# Organic & Biomolecular Chemistry

**PAPER**

# Direct participation of counter anion in acid hydrolysis of glycoside†

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The mechanism of acid hydrolysis of glycoside has been investigated since the end of the 19th century accompanied by lots of literatures published on the mechanism, although little attention has surprisingly been paid to the action of counter anion of acid. In this paper, it was investigated whether or not counter anion of acid directly participates in acid hydrolysis of glycosides, methyl α- and β-D-glucopyranosides (MGP) in water, aqueous 74%, and 82% 1,4-dioxane systems. Because proton activity of a reaction system is the important rate-determining parameter in the universally acknowledged mechanism, it was carefully estimated in this study. The results suggested that bromide anion directly participates in the acid hydrolysis reaction of MGP in a water solvent system and the participation of bromide anion is further pronounced in aqueous 74% and 82% 1,4-dioxane solvent systems. It was also suggested that chloride anion directly participates in these dioxane solvent systems.

## Introduction

Acid hydrolysis of glycoside has been investigated since the end of the 19th century, especially focusing on the mechanism and effect of the structure on the rate.[1–28] The mechanism has been established and universally acknowledged at least for most glycopyranosides, as shown in Scheme 1. The first step is protonation of the exocyclic oxygen of the glycosidic bond affording the conjugate acid, and rapidly attains equilibrium. The conjugate acid liberates the aglycon to afford the cyclic cation. This second step is the slowest and rate-determining. Only the conjugate acid can advance to the rate-determining step. Owing to these mechanisms, acid hydrolysis of glycoside shows characteristics of specific acid catalysis.[3,5,7] The water addition and consecutive release of a proton afford the hydrolysis product. It is believed that water does not steadily assist the release of the aglycon,[7,9] and hence, the discrete cyclic cation forms. Consequently, the reaction is apparently unimolecular and shows characteristics of $S_N1$-type substitution reaction (A1 mechanism).[9] On the basis of these characteristics, concentration of glycoside and proton activity, *viz.* only concentration of the conjugate acid of glycoside, are the only practical rate-determining parameters in acid hydrolysis of glycoside. Solvent dissociating power and temperature are the other
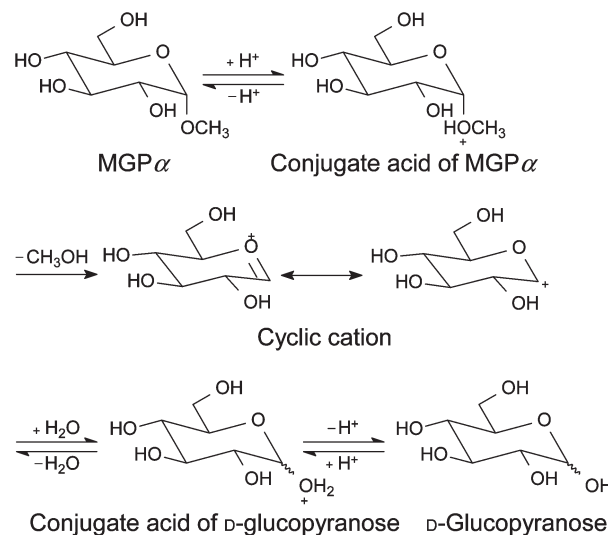


**Scheme 1** The universally acknowledged mechanism of acid hydrolysis reaction of glycoside. A glycoside compound, methyl α-D-glucopyranoside (MGPα), is representatively described.

rate-determining parameters, although the power is referred to only when reactions are compared between different solvent systems.

When a chemical reaction using various acids is concerned, the counter anions are always potential species to influence the reaction. However as described above, it is generally accepted that proton activity is the only practical rate-determining parameter in acid hydrolysis of glycoside. On the basis of this general acceptance, counter anion can influence acid hydrolysis of glycoside only indirectly *via* its interaction with proton

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†Electronic supplementary information (ESI) available: Figures of the same kind as Fig. 1 and 2 for the other systems. See DOI: 10.1039/c2ob25451d
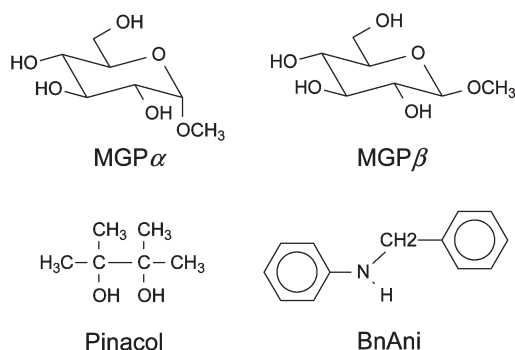
**Fig. 1**   Structure of model compounds used as starting materials.

affecting the strength of proton activity, although some counter anions have relatively strong nucleophilicity and others do not. These backgrounds have motivated us to confirm whether or not counter anions are certainly inert in acid hydrolysis of glycoside. It is surprising, furthermore, that only a few researches have focused on the role of counter anion. Painter ruled out the possibility of the direct participation of counter anions in acid hydrolysis reaction of glycosides, methyl α- and β-D-glucopyranosides (MGPα, MGPβ), although the possibility seemed to be suspectedly remained for bromide anion in the hydrolysis of MGPβ.[14] Zaranyika *et al.* and Charmot *et al.* discussed on the role of counter anion in acid hydrolysis of polysaccharide with crystalline structure[18,19] and on catalytic action of dihydrogenphosphate,[28] respectively. Only these papers currently seem to focus on the role of counter anion in acid hydrolysis of glycoside. Therefore, we decided to examine the effect of counter anion on acid hydrolysis of glycoside using MGPα and MGPβ, although it was suggested that the mechanism of MGPβ might possibly differ from that of MGPα.[14,26]

In this study, a pair of MGPα and MGPβ was hydrolyzed in hydrochloric, hydrobromic, or sulfuric acid solution, and their disappearances were examined in detail to understand the role of counter anion in acid hydrolysis of glycoside. Other solvent systems using aqueous 74% and 82% 1,4-dioxane solutions were also applied to examine the effect of solvent constitution on the action of counter anion. Proton activity of an acid hydrolysis reaction system relative to that of another system was carefully estimated in this study.

Chemical structures of the compounds used as starting materials are shown in Fig. 1. MGPα, MGPβ, 2,3-dimethylbutane-2,3-diol (pinacol), and *N*-benzyl aniline (BnAni) were applied to starting compounds. All kinds of reactions employed in this study are summarized in Table 1.

## Results and discussion

### Method for obtaining appropriate pseudo-first-order reaction rate constant

In this study, each of a pair of MGPα and MGPβ, pinacol, or BnAni was acid hydrolyzed, and their disappearance behaviours were kinetically examined to discuss the effect of counter anion on the hydrolysis rates. Because the difference in the hydrolysis rates between some reaction systems was often small, it was

**Table 1**   List of all the reaction systems employed in this study[a]

Solvent: H₂O (0% 1,4-dioxane)

|        | HCl | HBr | $H_2SO_4$ | $CH_3SO_3H$ |
|--------|-----|-----|-----------|-------------|
| MGP[b] | Done[c] | Done | Done | Not done |
| Pinacol | Done | Done | Done | Not done |
| BnAni | Not done[d] | Not done | Not done | Done |

Solvent: aqueous 74% 1,4-dioxane

|        | HCl | HBr | $H_2SO_4$ | $CH_3SO_3H$ |
|--------|-----|-----|-----------|-------------|
| MGP | Done | Done | Done | Not done |
| Pinacol | Done | Done | Done | Done |
| BnAni | Not done | Not done | Not done | Done |

Solvent: aqueous 82% 1,4-dioxane

|        | HCl | HBr | $H_2SO_4$ | $CH_3SO_3H$ |
|--------|-----|-----|-----------|-------------|
| MGP | Done | Done | Done | Not done |
| Pinacol | Done | Done | Done | Done |
| BnAni | Not done | Not done | Not done | Done |

