Tetrahedron Letters,Vol.27,No.50,pp 6095-6098,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

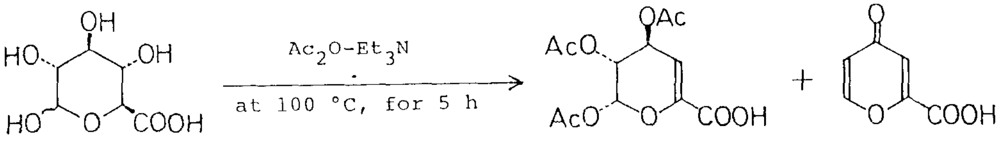
ANOMER-SPECIFICITY IN THE DEGRADATION REACTION OF D-GLUCOPYRANURONIC ACID TETRA-ACETATE LEADING TO COMANIC ACID IN THE ACETIC ANHYDRIDE-BASE SYSTEM

Kiyohiko Tajima
The Noguchi Institute, Kaga 1-8-1, Itabashi-ku, Tokyo 173

Summary: Degradation reaction of 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronic acid(2) was investigated in acetic anhydride-base system. And it was made clear that the second β-elimination in the degradation reaction of 2 to comanic acid(4) occurred advantageously in β-anomer of 2 to afford 4 selectively under milder condition.

We have already reported that the degradation of α-D-galactopyranuronic acid or its tetraacetate in acetic anhydride-base system proceeded by a combination of elimination reaction and recyclization reaction to give the 4,5-unsaturated compound(3-α), 3-acetoxy-6-(diacetoxymethyl)-2*H*-pyran-2-one(5) or comanic acid(4), and the directions of the degradation reactions could be controlled by suitable combinations of the following ruling factors; kind of base catalyst, concentration of acetoxy anion in the reaction system, reaction temperature, and reaction time.[1)]

On the other hand, when the degradation reaction of a commercially available mixture of anomers of D-glucopyranuronic acid was tried in acetic anhydride-triethylamine(volume ratio 3 : 1) at 100 °C for 5 h, 4 and α-anomer of 4,5-unsaturated compound(3-α) were obtained in 34.9% and 8.9% yields, respectively, and the rest of the substrate was degraded to a tarry material. However, β-anomer of 4,5-unsaturated compound(3-β) was not obtained at all, although it was assumed that the degradation reaction of 1 to these compounds proceeded *via* a mixture of anomers of tetraacetate(2).

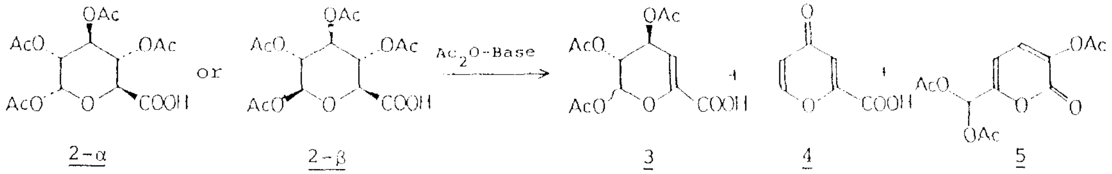


1 3-α 8.9% 4 34.9%

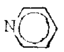
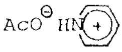
From this result, the author was interested in the relationship between the degradation reaction and the conformation of the acetoxyl group on C-1 of 2 and tried the degradation reaction using respective anomer(2-α and 2-β)[2)] to obtain the results of the degradation reaction accurately. All the results are listed in Table 1.

When the degradation reaction was tried at room temperature using triethylamine as a base for 16 h, 2-α or 2-β gave the 4,5-unsaturated compound(3-α)[1)] or (3-β)[3)], respectively, as the main product, and 4 was obtained in only trace

Table 1. Degradation Reaction of D-Glucopyranuronic Acid Tetraacetate in Acetic Anhydride-Base



2-α 2-β 3 4 5

Base	Reaction temp./°C	Reaction time/h	Substrate	Yield/% 3★	Yield/% 4	Yield/% 5
Et_3N	r.t.	16	2-α 2-β	74.7 73.4	trace 8.8	- -
DBU	r.t.	16	2-α 2-β	76.3 75.5	trace 10.3	- -
Et_3N	50	16	2-α 2-β	71.1 -	3.4 90.0	- -
〃	75	16	2-α	57.2	37.1	-
〃	100	5	2-α 2-β	24.8 -	56.0 94.0	- -
〃	100	16	2-α 2-β	5.2 -	80.2 93.5	- -
	100	16	2-α 2-β	70.5 -	trace 73.5	- -
	100	17	2-α 2-β	73.9 12.9	trace 75.8	trace trace

