# THE INTERMEDIACY OF SULFATE ESTERS IN SULFURIC ACID CATALYZED ACETYLATION OF CARBOHYDRATES*

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Abstract - The acetylation of 1,2,3,4-tetra-*O*-acetyl-beta-D-glucopyranose in excess acetic anhydride/acetic acid/sulfuric acid was shown by kinetic studies and observation of intermediates to proceed via a rapid formation of the corresponding 6-sulfate ester, followed by rate-controlling acetolysis of the sulfate to give glucose pentaacetate product. The same mechanism is proposed, based on kinetic data, for acetylation of the secondary alcohol 1,2,3,6-tetra-O-acetyl-beta-D-glucopyranose.

## INTRODUCTION

In a series of papers published between 1942 and 1955, Malm and associates proposed that in the acetylation of cellulose by acetic anhydride in acetic acid containing sulfuric acid catalyst, the sulfuric acid initially combines

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*Dedicated to Prof. E. C. Taylor on the occasion of his 70th birthday.

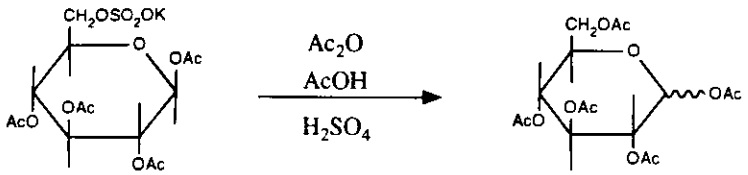
with cellulose hydroxyls to give hydrogensulfate esters. These *O*-hydrogensulfates were proposed to then undergo a slow conversion to *O*-acetates.[1-3]

While this reaction sequence has been generally accepted in the context of cellulose chemistry,[4] little notice of Malm's proposal appears to have been taken outside that field. Moreover, Malm's conclusions were based on analytical methods[1] which required quantitative removal of free sulfate from precipitated polymer particles - a procedure we have been unable to completely validate.

In view of the analytical limitations of Malm's work and the fact that sulfuric acid catalyzed acetylation does not a priori require the intermediacy of *O*-hydrogensulfate esters, we have examined this chemistry in the context of a simple monosaccharide model compound.

## RESULTS AND DISCUSSION

We first determined the fate of the primary sulfate ester 1,2,3,4-tetra-*O*-acetyl-beta-D-glucopyranose-6-sulfate potassium salt (**1**)[5] in a large excess of acetic anhydride-acetic acid-sulfuric acid (36%-63%-1% by wt). (Unlike the free hydrogensulfate and other salts, **1** is a stable, non-hygroscopic solid soluble in our reaction mixtures). It was observed that **1** was rapidly and cleanly (90% yield isolated) transformed into a mixture of alpha- and beta-glucose pentaacetates (**2**) at room temperature. A control experiment in which the pure beta anomer of pentaacetylglucose was subjected to the reaction conditions led to 95% recovery of an identical mixture of the two anomers; this acid-catalyzed anomerization of glucose pentaacetate is presumed to be irrelevant to the chemistry of the 6-sulfate ester group.

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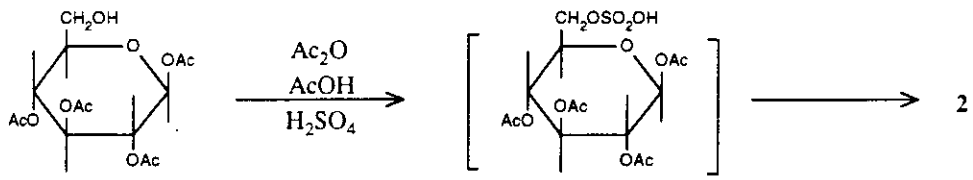
Good pseudo first-order kinetic behavior was observed for this acetolysis. At 24°C the rate constant was $1.7 \times 10^{-3}$ $s^{-1}$ ($t_{½}$ = 400 s); measurements at 10°C and 4°C allowed determination of the activation parameters $E_a$ = 18.4 kcal/mol and $\Delta S^{\ddagger}$ = -16 eu.

Attention was then turned to the acetylation of 1,2,3,4-tetra-O-acetyl-beta-D-glucopyranose (**3**) under conditions identical to those used for acetolysis of the corresponding sulfate. We observed production of the identical product mixture (**2**) with a pseudo first-order rate constant identical, within experimental error, to that found for sulfate acetolysis.