[a] Concentration of the acids and temperature were 0.20 mol l⁻¹ and 85 °C in all systems employed. [b] Pair of MGPα and MGPβ. [c] Reaction was done. [d] Reaction was not done.
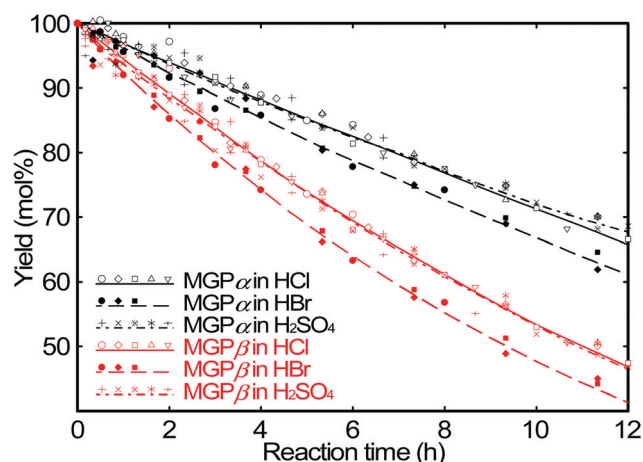


**Fig. 2**   Actual experimental data points observed when a pair of MGPα and MGPβ was acid-hydrolyzed in the H₂O solvent systems, and the best fit curves obtained from these data points of each reaction. The hydrolysis with HCl, HBr, or H₂SO₄ was repeated 5, 3, or 5 times, respectively.

required to draw disappearance curves of the compounds that exactly fitted to experimental data points of each of the reaction systems. Fig. 2 representatively displays experimental data points and the disappearance curves that fit best to these points, when a pair of MGPα and MGPβ was treated in the H₂O solvent systems. (See ESI† on the other systems.) Each of the curves was hand-drawn. The hand-drawn curves always seemed to fit to the experimental data points better than those prepared by computational approximations. This was because several experimental data points could fuzzily be judged as those with significant deviations caused by experimental error in the hand-drawing.

**Table 2** List of coefficients of determination ($R^2$) for the hand-drawn curves[a]

Solvent: H$_2$O (0% 1,4-dioxane)

|        | HCl        | HBr      | H$_2$SO$_4$ | CH$_3$SO$_3$H |
|--------|------------|----------|-------------|---------------|
| MGPα   | 0.987      | 0.985    | 0.980       | Not done      |
| MGPβ   | 0.996      | 0.995    | 0.992       | Not done      |
| Pinacol| 0.995      | 0.994    | 0.991       | Not done      |
| BnAni  | Not done[b]| Not done | Not done    | 0.994         |

Solvent: aqueous 74% 1,4-dioxane

|        | HCl      | HBr      | H$_2$SO$_4$ | CH$_3$SO$_3$H |
|--------|----------|----------|-------------|---------------|
| MGPα   | 0.997    | 0.996    | 0.996       | Not done      |
| MGPβ   | 0.998    | 0.997    | 0.999       | Not done      |
| Pinacol| 0.981    | 0.990    | 0.993       | 0.993         |
| BnAni  | Not done | Not done | Not done    | 0.997         |

Solvent: aqueous 82% 1,4-dioxane

|        | HCl      | HBr      | H$_2$SO$_4$ | CH$_3$SO$_3$H |
|--------|----------|----------|-------------|---------------|
| MGPα   | 0.997    | 0.998    | 0.993       | Not done      |
| MGPβ   | 0.993    | 0.999    | 0.998       | Not done      |
| Pinacol| 0.995    | 0.994    | 0.998       | 0.992         |
| BnAni  | Not done | Not done | Not done    | 0.999         |

[a] Concentration of the acids and temperature were 0.20 mol l$^{-1}$ and 85 °C in all systems employed. [b] Reaction was not done.
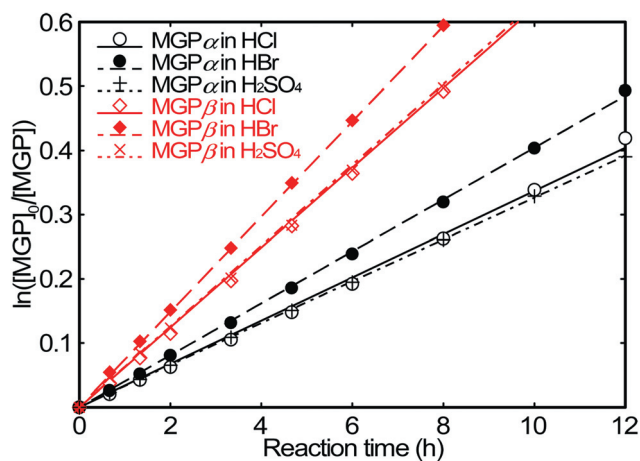
On the other hand, computational approximations treated all the experimental data points equally to draw a curve even when some of the data points were largely deviant. Indeed, the curves obtained by computation were almost the same with the hand-drawn curves when these curves were prepared after deleting the data points that were judged as those with significant deviations in the hand-drawing. As a reference, the coefficients of determination for the hand-drawn curves are listed in Table 2. Most of the coefficients were more than 0.990. Even the worst one was 0.980. These results ensured the appropriateness of the hand-drawn best fit curves.

Several data points on each of the best-fit curves were utilized for preparation of the logarithmic plot for the disappearance of the starting compound, which gave a pseudo-first-order reaction rate constant. Fig. 3 shows the representative logarithmic plots for the hydrolyses of a pair of MGPα and MGPβ in the H$_2$O solvent systems. (See ESI† on the other systems.)

### General description of acid hydrolysis

The disappearance curves of MGPα and MGPβ in all the reaction systems could be approximated to pseudo-first-order reactions with the correlation coefficients very close to unity, with the exceptions of several systems (Table 3). MGPα was always hydrolyzed slower than MGPβ in all cases (Table 3), which is in accordance with previous findings.[11] In the following text, the term MGP indicates both MGPα and MGPβ. No compounds other than D-glucose were detected as degradation products in any reaction system employed. It is rational to presume, therefore, that D-glucose was the sole reaction product in all reaction systems employed, although it was not quantified.



**Fig. 3** Representative logarithmic plots for the disappearances of MGPα and MGPβ in the H$_2$O solvent systems. [MGP]: concentration of MGPα or MGPβ, [MGP]$_0$: initial concentration of MGPα or MGPβ.

**Table 3** List of pseudo-first-order reaction rate constants ($k_{obs}$) obtained from acid hydrolysis reactions of MGP[a]

Solvent: H$_2$O (0% 1,4-dioxane)

|           | HCl  |      | HBr  |      | H$_2$SO$_4$ |      |
|-----------|------|------|------|------|-------------|------|
| α, β      | MGPα | MGPβ | MGPα | MGPβ | MGPα        | MGPβ |
| $k_{obs}$[b] | 3.37 | 6.22 | 4.04 | 7.41 | 3.26        | 6.29 |
| $R^2$[c]  | 0.997| 0.999| 1.00 | 1.00 | 1.00        | 0.999|

Solvent: aqueous 74% 1,4-dioxane

|           | HCl  |      | HBr  |      | H$_2$SO$_4$ |      |
|-----------|------|------|------|------|-------------|------|
| α, β      | MGPα | MGPβ | MGPα | MGPβ | MGPα        | MGPβ |
| $k_{obs}$ | 12.3 | 24.7 | 14.2 | 25.1 | 7.69        | 14.7 |
| $R^2$     | 0.998| 0.999| 0.999| 0.991| 1.00        | 0.999|

Solvent: aqueous 82% 1,4-dioxane

|           | HCl  |      | HBr  |      | H$_2$SO$_4$ |      |
|-----------|------|------|------|------|-------------|------|
| α, β      | MGPα | MGPβ | MGPα | MGPβ | MGPα        | MGPβ |
| $k_{obs}$ | 35.5 | 63.8 | 48.6 | 85.1 | 16.6        | 34.6 |
| $R^2$     | 0.998| 1.00 | 0.996| 0.988| 0.997       | 0.999|

[a] Concentration of the acids and temperature were 0.20 mol l$^{-1}$ and 85 °C in all systems employed. [b] Unit: ×10$^{-2}$ h$^{-1}$. [c] Square of correlation coefficient.

therefore, that D-glucose was the sole reaction product in all reaction systems employed, although it was not quantified.