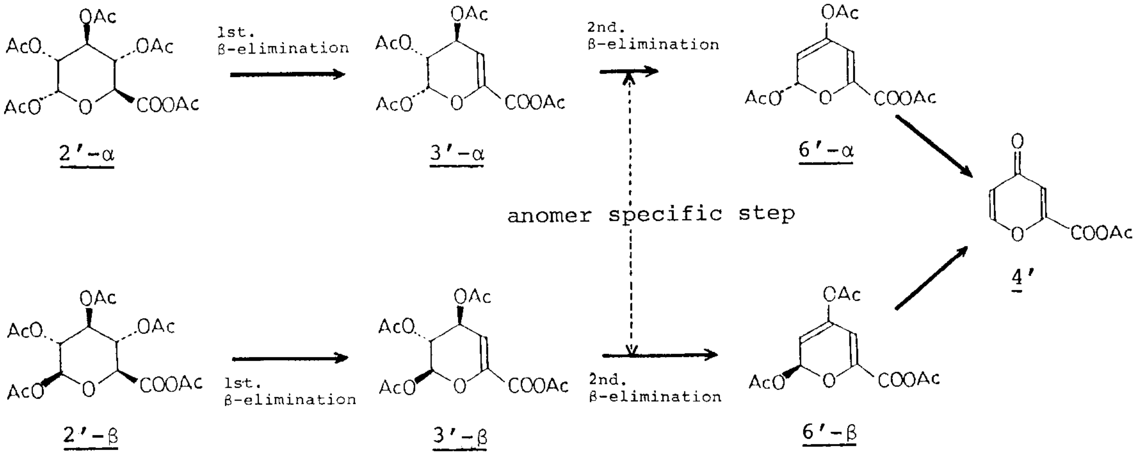
★ α-anomer or β-anomer of 3 was obtained from 2-α or 2-β, respectively.

and 8.8% yield, respectively. And even when stronger base, 1,8-diazabicyclo[5.4.0]-undec-7-ene(DBU), was used in place of triethylamine, 2-α and 2-β also gave 3-α and 3-β along with 4 in trace and 10.3% yield, respectively, at room temperature.

Then, the effect of reaction temperature was investigated at elevated temperature using triethylamine as a base. By the degradation reaction for 16 h, although 2-β was degraded to 4 in 90.0% yield at 50 °C, 2-α had to be treated at 100 °C to give 4 in 80.2% yield. Further, 4 was selectively obtained from 2-β also in the degradation reactions using weeker base at comparatively high temperature. And also, in the case of high concentration of acetoxy anion in the reaction system, for example, in acetic anhydride-acetic acid-pyridine(volume ratio 10:3.3:1), 2-β gave only a trace of 3-acetoxy-6-(diacetoxymethyl)-2*H*-pyran-2-one(5)1) by the treatment at 100 °C for 25 h. This result showed little influence of acetoxy anion on the direction of the degradation reaction of 2 to 4 in acetic anhydride-base system.

A typical example of the degradation reactions was carried out as follows. A solution of 0.208 g(0.57 mmol) of 2-β and 0.3 ml(2.15 mmol) of triethylamine in 3 ml of acetic anhydride was stirred at 50 °C for 16 h and the reagents were evaporated under reduced pressure. To the residue was added 10 ml of water and insoluble substance was filtered off. The filtrate was treated with ion exchange resin(DOWEX 50W-X2) to give 4 in 90.0% yield.

The degradation reaction of 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronic acid(2) was assumed to be composed of double β-elimination reactions and acetoxy anion catalyzed acetic anhydride elimination in the mixed anhydride(2') between 2 and acetic acid, and proceeded as shown below ; 2' was converted to the 4,5-unsaturated mixed anhydride(3') by the first β-elimination, then underwent the second β-elimination to give 2,3:4,5-di-unsaturated mixed anhydride(6'), finally acetic anhydride was eliminated from 6' by acetoxy anion to afford 4'.[4]