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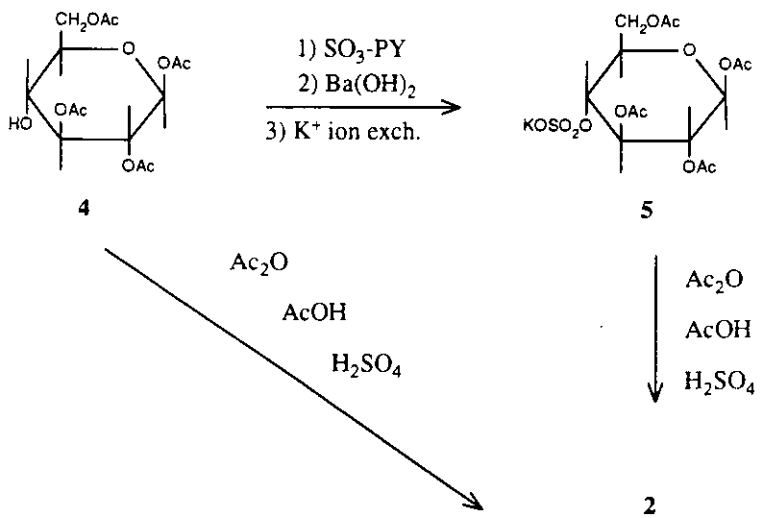
This coincidence of rate constants for hydroxylacetylation and sulfate acetolysis is consistent with Malm's acetylation mechanism involving rapid sulfation followed by rate-determining sulfate acetolysis. That this is indeed the case was established by direct observation of the intermediate sulfate in an acetylation reaction: Alcohol (**3**) was placed in an excess of the acetylation medium used for kinetic studies, and the reaction was quenched with phosphate buffer after 45 seconds. Ion-chromatographic and

hplc analyses showed the presence of only sulfate (**1**) and pentaacetates (**2**); **3** was barely detectable and the mass balance was 101%.

The unexpected confirmation of Malm's proposed sulfate intermediate in sulfuric acid catalyzed acetylation of **3** prompted us to examine the case of a secondary carbohydrate alcohol. The known 1,2,3,6-tetra-*O*-acetyl-beta-**D**-glucopyranose (**4**) was sulfated with sulfur trioxide-pyridine and the crude barium sulfate was isolated; conversion to the potassium salt (**5**) *via* ion exchange gave pure crystalline product in 23% yield. Reaction of **5** under the acetylation conditions described above for **1** gave anomeric mixture (**2**) in quantitative yield; the pseudo first-order rate constant at 24° was 1.9 x $10^{-4}$ $s^{-1}$ ($t_{½}$ = 3660 s). Acetylation of alcohol (**4**) under the same conditions gave **2** at a rate of 1.8 x $10^{-4}$ $s^{-1}$ ($t_{½}$ = 3800 s). Again, the kinetic data are consistent with a rapid sulfation followed by rate-determining acetolysis. Careful nmr analysis ruled out the formation of significant amounts of pentaacetyl galactoses. It is interesting to note that acetolysis of our secondary sulfate was approximately an order of magnitude slower than primary sulfate acetolysis, but that aqueous acid hydrolysis of a secondary sulfate has been found to proceed faster than that of a primary sulfate.[6]



These results raise several questions for further study. In particular, the role of the mixed sulfuric-acetic anhydride in the sulfation process and the mechanism of the sulfate acetolysis are under study.

**EXPERIMENTAL**

Analytical Methods: Gas chromatography was done with a DB5-30W capillary column programmed from 120°C to 300°C at 15°/m. Hplc analyses used 150 x 4.6 mm, $5_{\mu}$, Spherisorb ODS2 column eluted with 70:30 acetonitrile:water; detection was by uv at 220 nm. Both gc and hplc responses were calibrated with known concentrations of the pure compounds being analyzed. Ion chromatography utilized a Dionix IonPac AS5 analytical column preceded by an AG5 guard column; an AMMS micromembrane suppressor was used before the LDC/Milton Roy conductivity detector. The supressor regenerant was 12.5 mmol sulfuric acid at a flow rate of 3 ml/m; eluant was 12 mmol NaOH at 1 ml/m. All acetylation and acetolysis reactions were carried out with freshly prepared (10 m or less) mixtures of 36 wt % acetic anhydride, 63% acetic acid, and 1% sulfuric acid. The buffer used for quenching aliquots from kinetic runs was 0.05 M each of monobasic and dibasic sodium phosphate in 1:1 acetonitrile:water.

Acetolysis of Sulfate **1**: To 10 ml of the above-described acetolysis reagent was added 0.047 g (0.1 mmol) of sulfate (**1**).[5] The solution was allowed to stand at room temperature 6 h. The mixture was poured into 100 ml of water, neutralized with sodium bicarbonate, and extracted with ethyl acetate. The organic phase yielded 35.5 mg (90%) of a syrup shown by gc and nmr to comprise an approximately 2:1 mixture of alpha and beta glucose pentaacetates (**2**). In a control experiment, pure beta-D-glucose pentaacetate was subjected

to identical reaction and workup conditions; there was recovered in 95% yield the same mixture of alpha- and beta- pentaacetates.