The disappearance curves of pinacol and BnAni in all the reaction systems employed could be approximated to pseudo-first-order reactions with the correlation coefficients very close to unity, with the exceptions of several systems (Tables 5 and 7, respectively). Almost no compounds other than 3,3-dimethylbutan-2-one (pinacolone in Scheme 2) and benzyl alcohol + aniline (Scheme 3) were detected as reaction products in the pinacol and BnAni reactions, respectively. Several minor reaction products other than pinacolone were detected in the pinacol reactions in the aqueous 1,4-dioxane solvent systems. It is rational to

**Scheme 2** The universally acknowledged mechanism of the pinacol rearrangement.



**Scheme 3** Estimated mechanism of acid hydrolysis reaction of BnAni.

presume, however, that pinacolone was almost the sole reaction product in the pinacol reaction, and benzyl alcohol and aniline were the only products in the BnAni reaction in all reaction systems employed, although these compounds were not quantified.

There are four rate-determining parameters in the acid hydrolysis reactions employed in this study: proton activity, concentration of compound, solvent dissociating power, and temperature. Because all of the hydrolysis reactions could be approximated to pseudo-first-order reactions, concentration of compound is not focused on in the following text. Temperature is not referred to in the following text, since all the hydrolysis reactions were conducted at 85 °C. Solvent dissociating power is discussed only when the acid hydrolysis reactions in different solvent systems are compared. Because of these factors, proton activity is mainly discussed in the following text.

### Theory for estimation of relative proton activity

Measurement of the Hammett acidity function is a common way to estimate proton activity of a reaction system. Hence, proton activity of the reaction systems employed was estimated from the UV absorbances of 4-nitroaniline at 380, 372, or 370 nm ($A_{system}$) when it was dissolved in the reaction systems with the 0% ($H_2O$), aqueous 74%, or aqueous 82% 1,4-dioxane solution, respectively, at room temperature. The values of $A_n$ are defined as the UV absorbances of 4-nitroaniline in the neutral 0%, aqueous 74%, and aqueous 82% 1,4-dioxane solutions. The values of $A_a$ are similarly defined as the UV absorbances of the

conjugate acid of 4-nitroaniline in the acid 0%, aqueous 74%, and aqueous 82% 1,4-dioxane solutions containing 72% $H_2SO_4$. It is assumed that the existence of the conjugate acid of 4-nitroaniline and 4-nitroaniline itself can be ignored in the neutral solutions and the acid solutions containing 72% $H_2SO_4$, respectively. On the basis of $A_n$, $A_a$, and observed $A_{system}$, the proportion of 4-nitroaniline applied to the UV measurement that is present as its conjugate acid can be calculated using the following equation: Conjugate acid (%) = $(A_n - A_{system})/(A_n - A_a) \times 100$. As can be recognized from the values of $A_n$ and $A_a$, the value of $A_{system}$ observed in a system becomes smaller with the increase in proton activity of the system. Proton activity of a reaction system employed can be compared with that in another employed reaction system on the basis of the values of $A_{system}$ in these systems. However, proton activity observed by this method should not be compared between systems with different content of 1,4-dioxane but between those with the same content of 1,4-dioxane.

Proton activity should also be estimated at 85 °C, which was employed in the acid hydrolysis reactions of MGP, because proton activity of a system at room temperature must be different from that at an elevated temperature. To estimate proton activity at 85 °C, it should be appropriate to compare the rates of a standard chemical reaction between the employed reaction systems because it is difficult to measure stably the UV absorbance at 85 °C. It is prerequisite for this standard chemical reaction, however, that its mechanism shows characteristics of specific acid catalysis and $S_N1$-type substitution reaction without participation or assistance of any nucleophile (A1 mechanism). If these prerequisites are not satisfied, not only proton activity but also concentration of possible nucleophiles can be a rate-determining parameter, and consequently, proton activity cannot be estimated. The pinacol rearrangement (conversion of pinacol to pinacolone under acidic conditions) seemed to satisfy these prerequisites and was applied to the standard chemical reaction. The mechanism of the pinacol rearrangement is shown in Scheme 2. Protonation of the oxygen of a hydroxyl group and subsequent release of the $H_2O$ molecule afford the tertiary carbocation. A methyl anion on the other tertiary carbon migrates to the cation center, and consecutive release of the proton affords pinacolone. The discrete tertiary carbocation is believed to form without any assistance of the methyl anion migration to release the $H_2O$ molecule.[29] Because only the conjugate acid of pinacol can advance to the rate-determining step, the release of the $H_2O$ molecule, the pinacol rearrangement shows characteristics of specific acid catalysis, and hence, concentration of pinacol and proton activity, *viz.* concentration of the conjugate acid of pinacol, are the only practical rate-determining parameters. Furthermore, counter anion and solvent cannot participate in the reaction owing to the large steric hindrance of the reaction center of pinacol. On the basis of these reaction characteristics, proton activity of the employed reaction systems was estimated from the disappearance rates of pinacol in the pinacol rearrangement under conditions identical to those of the acid hydrolysis reaction of MGP.

### Effect of counter anion in water

Pseudo-first-order reaction rate constants obtained from the acid hydrolysis of MGP are listed in Table 3. In the $H_2O$ solvent

**Table 4** List of UV absorbances of 4-nitroaniline (98 mg l^{−1}) measured at room temperature and proportion of its conjugate acid (CA) present

Solvent: H$_2$O (0% 1,4-dioxane)

| Condition | Neutral | | Acid (72% H$_2$SO$_4$) |
|---|---|---|---|
| $A_n$ or $A_a$ | 0.937 | | 0.000 |

| Acid[a] | HCl | HBr | H$_2$SO$_4$ |
|---|---|---|---|
| $A_{system}$[b] | 0.258 | 0.261 | 0.266 |
| CA (%) | 72.5 | 72.1 | 71.6 |
| $H_0$[c] | 0.57 (ca. 0.65) | 0.58 (ca. 0.65) | 0.59 (ca. 0.55) |

Solvent: aqueous 74% 1,4-dioxane

| Condition | Neutral | | Acid (72% H$_2$SO$_4$) |
|---|---|---|---|
| $A_n$ or $A_a$ | 1.088 | | 0.000 |

| Acid | HCl | HBr | H$_2$SO$_4$ |
|---|---|---|---|
| $A_{system}$ | 0.969 | 0.954 | 0.972 |
| CA (%) | 10.9 | 12.3 | 10.7 |

Solvent: aqueous 82% 1,4-dioxane

| Condition | Neutral | | Acid (72% H$_2$SO$_4$) |
|---|---|---|---|
| $A_n$ or $A_a$ | 1.101 | | −0.016 |

| Acid | HCl | HBr | H$_2$SO$_4$ |
|---|---|---|---|
| $A_{system}$ | 0.947 | 0.947 | 0.975 |
| CA (%) | 13.8 | 13.8 | 11.3 |

[a] Concentration of the acids were 0.20 mol l^{−1}. [b] $A_{system}$: $A_{HCl-0}$, $A_{HBr-0}$, $A_{H_2SO_4-0}$, $A_{HCl-74}$, $A_{HBr-74}$, $A_{H_2SO_4-74}$, $A_{HCl-82}$, $A_{HBr-82}$, or $A_{H_2SO_4-82}$. [c] $H_0$: The Hammett acidity functions were calculated on the basis of CA and the p$K_a$ value of 4-nitroaniline (0.99). The values in the parentheses are those estimated from the data in the ref. 30.

