetates (0.5–2.5 g) were heated at 100° for 2 hr with equimolar amounts of LTA in 25–100 ml of acetic acid. The mixtures were worked up in the manner described for LTA oxidations of ketones and the products were similarly identified. Results are summarized in Table III.

Experimental Procedure for the Deuterium Exchange.—Solutions containing the ketone and deuterated acetic acid-d₄ (1:4, v/v) were placed in an nmr tube, and the tubes were sealed and heated in an oil bath at 100 ± 2°. The tubes were withdrawn at 1-hr intervals and the nmr spectra were taken. The rate of substitution was monitored using the nonenolizable protons as internal standards. The rate study was run in duplicate and the probe's temperature was kept at 47°. The rates

(20) Nmr spectra were recorded on a Varian A-60 spectrophotometer; chemical shifts are reported in τ values using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Gas chromatography was performed on an F & M Model 720 thermal conductivity gas chromatograph using 2-, 4-, or 10-ft columns containing 20% silicone rubber on Chromosorb W, 20% ethylene glycol adipate (EGA) on Chromosorb W, and 10% Carbowax on Chromosorb W. Boiling points are uncorrected.

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TABLE III
 PRODUCTS FROM THE REACTION OF ENOL ACETATES OF THE KETONES 1, 2, AND 3 WITH LTA IN ACETIC ACID

Compd	Total yield, % (distilled)	Acetoxy ketone found	Product ratio, %	
			Acetoxy ketone	Enol acetate
(trans) $\text{CH}_3(\text{CH}_2)_4\text{CH}=\overset{\text{OAc}}{\text{C}}\text{CH}_3^a$	50	$\text{CH}_3(\text{CH}_2)_4\overset{\text{OAc}}{\text{C}}\text{HCOCH}_3$	22	78
(cis) $\text{CH}_3(\text{CH}_2)_4\text{CH}=\overset{\text{OAc}}{\text{C}}\text{CH}_3^b$	75	$\text{CH}_3(\text{CH}_2)_4\overset{\text{OAc}}{\text{C}}\text{HCOCH}_3^c$	30	70
$\text{PhCH}=\overset{\text{OAc}}{\text{C}}\text{CH}_3^d$	81	$\text{PhCH}\overset{\text{OAc}}{\text{C}}\text{COCH}_3$	50	50
$\text{PhCH}_2\overset{\text{OAc}}{\text{C}}=\text{CH}_2$	72	$\text{PhCHCOCH}_2\text{OAc}$	64	36
$(\text{CH}_3)_2\overset{\text{OAc}}{\text{C}}\text{H}=\text{CH}_2$	63	$(\text{CH}_3)_2\text{COCH}_2\text{OAc}$	72	28
$(\text{CH}_3)_2\overset{\text{OAc}}{\text{C}}=\text{CCH}_3$	68	$(\text{CH}_3)_2\overset{\text{OAc}}{\text{C}}\text{COCH}_3$	5	95

^a The trans isomer only. ^b Mixture of *cis*-2-octen-2-yl acetate and 1-octen-2-yl acetate (8.45:1). ^c A trace amount (<1%) of the 1-acetoxy-2-octanone was found. ^d The *cis* and *trans* isomers of this compound could not be separated on our columns.