Kinetics of Acetolysis of Sulfate (1): To 10 ml of acetolysis reagent mixture in a 24°C±1° water bath was added in one portion at t=0 0.100 g (0.21 mmol) of sulfate (1). Dissolution was instantaneous. Aliquots of 1.0 ml were withdrawn at intervals to 2000 s and added to 5.0 ml of the phosphate buffer described above. Analysis by gc and hplc gave the concentration of products (2); several ion chromatography analyses of the buffered aliquots for residual (1) validated this procedure by giving total mass balances of 100% ± 5%. Control experiments in which starting material (1) and product (2) were added to buffered acetolysis reagent and analyzed 24 h later showed that no changes in structure or concentration of these materials occurred in the buffer system. This kinetic procedure was repeated at 10°C and 4°C. Linear first-order plots were obtained in each case. The rate constants were: 24°C, $1.7 \times 10^{-3}$ $s^{-1}$; 10°C, $3.9 \times 10^{-4}$ $s^{-1}$; 4°C, $1.7 \times 10^{-4}$ $s^{-1}$. These data give $E_a$ = 18.4 kcal/mol, $\Delta S^{\ddagger}$ = -16.7 eu, and log A = 10.7 $s^{-1}$.

Kinetics of Acetylation of 1,2,3,4-Tetra-O-acetyl-beta-D-glucopyranose (3): To 10 ml of acetylation reagent at 24°C was added 0.100 g (0.29 mmol; 0.0058 molar) of 3. One ml aliquots were withdrawn at intervals to 2000 s, quenched to 5 ml in phosphate buffer, and analyzed by hplc for 2. A 45 s aliquot was additionally analyzed by ion chromatography for sulfate (1). Two repetitions gave rate constants of 1.6 and $1.7 \times 10^{-3}$ $s^{-1}$. Analysis of the 45 s sample disclosed the presence of 1 (0.00386 molar) and 2 (0.00196 molar); barely detectable traces of 3 remained.

1,2,3,6-Tetra-O-acetyl-beta-D-glucopyranose-4-sulfate Potassium Salt (5): Glucose tetraacetate (4)[7] (0.87 g, 2.5 mmol) was dissolved in 20 ml of dry pyridine at room temperature. There was added in one portion 0.50 g

of pyridine-sulfur trioxide complex. After 24 h at room temperature, tlc (silica, 15% MeOH in $CHCl_3$) showed the presence of the polar sulfate and traces of residual (**4**). An additional 0.20 g of py-$SO_3$ was added and the mixture stirred a further 20 h. The mixture was then diluted with 50 ml of water and the pH adjusted to ca. 8 with saturated aqueous barium hydroxide. Volatiles were removed in vacuum at 50°C and the residue was reslurried in 30 ml of water. The pH was again adjusted to 7-8 with saturated aqueous barium hydroxide and the resulting mixture again stripped to dryness. The pH adjustment and evaporation was repeated twice more until the pH of the residue, reslurried in water, was stable at about 7. The resulting slurry was then centrifuged and the clear orange supernatant was decanted and evaporated at 50°C. The resulting syrupy barium salt was chromatographed on a silica gel flash column (10% MeOH/$CHCl_3$) and the major product isolated as a light yellow syrup. Nmr analysis of this material suggested a purity level of **5** of *ca.* 80%.

The above procedure was repeated using 1.70 g (4.88 mmol) of **4** and the products were combined. An Amberlyst IR-120 column (100 g wet wt) was prepared in the potassium form and the crude barium sulfate in 100 ml of water passed through the column. The column was washed with 400 ml of water and the total elute was evaporated in vacuum at 50°C. The syrupy residue was triturated with 95% EtOH to give white solid potassium salt (**5**). The crude **5** was recrystallized from 15 ml of 93% EtOH to afford 0.79g (23%) of **5** monohydrate as microcrystals of mp 202-205° (decomp). $^1$H Nmr ($D_2O$): 5.93 (d, J = 11 Hz, 1H), 5.48 (t, J = 12 Hz, 1H), 5.22 (m, 1H), 4.63 (1H), 4.41 (m, 2H), 4.13 (m, 1H), 2.2-2.1 (3 lines, 12 H). $^{13}$C Nmr ($D_2O$): 175.6, 175.3, 174.3, 173.5, 93.4, 74.9, 74.5, 74.2, 72.1, 64.0, 22.1, 21.9, 21.8. Ms (negative ion FAB from a potassium acetate-m-nitrobenzyl alcohol matrix):

m/z 466; calc., 466. Anal. calcd. for $C_{14}H_{19}O_{13}SK$ + 1 $H_2O$: C, 34.7; H, 4.37; S, 6,62. Found: C, 34.4; H, 4.17; S, 6.76.

Kinetics of Acetolysis of Sulfate (**5**): Sulfate (**5**) was acetolysed and aliquots analyzed exactly as described above in the case of sulfate (**1**); sampling was continued through 7200 s. The pseudo first-order rate constant at 24°C was 1.9 x $10^{-4}$ $s^{-1}$.

Kinetics of Acetylation of Alcohol (**4**): Alcohol (**4**) was acetylated under sulfate acetolysis conditions exactly as described in the case of alcohol (**3**) above. Measurements were continued to 7200 s. There was obtained a rate constant of 1.8 x $10^{-4}$ $s^{-1}$.

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