**Table 5** List of pseudo-first-order reaction rate constants ($k_{obs}$) obtained from the pinacol rearrangement[a]

Solvent: H$_2$O (0% 1,4-dioxane)

| | HCl | HBr | H$_2$SO$_4$ |
|---|---|---|---|
| $k_{obs}$[b] | 10.3 | 10.4 | 10.5 |
| $R^2$[c] | 0.993 | 0.999 | 0.985 |

Solvent: aqueous 74% 1,4-dioxane

| | HCl | HBr | H$_2$SO$_4$ | CH$_3$SO$_3$H |
|---|---|---|---|---|
| $k_{obs}$ | 2.35 | 3.21 | 3.47 | 2.72 |
| $R^2$ | 0.991 | 0.996 | 0.997 | 0.998 |

Solvent: aqueous 82% 1,4-dioxane

| | HCl | HBr | H$_2$SO$_4$ | CH$_3$SO$_3$H |
|---|---|---|---|---|
| $k_{obs}$ | 3.67 | 7.26 | 6.31 | 2.89 |
| $R^2$ | 0.966 | 0.996 | 0.999 | 1.00 |

[a] Concentration of the acids and temperature were 0.20 mol l^{−1} and 85 °C in all systems employed. [b] Unit: ×10^{−2} h^{−1}. [c] Square of correlation coefficient.

systems, the rate constant of MGP in the HCl system is almost the same as that in the H$_2$SO$_4$ system. This result suggests that proton activity of these systems is the same and a molecule of H$_2$SO$_4$ releases only one proton. The hydrolysis of MGP was slightly but clearly more rapid in the HBr system than those in the other two acid systems, although the concentrations of these three acids were the same. The rate constants of both MGPα and MGPβ in the HBr system are about 1.2 times as large as those in the HCl and H$_2$SO$_4$ systems. Proton activity is the only practical rate-determining parameter on the basis of Scheme 1. Hence, proton activity of the HBr system is possibly higher than those of the other two acid systems. Alternatively, it may be suggested that Br⁻ directly participates in the hydrolysis of MGP, if the proton activities of the HCl and HBr systems are not different. It is required to estimate proton activity of three acid systems.

Table 4 lists UV absorbances of 4-nitroaniline at 380, 372, or 370 nm ($A_{system}$) in the 0% (H$_2$O), aqueous 74%, or aqueous 82% 1,4-dioxane solvent systems, respectively, and the proportions of 4-nitroaniline applied to the UV measurement that was present as its conjugate acid when 4-nitroaniline was dissolved in each of the reaction systems employed. The Hammett acidity functions ($H_0$) in the H$_2$O systems of this study are indicated in Table 4 with those estimated from the data in the literature.[30] Proton activity of the reaction systems at room temperature can be estimated from $A_{system}$, as described in the previous section. In the H$_2$O solvent systems, $A_n$ and $A_a$ were 0.937 and 0.000, respectively. As can be seen, A$_{HBr-0}$ was

slightly larger than A$_{HCl-0}$, although there were no noticeable differences between A$_{HCl-0}$, A$_{HBr-0}$, and A$_{H_2SO_4-0}$. These values suggest that proton activities of three acid reaction systems are not different at least at room temperature in the H$_2$O solvent systems.

Table 5 lists pseudo-first-order reaction rate constants obtained from the pinacol rearrangement in the reaction systems employed. Proton activity at 85 °C can be estimated from this rate constant as described in the previous section. The rate constants in three acid systems are not different from one another (Table 5). It is suggested, therefore, that proton activities of three acid reaction systems are not different even under conditions of the actual hydrolysis reaction of MGP in the H$_2$O solvent systems.

Because proton activity of the H$_2$O solvent systems with three acids is not found to be different, it is proposed that Br⁻ directly participates in the hydrolysis reaction of MGP. A possible participation mechanism is that Br⁻ assists the CH$_3$OH liberation in Scheme 1 from the opposite side, which is similar to S$_N$2-type substitution reaction. Another possible mechanism is that Br⁻ assists the α-D-glucopyranose liberation attacking the CH$_3$ carbon of the aglycon of the cyclic cation from the opposite side. Since Br⁻ is not lost and the concentration of Br⁻ is not changed in either mechanism, the acid hydrolysis reaction of MGP follows the pseudo-first-order reaction rate law even when Br⁻ participates in the hydrolysis reaction. It is a further research topic to examine possibilities of these mechanisms utilizing a glycoside compound with an aglycon sterically bulkier than CH$_3$ group.

The results obtained cannot completely rule out the possibility that the faster hydrolysis of MGP in the HBr system might result from its possibly higher solvent dissociating power than those in the other two acid systems. If this is the case, Br⁻ indirectly participates in the reaction. This possibility seems to be doubtful,

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however, because the powers of the HCl and $H_2SO_4$ systems should not be different from each other based on the hydrolysis rates in these systems. Although there might be other possible mechanisms for explaining the faster hydrolysis of MGP in the HBr system, the direct participation of $Br^-$ should be the most plausible.

### Effect of counter anion in aqueous 74% 1,4-dioxane

In the aqueous 74% 1,4-dioxane solvent systems, the rate constants of the hydrolysis reactions of MGP in the HCl and HBr systems are larger than that in the $H_2SO_4$ system (Table 3). The rate constant in the HCl system is slightly smaller than that in the HBr system. These results may suggest the direct participation of not only $Br^-$ but also $Cl^-$ in the hydrolysis reaction of MGP. To confirm this possibility, proton activity of three acid systems should be estimated.

The maximal absorption wavelength of 4-nitroaniline was 372 nm in the aqueous 74% 1,4-dioxane solutions, and the values of $A_n$ and $A_a$ were 1.088 and 0.000, respectively. The value of $A_{HCl-74}$ was not different from $A_{H_2SO_4-74}$, although $A_{HBr-74}$ was slightly smaller than the other two (Table 4). These results suggest that proton activity of the HCl system is not different from that of the $H_2SO_4$ system at least at room temperature, although proton activity of the HBr system may be slightly higher than those of the other two acid systems.

The rate constants of the pinacol rearrangement obtained from the aqueous 74% 1,4-dioxane solvent systems with three acids are not significantly different from one another, but decrease in the order of: $H_2SO_4$ > HBr > HCl (Table 5). It should be focused on that the rate in the $H_2SO_4$ system is greater than those in the other two acid systems. It seems clear that nucleophilicity of $HSO_4^-$ (and $SO_4^{2-}$) is very low and $HSO_4^-$ (and $SO_4^{2-}$) does not directly participate in the sterically largely hindered pinacol rearrangement. Solvent dissociating power of three acid systems should not either be considered to be different. A possible explanation for the faster pinacol rearrangement in the $H_2SO_4$ system is that $HSO_4^-$ further dissociates to $SO_4^{2-}$ in the aqueous 74% 1,4-dioxane solvent system at 85 °C, which makes proton activity of the $H_2SO_4$ system higher than those of the other two acid systems, although this phenomenon does not seem to appear at room temperature on the basis of the comparison of the UV absorbances of 4-nitroaniline between three acid systems. To confirm this phenomenon, the rate of the pinacol rearrangement in another acid system, 0.2 mol l$^{-1}$ $CH_3SO_3H$ in the aqueous 74% dioxane solution, was examined. The rate constant is smaller than that in the $H_2SO_4$ system and between those in the HCl and HBr systems (Table 5). This result should confirm that some $H_2SO_4$ molecules release two protons in the aqueous 74% 1,4-dioxane solvent system at 85 °C. The higher proton activity of the $H_2SO_4$ system must result in the fast pinacol rearrangement. The rate difference between the HCl and HBr systems probably results from the difference in proton activity between these two systems as suggested by the above UV absorbances. It may be possible that $Br^-$ directly participates in the pinacol rearrangement in the aqueous 74% 1,4-dioxane solvent system to a very small extent even though no nucleophile has been assumed to participate in the pinacol rearrangement. If

this is the case, the assumption of complete absence of the nucleophile participation in the pinacol rearrangement is valid only in the $H_2O$ solvent systems.