TABLE IV

Compd ^a	Nmr spectra, τ	Compd ^a	Nmr spectra ^b
3-Acetoxy-2-octanone	9.1 (m, 3 H), 8.7 (m, 8 H), 7.91 (s, 3 H), 7.90 (s, 3 H), 5.2 (m, 1 H)	3-Propionyloxy-3-methyl-2-butanone	8.9 (t, 3 H), 8.6 (s, 6 H), 7.95 (s, 3 H), 7.75 (q, 2 H)
1-Acetoxy-2-octanone	9.1 (m, 3 H), 8.7 (m, 10 H), 7.9 (s, 3 H), 7.7 (m, 2 H), 5.3 (s, 2 H)	1-Propionyloxy-3-methyl-2-butanone	8.85 (m, 9 H), 7.65 (m, 3 H), 5.4 (s, 2 H)
3-Propionyloxy-2-octanone	9.1 (m, 6 H), 8.8 (m, 8 H), 7.9 (s, 3 H), 7.6 (q, 2 H), 5.1 (m, 1 H)	3-Methyl-3-trifluoroacetoxy-2-butanone	7.81 (s, 3 H), 8.45 (s, 6 H)
1-Propionyloxy-2-octanone	9.1 (m, 6 H), 8.8 (m, 10 H), 7.6 (q, 2 H), 5.45 (s, 2 H)	1-Trifluoroacetoxy-3-methyl-2-butanone and 1-hydroxy-3-methyl-2-butanone	5.68 (s, 0.764 H), 6.26 (s, 1.24 H), 6.33 (s, 0.62 H), 7.45 (m, 1 H), 8.83 (d, 6 H)
1-Hydroxy-2-octanone and 1-trifluoroacetoxy-2-octanone	7.9 (s, 3 H), 6.35 (s, 2 H), 2.7 (s, 5 H)	3-Acetoxy-2-butanone	8.75 (d, 3 H), 7.95 (s, 6 H), 5.05 (q, 1 H)
1-Propionyloxy-1-phenyl-2-propanone	8.8 (t, 3 H), 7.95 (q, 2 H), 6.4 (s, 1 H), 2.7 (s, 5 H)	1-Acetoxy-2-butanone	8.9 (t, 3 H), 7.93 (s, 3 H), 7.7 (q, 2 H), 5.5 (s, 2 H)
1-Propionyloxy-3-phenyl-2-propanone	8.8 (t, 3 H), 7.65 (q, 2 H), 6.3 (s, 2 H), 5.38 (s, 2 H), 2.7 (s, 5 H)	<i>trans</i> -2-octen-2-yl acetate	9.1 (m, 3 H), 8.7-8.8 (m, 8 H), 8.15 (s, 3 H), 7.92 (s, 3 H), 5.1 (t, 1 H)
1-Phenyl-1-trifluoroacetoxy-2-propanone	7.9 (s, 3 H), 4.0 (s, 1 H), 2.58 (s, 5 H)	<i>cis</i> -2-octen-2-yl acetate	9.1 (m, 3 H), 8.7 (m, 8 H), 8.2 (s, 3 H), 7.95 (s, 3 H)
3-Acetoxy-3-methyl-2-butanone	8.6 (s, 6 H), 7.95 (s, 6 H)	1-phenyl-2-propen-2-yl acetate	8.05 (s, 3 H), 6.5 (s, 2 H), 5.5 (s, 1 H), 5.3 (s, 1 H), 2.8 (s, 5 H)
1-Acetoxy-3-methyl-2-butanone	8.8 (d, 6 H), 7.8 (s, 3 H), 7.4 (m, 1 H), 5.4 (s, 2 H)	<i>cis</i> - and <i>trans</i> -1-phenyl-1-propen-2-yl acetate	7.9 (s, 6 H), 4.2 (s, 1/2 H), 2.75 (s, 5 H)

^a Satisfactory analytical data for C and H ($\pm 0.3\%$) were found for these compounds: Ed.

were calculated from the slopes of the first-order plots of $\ln c/c_0$ vs. t by means of a least square determination (c_0 = initial concentration, c = concentration at time t).

Nmr data appear in Table IV.

Registry No.—LTA, 546-67-8; 2-butanone, 78-93-3; 2-octanone, 111-13-7; 3-methyl-2-butanone, 563-80-4; phenylacetone, 103-79-7; 3-acetoxy-2-octanone, 36959-98-5; 3-acetoxy-2-octanone, 36959-99-6; 3-propionyloxy-2-octanone, 36906-00-6; 1-propionyloxy-2-octanone, 36906-01-7; 1-acetoxy-1-phenyl-2-propanone, 19275-80-0; 1-acetoxy-3-phenyl-2-propanone, 36960-03-9; 1-propionyloxy-1-phenyl-2-propanone, 36960-04-0; 1-propionyloxy-3-phenyl-2-propanone, 36960-05-1; 3-acetoxy-3-

methyl-2-butanone, 10235-71-9; 1-acetoxy-3-methyl-2-butanone, 36960-07-3; 3-propionyloxy-3-methyl-2-butanone, 36960-08-4; 1-propionyloxy-3-methyl-2-butanone, 36960-09-5; 3-acetoxy-2-butanone, 4906-24-5; 1-acetoxy-2-butanone, 1575-57-1; *trans*-2-octen-2-yl acetate, 36960-12-0; *cis*-2-octen-2-yl acetate, 36960-13-1; 1-phenyl-2-propen-2-yl acetate, 25522-54-7; *cis*-1-phenyl-1-propen-2-yl acetate, 19980-46-2; *trans*-1-phenyl-1-propen-2-yl acetate, 19980-44-0; 1-hydroxy-2-octanone, 7019-19-4; 1-trifluoroacetoxy-2-octanone, 36960-18-6; 1-phenyl-1-trifluoroacetoxy-2-propanone, 36960-19-7; 3-methyl-3-trifluoroacetoxy-2-butanone, 36960-20-0; 1-trifluoroacetoxy-3-methyl-2-butanone, 36960-21-1; 1-hydroxy-3-methyl-2-butanone, 36960-22-2.