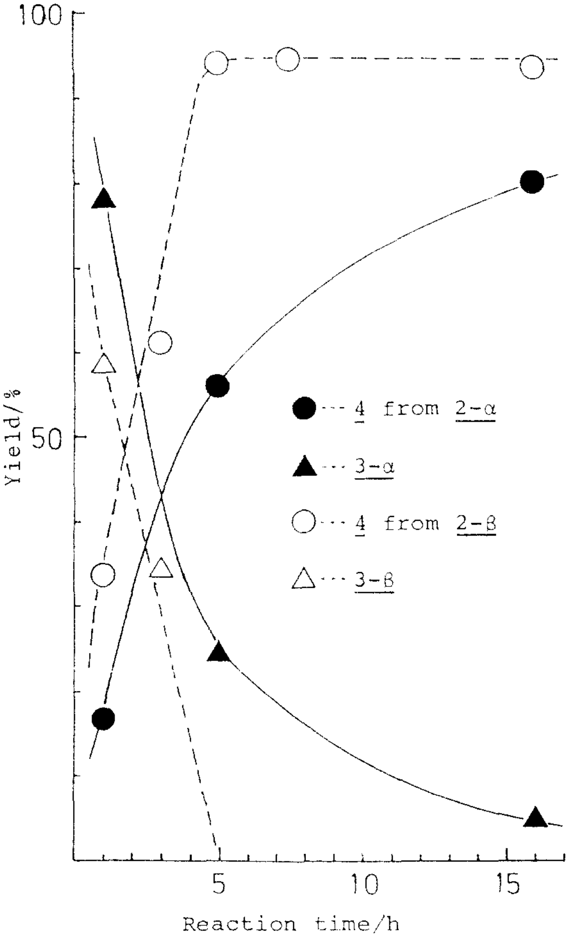


The favoring effect of the trans elimination over the cis elimination has been known in ionic β-elimination reaction and also reported in β-elimination reaction in pyranuronic acid derivatives. For example, methyl esters of methyl pyranosides of 2,3,4-tri-*O*-methyl-α-D-mannuronic acid, -α-D-glucuronic acid, and -β-D-galacturonic acid undergo cis, cis, and trans elimination, respectively, to give the 4,5-unsaturated esters by treatment with sodium methoxide in methanol at room temperature, but the second β-elimination occurs only in the methyl(methyl-2,3-di-*O*-methyl-4-deoxy-β-L-mannopyranoside)uronate to yield a 2,3:4,5-di-unsaturated ester(trans elimination) and not in the other two compounds(cis elimination).[5] Also in the present degradation reaction, double β-elimination was possible and, from the results of the degradation reaction of 2-α or 2-β using triethylamine or DBU at room temperature, yields of the main product, 4,5-unsaturated compound(3-α or 3-β) afforded by the first β-elimination were almost same and there was no difference in reactivity between 2'-α and 2'-β in the first β-elimination. However, at elevated temperature, degradation reaction of 2-α and 2-β in acetic anhydride-triethylamine for 16 h showed that 2-β degraded to 4 more easily than 2-α and the rest from 2-α was 3-α and not 2,3:4,5-di-unsaturated compound(6-α). To confirm this anomer specificity in the degradation reaction, both anomers were degraded in the acetic anhydride-triethylamine(volume ratio=10 : 1)system at 100 °C and change in yields of 4 and 3 with reaction time were investigated. Results were summarized in

Fig. 1. From these results it was made clear that 3'-β was more reactive than 3'-α in the second β-elimination and it was reasonable to speculate that a ruling factor of the second β-elimination was conformation of the acetoxyl group on C-1 of 3'.

It was interesting problem whether this anomer specific β-elimination was possible in other solvent-base system or not. In order to investigate this point, the degradation of 2-β was tried in acetone-triethylamine at 50 °C for 16 h in the presence of an equimolar acetic anhydride, which was essential to prepare the mixed anhydride (2'-β). In this case, the degradation of 2-β did not proceed smoothly and 4 was obtained in only 23.1% yield along with 3-β in 69.5% yield. From this result it was assumed that acetic anhydride in excess played some role in the second anomer specific β-elimination in the degradation reaction of 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronic acid (2) in acetic anhydride-base system. Although the mechanism of this specific effect by the combination of conformation of acetoxyl group on C-1 of 2 and acetic anhydride has not been investigated, this anomer specificity was found to be effective in controlling degradation reaction of 2 to 4 in acetic anhydride-base system.

Fig. 1. Degradation of D-Glucopyranuronic Acid Tetraacetate (2-α and 2-β) in Acetic Anhydride-Et_3N at 100 °C



The auther wishes to thank Professor Teruaki Mukaiyama of the University of Tokyo for helpful discussion and encouragement.

References

1) K. Tajima, Chem. Lett., 1985, 49.
2) Anomers of 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronic acid were separated by the method of E. M. Fry; J. Amer. Chem. Soc., 77, 3915(1955).
3) Physical constants of the product are as follows. IR(NaCl) 1740, 1660, 1430, 1370, 1220, 1120, 1032 cm^{-1}; NMR($CDCl_3$) δ 2.10(s, 9H, 3×$OCOCH_3$), 5.07-5.40(m, 2H, H-2 and H-3), 6.24-6.50(m, 2H, H-1 and H-4), 8.87(s, carboxyl).
4) A similar reaction mechanism has been reported; H. F. G. Beving and O. Theander, Acta Chem. Scand., B 29, 577(1975).
5) J. N. BeMiller and G. V. Kumari, Carbohydr. Res., 25, 419(1972).

(Received in Japan 26 August 1986)