In spite of the suggested highest proton activity in the $H_2SO_4$ system, the hydrolysis of MGP in this system was slower than those in the other two acid systems. This result strongly suggests that not only $Br^-$ but also $Cl^-$ directly participates in the hydrolysis reaction of MGP in the aqueous 74% 1,4-dioxane solvent systems. Possible mechanisms must be similar to those proposed in the previous section. Because it was suggested that the acid hydrolysis mechanism of glycopyranosides is not exocyclic cleavage (Scheme 1) but mainly endocyclic anomeric C–O bond cleavage under anhydrous conditions with the presence of a Lewis acid,[13,16,20,22,24] however, other possible mechanisms, such as attack on the anomeric carbon from the direction opposite from the endocyclic anomeric C–O bond, may be proposed. The rate constant of MGP in the HBr system is about 1.7–1.8 times as large as that in the $H_2SO_4$ system, although proton activity of the $H_2SO_4$ system must be higher than that of the HBr system. This ratio is about 1.2 in the $H_2O$ solvent system. The participation of $Br^-$ and $Cl^-$ should be more significant in the aqueous 74% 1,4-dioxane solvent systems than that of $Br^-$ in the $H_2O$ solvent system. The slightly faster hydrolysis of MGP in the HBr system than in the HCl system may result from either or both of higher proton activity in the former than in the latter system, as suggested above, and more active participation of $Br^-$ in the hydrolysis reaction of MGP than $Cl^-$.

It should be shown that the molar ratio of 1,4-dioxane to $H_2O$ in aqueous 74% 1,4-dioxane solution (v/v) is about 0.6.

### Effect of counter anion in aqueous 82% 1,4-dioxane

In the aqueous 82% 1,4-dioxane solvent systems, the rate constants for the hydrolysis reactions of MGP decrease in the order of: HBr > HCl > $H_2SO_4$ (Table 3). A fairly large difference was observed not only between the $H_2SO_4$ and the other two acid systems but also between the HCl and HBr systems, which is not the same as for those observed in the aqueous 74% 1,4-dioxane solvent systems. Similar to the aqueous 74% 1,4-dioxane solvent systems, it is suggested that not only $Br^-$ but also $Cl^-$ directly participates in the hydrolysis reaction of MGP and the former is more active than the latter. To confirm this, proton activity of three acid systems must be estimated.

The maximal absorption wavelength of 4-nitroaniline was 370 nm in the aqueous 82% 1,4-dioxane solutions, and the values of $A_n$ and $A_a$ were 1.101 and −0.016, respectively. As shown in Table 4, $A_{HCl-82}$ was the same as $A_{HBr-82}$, and $A_{H_2SO_4-82}$ was larger than the other two. These results suggest that proton activity of the $H_2SO_4$ system is lower than those of the other two acid systems at least at room temperature. Because the low proton activity of the $H_2SO_4$ system possibly resulted in the slowest hydrolysis reaction of MGP, proton activity should also be estimated at 85 °C from the rate of the pinacol rearrangement.

The rate constant of the pinacol rearrangement in the HCl system is smaller than those in the other two acid systems (Table 5). The rate constant in the HBr system is slightly larger than that in the $H_2SO_4$ system (Table 5). The reason for the fast pinacol rearrangement in the $H_2SO_4$ system can be attributed to

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the high proton activity of this system, which could be confirmed, similarly to the aqueous 74% 1,4-dioxane solvent system, by the slow pinacol rearrangement in the 82% 1,4-dioxane solvent system with 0.2 mol l$^{-1}$ CH$_3$SO$_3$H. Similarly to the 74% 1,4-dioxane solvent systems, there are two possible explanations for the observation that the pinacol rearrangement is faster in the HBr than in the HCl system. Proton activity of the HBr system is higher than that of the HCl system and/or Br$^-$ directly participates in the pinacol rearrangement in the aqueous 82% 1,4-dioxane solvent systems. The latter may be more plausible owing to the fact that the difference in the rates of the pinacol rearrangement between the HBr and HCl systems is larger in the 82% aqueous 1,4-dioxane solvent systems than that in the 74% systems.

Because the hydrolysis of MGP was much slower in the H$_2$SO$_4$ system than those in the other two acid systems despite the higher proton activity in the former system at 85 °C, it is strongly suggested that not only Br$^-$ but also Cl$^-$ directly participates in the hydrolysis reaction of MGP. Br$^-$ may participate more actively than Cl$^-$. Possible participation mechanisms are the same as those described in the previous section. The rate constants in the HBr system are about 2.5–2.9 times as large as those in the H$_2$SO$_4$ system, although proton activity of the H$_2$SO$_4$ system should be higher than that of the HBr system. These ratios are about 1.2 and 1.7–1.8 in the H$_2$O and the aqueous 74% 1,4-dioxane solvent systems, respectively. The participation of not only Br$^-$ but also Cl$^-$ should be more significant in the aqueous 82% 1,4-dioxane solvent systems than that in the H$_2$O and the aqueous 74% 1,4-dioxane solvent systems.

It should be shown that the molar ratio of 1,4-dioxane to H$_2$O in aqueous 82% 1,4-dioxane solution (v/v) is about 1.0.

## Comparison of effect of counter anion between different solvent systems

Table 6 lists ratios of the rate constants for the hydrolysis reaction of MGPβ to MGPα in the reaction systems employed. These ratios seem to have a tendency to be small and large in the HBr and H$_2$SO$_4$ systems, respectively, in three different solvent systems. This may suggest that the pronounced direct participation of the counter anion in the hydrolysis reaction of MGP decreases this ratio. If this is the case, the direct participation of counter anion may be more significant in the hydrolysis reaction of MGPα than in that of MGPβ owing to the decrease of the ratio with the increase of the 1,4-dioxane content.

The hydrolysis rate of MGP increases with increasing 1,4-dioxane content in the solution, when the rates are compared between three different solvent systems with a particular acid (Table 3). Concentration of the conjugate acid of MGP and solvent dissociating power are the factors that determine the relative rate of the hydrolysis reaction of MGP in three different solvent systems, when the rates are compared between these systems and absence of participation of counter anion is assumed. MGP is hydrolyzed more rapidly in a solvent with higher solvent dissociating power than in another solvent even when the proton activity of these systems is the same. Therefore, relative solvent dissociating power of three different solvent systems should be examined to discuss the difference in the rate

**Table 6** List of ratio of the rate constant for the hydrolysis reaction of MGPβ to MGPα[a]

Solvent: H$_2$O (0% 1,4-dioxane)

|  | HCl | HBr | H$_2$SO$_4$ |
| --- | --- | --- | --- |
| Ratio | 1.85 | 1.83 | 1.99 |

Solvent: aqueous 74% 1,4-dioxane

|  | HCl | HBr | H$_2$SO$_4$ |
| --- | --- | --- | --- |
| Ratio | 2.08 | 1.77 | 1.91 |

Solvent: aqueous 82% 1,4-dioxane

|  | HCl | HBr | H$_2$SO$_4$ |
| --- | --- | --- | --- |
| Ratio | 1.80 | 1.75 | 2.08 |

[a] Concentration of the acids and temperature were 0.20 mol l$^{-1}$ and 85 °C in all systems employed.

of the hydrolysis of MGP between three solvent systems. The other factor for the determination of the rate of the hydrolysis of MGP, concentration of the conjugate acid of MGP, can be recognized from the CA column of Table 4. Concentration of the conjugate acid of MGP may be estimated to be highest in the H$_2$O solvent system and similar in the other two solvent systems, although the actual difference in the concentration between three solvent systems is unclear at 85 °C. The hydrolysis reaction of MGP should be fastest in the H$_2$O solvent system among three solvent systems only on the basis of the concentration of the conjugate acid of MGP.

To estimate relative solvent dissociating power between the 0% (H$_2$O), aqueous 74%, and aqueous 82% 1,4-dioxane solvent systems, it should be appropriate to compare the rates of a chemical reaction in these systems using a particular acid. The prerequisites for this chemical reaction are as follows: (1) the rate is not dependent on proton activity but only solvent dissociating power, (2) the rate-determining step is not ionization but dissociation, and (3) no nucleophile participates in the reaction. Because it is difficult to prepare H$_2$O, aqueous 74%, and 82% 1,4-dioxane solvent systems with the proton activities identical to one another, the prerequisite (1) is required. The prerequisite (2) is based on the conjugate acid of MGP dissociating to the cyclic cation and the neutral CH$_3$OH molecule in the rate-determining step (Scheme 1). Acid hydrolysis of a quaternary ammonium cation releasing the neutral amine compound seems to satisfy prerequisites (1) and (2). Application of CH$_3$SO$_3$H can satisfy prerequisite (3). An acid hydrolysis reaction of D-glucopyranosyl aniline using CH$_3$SO$_3$H seems to be the best reaction. Because this compound could not easily be obtained, however, BnAni was chosen due to its easy availability. The mechanism of acid hydrolysis reaction of BnAni is shown in Scheme 3. The conjugate acid of BnAni is the only species present in any solvent system that results in the independence of the reaction rate on proton activity of the system. The conjugate acid dissociates to the benzyl cation and the neutral aniline molecule, although the latter compound is consecutively protonated. On the basis of these theories, BnAni was acid-hydrolyzed in the

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**Table 7** List of pseudo-first-order reaction rate constants ($k_{obs}$) obtained from the hydrolysis reaction of BnAni[a]

| System[b] | 0% ($H_2O$) | 74% | 82% |
|---|---|---|---|
| $k_{obs}$[c] | 1.16 | 3.90 | 5.70 |
| $R^2$[d] | 0.995 | 0.997 | 0.981 |

[a] The applied acid and temperature were 0.2 mol $l^{-1}$ $CH_3SO_3H$ and 85 °C in all systems. [b] The percentages in the line show the 1,4-dioxane contents (v/v) in the systems. [c] Unit: $\times 10^{-2}$ $h^{-1}$. [d] Square of correlation coefficient.

$H_2O$, aqueous 74%, and aqueous 82% 1,4-dioxane solvent systems using $CH_3SO_3H$ as an acid to examine the relative solvent dissociation power of three different solvent systems.

Table 7 lists pseudo-first-order reaction rate constants obtained from the acid hydrolysis reaction of BnAni in three solvent systems using $CH_3SO_3H$ as an acid. The approximation of the disappearances of BnAni to pseudo-first-order reactions was good (Table 7 and see ESI†). The rate of the BnAni hydrolysis decreased in the order of: 82% > 74% > 0% ($H_2O$) 1,4-dioxane solvent systems. This order is the reverse of that observed for common $S_N1$-type substitution reactions,[31] in which the rate-determining step is not dissociation of a cation to another cation and a neutral molecule but ionization of a neutral molecule to a positively and negatively charged ions. Therefore, it can be possible to consider that solvent system with higher content of 1,4-dioxane also have higher solvent dissociation power in the rate-determining step of the hydrolysis reaction of MGP (Scheme 1), although the structure of the conjugate acid of BnAni is different from that of MGP. BnAni consists of two relatively hydrophobic substructures, benzyl group and aniline, while MGP consists of two relatively hydrophilic structures, glucosyl group and methanol. Although this fact may influence the rate of the hydrolysis reactions, the hydrolysis reaction of MGP may be fastest in the 82% 1,4-dioxane solvent system among three solvent systems only on the basis of the solvent dissociation powers.

Because the effects of concentration of the conjugate acid of MGP and solvent dissociating power on the rate of the hydrolysis reaction of MGP are not consistent with each other in three solvent systems, it cannot be suggested which solvent system has the highest potential ability to move the hydrolysis reaction of MGP forward. However, this result does not reduce the importance of the suggestion that the counter anions, $Br^-$ and $Cl^-$, directly participate in the hydrolysis reaction of MGP when the observed difference in the rate between the different acid systems in each of the solvent systems is taken into consideration.

It is rationally assumed in this paper, as described in the previous sections, that solvent dissociating power is not different between different acid systems when the solvent contains a particular level of 1,4-dioxane.

As described in the previous sections, $Br^-$ and $Cl^-$ are suggested to directly participate in the hydrolysis reaction of MGP in all the solvent systems and the aqueous 1,4-dioxane solvent systems, respectively. Furthermore, their participations are enhanced with the increase of the 1,4-dioxane content in the solvent. This enhancement should be attributed to the presumed

phenomenon that the solvation of $Br^-$ and $Cl^-$ decreases with the increase of the 1,4-dioxane content in the solvent. When these anions are naked rather than solvated by the solvent molecules, their nucleophilicity is high. Acceptor number (AN or acceptivity), which can be an index of the strength as electron pair acceptor and of the ability to solvate anions and nucleophiles, of $H_2O$ and 1,4-dioxane is 54.8 and 10.8, respectively. AN of aqueous 74% and 82% 1,4-dioxane is estimated at 41.1 and 38.5, respectively, based on the data shown in the literature.[32] It was shown that there is a clearly linear relationship between AN of a solvent and the logarithm of the second order rate constant of an $S_N2$ type substitution reaction, $CH_3 - I + I^-$* (radioactive), in the solvent.[33,34] These data reinforce the above described attribution of the enhanced participation of $Br^-$ and $Cl^-$ with the increase of the 1,4-dioxane content in the solvent. It was also reported that the rate of another $S_N2$ type substitution reaction, $CH_3 - OTs + X^-$ (halide anion), in an aqueous *N,N*-dimethylformamide solution decreases in the order of: $I^- > Br^- > Cl^-$, while the order is exactly the reverse in pure *N,N*-dimethylformamide (AN: 16.0),[35] suggesting the dependence of nucleophilicity of halide anions on solvent. This dependency probably explains the phenomena observed in this study that only $Br^-$ directly participates in the hydrolysis reaction of MGP in the $H_2O$ solvent system, and on the other hand, both anions directly participate in the aqueous 1,4-dioxane solvent systems.

## Conclusions

The following features are suggested from the results obtained in this study. Bromide anion directly participates in the acid hydrolysis reaction of MGP and the participation is further pronounced with the increase of the 1,4-dioxane content in solvent system probably owing to the lower solvation of bromide anion in solvent system with higher content of 1,4-dioxane. Chloride anion also directly participates in the hydrolysis reaction of MGP in the dioxane solvent systems. Bromide anion may directly participate even in the pinacol rearrangement in the dioxane solvent systems, although the reaction center of the pinacol rearrangement is sterically highly hindered.

## Experimental

### Materials

All the chemicals used in this study were commercially available. Deionized $H_2O$ was used in all the experiments. 1,4-Dioxane was refluxed with $NaBH_4$ and subsequently distilled.

### Acid hydrolysis reaction

All the reactions were run in a three-necked round-bottomed glass flask (50 ml) equipped with a condenser, thermometer, and magnetic stirrer. The air in the flask was primarily replaced with $N_2$. To the flask was added 27 ml of a 0.222 mol $l^{-1}$ HCl, HBr, or $H_2SO_4$ solution, and the temperature was raised to 85 °C. Then, 3 ml of a solution containing each of a pair of MGPα and MGPβ (50 mmol $l^{-1}$ each), pinacol (200 mmol $l^{-1}$), or BnAni (200 mmol $l^{-1}$) was added, and the reaction was started.

Concentration of the acids in the prepared solutions (30 ml) was 0.20 mol l$^{-1}$ in all cases. Initial concentration of the starting compounds was 5.0 mmol l$^{-1}$ for each of MGPα and MGPβ, 20.0 mmol l$^{-1}$ for piancol or BnAni. Aqueous 74% or 82% 1,4-dioxane solution (v/v) was substituted for the above H$_2$O solutions in the other two reaction series. CH$_3$SO$_3$H was also applied to some runs. Concentration of the acids and the starting compounds in the prepared aqueous 1,4-dioxane solutions was the same as that in the H$_2$O solutions. All kinds of reactions employed in this study are summarized in Table 1. Each kind of acid hydrolysis reaction was repeated at least 3 times to confirm the reproducibilities except that each of the reactions using CH$_3$SO$_3$H was repeated twice.

## Quantification of MGP

At prescribed times, 1 ml of the reaction solution was withdrawn and transferred to a glass flask containing potassium carbonate and an internal standard compound, *myo*-inositol, with cooling in a cold water bath. Then, the mixture was dried under reduced pressure. The dried sample was acetylated with acetic anhydride and sodium acetate at 120 °C for 3 h. The acetylated solution was injected into GC (GC-14B, Shimadzu Co., Kyoto, Japan) equipped with a flame ionization detector using He as carrier gas. Analysis conditions were as follows: The injector and detector were at 220 °C and 230 °C, respectively. Separation was achieved on a TC-17 capillary column (30 m × 0.25 mm × 0.25 μm, GL Sciences Inc., Tokyo, Japan). The temperature was increased from 200 °C to 220 °C at 4 °C min$^{-1}$ and maintained for 10 min.

## Quantification of pinacol

At prescribed times, 1 ml of the reaction solution was withdrawn and transferred to a glass tube containing potassium carbonate with cooling in a cold water bath. An internal standard compound, 2,4,6-trimethylphenol, dissolved in chloroform, was added to the flask and extracted. The chloroform layer was withdrawn and the aqueous layer was further extracted with fresh chloroform twice. The combined chloroform layer was dried with anhydrous sodium sulfate and then injected into the GC using helium as carrier gas. Analysis conditions were as follows: The injector and detector were at 220 °C and 230 °C, respectively. Separation was achieved on the TC-17 capillary column. The temperature was increased from 50 °C to 180 °C at 10 °C min$^{-1}$ with an initial interval of 5 min and final maintenance for 2 min.

## Quantification of BnAni

At prescribed times, 1 ml of the reaction solution was withdrawn and transferred to a glass tube containing potassium carbonate and an internal standard compound, 4-acetyl-1,2-dimethoxy-benzene, with cooling in a cold water bath. After filtration, the mixture was injected into HPLC (LC-10A, Shimadzu Co.) equipped with an SPD-M10A detector (226 nm, LC-10A, Shimadzu Co.). Conditions for HPLC analysis were as follows: Column: Luna 5 u C18(2) 100 A (150 mm ×

4.6 mm, Phenomenex, Inc.). oven temperature: 40 °C, flow rate: 1.0 ml min$^{-1}$, solvent system: CH$_3$OH/2.0 mmol l$^{-1}$ NaOH solution = 20/80 (v/v) for 10 min; gradient to 75/25 for 20 min; 20/80 for 10 min, total time: 40 min.

## Notes and references

1  W. A. Van Ekenstein, *Rec. Trav. Chim.*, 1894, **13**, 183–186.
2  (*a*) E. F. Armstrong and E. F. Caldwell, *Proc. R. Soc. London, B*, 1904, **73**, 526–537; (*b*) E. F. Armstrong, *Proc. R. Soc. London, B*, 1904, **74**, 188–194; (*c*) E. F. Armstrong and W. H. Glover, *Proc. R. Soc. London, B*, 1908, **80**, 312–321; (*d*) E. Fischer and H. Strauss, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 2467–2474; (*e*) E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 1928, **24**, 321–329.
3  J. N. Brönsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 1929, **25**, 59–76.
4  (*a*) E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 1929, **25**, 81–91; (*b*) E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 1929, **25**, 435–441; (*c*) E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 1929, **25**, 503–519; (*d*) W. N. Haworth, *Ber*, 1932, **65**, 43A–65A; (*e*) C. B. Purves and C. S. Hudson, *J. Am. Chem. Soc.*, 1937, **59**, 49–56; (*f*) C. B. Purves and C. S. Hudson, *J. Am. Chem. Soc.*, 1937, **59**, 1170–1174; (*g*) H. S. Isbell and H. L. Frush, *J. Res. Natl. Bur. Stand.*, 1940, **24**, 125–151; (*h*) J. H. Fisher, W. L. Hawkins and H. Hebbert, *J. Am. Chem. Soc.*, 1941, **63**, 3031–3035; (*i*) L. J. Heidt and C. B. Purves, *J. Am. Chem. Soc.*, 1944, **66**, 1385–1389; (*j*) J. A. Snyder and K. P. Link, *J. Am. Chem. Soc.*, 1952, **74**, 1883–1884; (*k*) A. Thompson, M. L. Wolfrom and E. J. Quinn, *J. Am. Chem. Soc.*, 1953, **75**, 3003–3004; (*l*) R. L. Nath and H. N. Rydon, *Biochem. J.*, 1954, **57**, 1–10; (*m*) C. A. Bunton, T. A. Lewis, D. R. Llewellyn and C. A. Vernon, *J. Chem. Soc.*, 1955, 4419–4423; (*n*) A. B. Foster and W. G. Overend, *Chem. Ind.*, 1955, 566–567.
5  M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, 1955, **77**, 3146–3148.
6  (*a*) P. Mamalis and H. N. Rydon, *J. Chem. Soc.*, 1955, 1049–1065; (*b*) J. A. Mills, *Adv. Carbohydr. Chem.*, 1955, **10**, 1–53; (*c*) G. N. Richards, *Chem. Ind.*, 1955, **77**, 228–228; (*d*) I. Augestad and E. Berner, *Acta Chem. Scand.*, 1956, **10**, 911–916; (*e*) F. Shafizadeh and A. Thompson, *J. Org. Chem.*, 1956, **21**, 1059–1062; (*f*) F. Shafizadeh, *Adv. Carbohydr. Chem.*, 1958, **13**, 9–61; (*g*) B. Capon and W. G. Overend, *Adv. Carbohydr. Chem.*, 1960, **15**, 11–51; (*h*) C. Armour, C. A. Bunton, S. Patai, L. H. Selman and C. A. Vernon, *J. Chem. Soc.*, 1961, 412–416; (*i*) B. E. C. Banks, Y. Meinwald and A. J. Rhind-Tutt, *J. Chem. Soc.*, 1961, 3240–3246; (*j*) J. F. Bunnett, *J. Am. Chem. Soc.*, 1961, **83**, 4978–4983; (*k*) A. N. Hall, S. Hollingshead and H. N. Rydon, *J. Chem. Soc.*, 1961, 4290–4295; (*l*) J. Nakano and B. G. Rånby, *Svensk Papperstidn.*, 1962, **2**, 29–33.
7  W. G. Overend, C. W. Rees and J. S. Sequeira, *J. Chem. Soc.*, 1962, 3429–3440.
8  (*a*) B. Capon, *Tetrahedron Lett.*, 1963, **4**, 911–913; (*b*) R. D. Marshall, *Nature*, 1963, **199**, 998–999; (*c*) T. E. Timell, *Chem. Ind.*, 1963, 1208–1209.
9  R. J. Withey and E. Whalley, *Can. J. Chem.*, 1963, **41**, 1849–1850.
10  (*a*) L. M. Semke, N. S. Thompson and D. G. Williams, *J. Org. Chem.*, 1964, **29**, 1041–1047; (*b*) T. E. Timell, *Can. J. Chem.*, 1964, **42**, 1456–1472; (*c*) T. E. Timell, *Chem. Ind.*, 1964, 503–504.
11  M. S. Feather and J. F. Harris, *J. Org. Chem.*, 1965, **30**, 153–157.
12  (*a*) T. E. Timell, W. Enterman, F. Spencer and E. J. Soltes, *Can. J. Chem.*, 1965, **43**, 2296–2305; (*b*) J. N. BeMiller, *Adv. Carbohydr. Chem.*, 1967, **22**, 25–108; (*c*) B. Capon, *J. Chem. Soc., Chem. Commun.*, 1967, **1**, 21–23; (*d*) B. Capon and D. Thacker, *J. Chem. Soc. B*, 1967, 185–189; (*e*) K. K. De and T. E. Timell, *Carbohydr. Res.*, 1967, **4**, 72–77; (*f*) M. D. Saunders, *Carbohydr. Res.*, 1967, **5**, 453–460; (*g*) B. Capon, *Chem. Rev.*, 1969, **69**, 407–498; (*h*) J. N. BeMiller and E. R. Doyle, *Carbohydr. Res.*, 1971, **20**, 23–30.
13  F. W. Lichtenthaler, J. Breunig and W. Fischer, *Tetrahedron Lett.*, 1971, **12**, 2825–2828.
14  T. Painter, *Acta Chem. Scand.*, 1973, **27**, 2463–2484.
15  (*a*) H. Lönnberg and A. Kankaanperä, *Acta Chem. Scand. A*, 1977, **31**, 306–312; (*b*) H. Lönnberg, A. Kankaanperä and K. Haapakka, *Carbohydr. Res.*, 1977, **56**, 277–287; (*c*) H. Lönnberg and M. Arminen, *Finn. Chem. Lett.*, 1978, 209–212; (*d*) H. Lönnberg and L. Valtonen, *Finn. Chem. Lett.*, 1978, 244–247; (*e*) H. Lönnberg and A. Vesala, *Carbohydr. Res.*, 1980, **78**, 53–59; (*f*) T. Painter, *Carbohydr. Res.*, 1980, **82**,

362–365; (g) N. S. Isaacs, K. Javaid and B. Capon, *J. Chem. Soc., Perkin Trans. 2*, 1982, 101–103; (h) A. Vesala, H. Lönnberg, R. Kappi and J. Arpalahti, *Carbohydr. Res.*, 1982, **102**, 312–315; (i) H. Lönnberg and O. Gylen, *J. Carbohydr. Chem.*, 1983, **2**, 177–188; (j) A. J. Bennet, M. L. Sinnot and W. S. S. Wijesundera, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1233–1236; (k) A. J. Bennet and M. L. Sinnot, *J. Am. Chem. Soc.*, 1986, **108**, 7287–7294; (l) A. J. Bennet, A. J. Davis, L. Hosie and M. L. Sinnot, *J. Chem. Soc., Perkin Trans. 2*, 1987, 581–584.

16 Y. Guindon and P. C. Andersonn, *Tetrahedron Lett.*, 1987, **28**, 2485–2488.

17 (a) R. B. Gupta and R. W. Franck, *J. Am. Chem. Soc.*, 1987, **109**, 6554–6556; (b) M. L. Sinnott, *Adv. Phys. Org. Chem.*, 1988, **24**, 113–204; (c) C. W. Andrews, J. P. Bowen and B. FraserReid, *J. Chem. Soc., Chem. Commun.*, 1989, 1913–1916.

18 M. F. Zaranyika, P. Moses and T. Mavunganidge, *J. Polym. Sci. A*, 1990, **28**, 3565–3574.

19 M. F. Zaranyika, *Bull. Chem. Soc. Ethiopia*, 1991, **5**, 33–36.

20 D. R. McPhail, J. R. Lee and B. FraserReid, *J. Am. Chem. Soc.*, 1992, **114**, 1905–1906.

21 (a) B. FraserReid, J. R. Merrit, A. L. Handlon and C. W. Andrews, *Pure Appl. Chem.*, 1993, **65**, 779–786; (b) S. Li, A. J. Kirby and P. Deslongchamps, *Tetrahedron Lett.*, 1993, **34**, 7757–7758; (c) J. L. Liras and E. V. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 2645–2646; (d) J. L. Liras, V. M. Lynch and E. V. Anslyn, *J. Am. Chem. Soc.*, 1997, **119**, 8191–8200.

22 R. Olsson, J. Berg and T. Frejd, *Tetrahedron*, 1998, **54**, 3935–3954.

23 (a) J. Kaczmarek, Z. Kaczynski, Z. Trumpakaj, J. Szafranek, M. Bogalecka and H. Lönnberg, *Carbohydr. Res.*, 2000, **325**, 16–29;

(b) M. N. Namchuk, J. D. McCarter, A. Becalski, T. Andrews and S. G. Withers, *J. Am. Chem. Soc.*, 2000, **122**, 1270–1277; (c) D. Indurugalla and A. J. Bennet, *J. Am. Chem. Soc.*, 2001, **123**, 10889–10898.

24 H. H. Jensen, L. Lyngbye and M. Bols, *Angew. Chem., Int. Ed.*, 2001, **40**, 3447–3449.

25 (a) K. J. Johansson, P. Konradsson and Z. Trumpakaj, *Carbohydr. Res.*, 2001, **332**, 33–39; (b) M. Mohr, R. A. Bryce and I. H. Hillier, *J. Phys. Chem. A*, 2001, **105**, 8216–8222; (c) P. J. Berti and K. S. E. Tanaka, *Adv. Phys. Org. Chem.*, 2002, **37**, 239–314; (d) H. H. Jensen and M. Bols, *Org. Lett.*, 2003, **5**, 3419–3421.

26 P. Deslongchamps, S. Li and Y. L. Dory, *Org. Lett.*, 2004, **6**, 505–508.

27 (a) N. A. Horenstein, *Adv. Phys. Org. Chem.*, 2006, **41**, 275–314; (b) S. Mikkola and M. Oivanen, *ARKIVOC*, 2009, **3**, 39–53.

28 A. Charmot and A. Katz, *J. Catal.*, 2010, **276**, 1–5.

29 C. A. Bunton, T. Hadwick, D. R. Llewellyn and Y. Pocker, *Chem. Ind. (London)*, 1956, **276**, 1–5.

30 M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1–45.

31 M. H. Abraham and G. F. Johnston, *J. Chem. Soc.*, 1971, **1971**, 1610–1615.

32 U. Mayer, W. Gerger and V. Gutmann, *Monatsh. Chem.*, 1977, **108**, 489–498.

33 E. R. Swart and L. J. Le Roux, *J. Chem. Soc.*, 1957, **1957**, 406–410.

34 U. Mayer, V. Gutmann and W. Gerger, *Monatsh. Chem.*, 1975, **106**, 1235–1257.

35 W. M. Weaver and J. D. Hutchison, *J. Am. Chem. Soc.*, 1964, **86**, 261–265.