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# Revisiting the mechanism of $\beta$ -O-4 bond cleavage during acidolysis of lignin VII: acidolyses of non-phenolic C<sub>6</sub>-C<sub>2</sub>-type model compounds using HBr, HCl and H<sub>2</sub>SO<sub>4</sub>, and a proposal on the characteristic action of Br<sup>-</sup> and Cl<sup>-</sup>

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## Abstract

A non-phenolic C<sub>6</sub>-C<sub>2</sub>-type lignin model compound with the  $\beta$ -O-4 bond, 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol (**I**), was acidolyzed in aqueous 82% 1,4-dioxane containing HBr, HCl, or H<sub>2</sub>SO<sub>4</sub> with a concentration of 0.2 mol/L at 85 °C to examine the differences between these acidolyses. Compound **I** primarily converted to an enol ether compound, 1-(2-methoxyphenoxy)-2-(3,4-dimethoxyphenyl)ethene (**II**), via the benzyl cation followed by acidolytic  $\beta$ -O-4 bond cleavage regardless of the acid-type, although the disappearance rates of compound **I** were remarkably different (HBr > HCl >> H<sub>2</sub>SO<sub>4</sub>). Acidolyses of compound **II** using these acids under the same conditions showed a similar tendency, but the rate differences were much smaller than in the acidolyses of compound **I**. Acidolyses of the  $\alpha$ -methyl-etherified derivative of compound **I** (**I- $\alpha$ -OMe**) using these acids under the same conditions suggested that the formation rates of the benzyl cation from compound **I- $\alpha$ -OMe** (also from compound **I**) are not largely different between the acidolyses using these acids, but those of compound **II** from the benzyl cation are remarkably different. Acidolysis of the  $\alpha$ -bromo-substituting derivative of compound **I** (**I- $\alpha$ -Br**) using HBr under the same conditions showed a characteristic action of Br<sup>-</sup> in the acidolysis. Br<sup>-</sup> adds to the benzyl cation generated from compound **I** or **I- $\alpha$ -OMe** to afford unstable compound **I- $\alpha$ -Br**, resulting in acceleration of the formation of compound **II** and of the whole acidolysis reaction.

**Keywords:** Acid hydrolysis, Acid rearrangement, Hydrobromic acid, Hydrochloric acid, Sulfuric acid

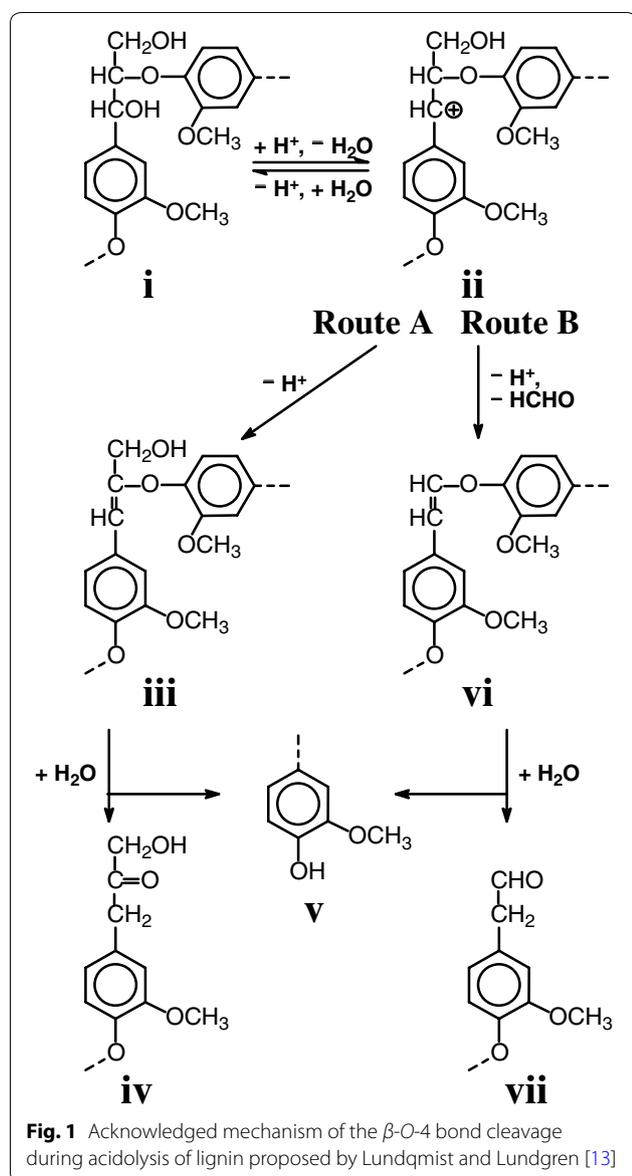
## Introduction

Acidolysis is one of the most basic chemical treatments, and has recently been introduced as a pretreatment in the chemical conversion of woody biomass. It has traditionally been utilized for the isolation and structural

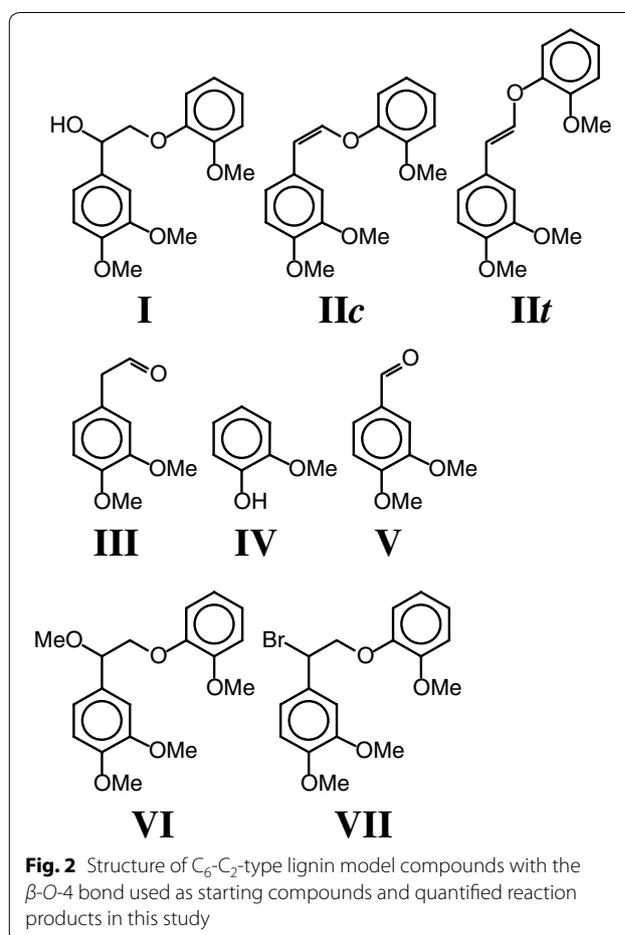
analysis of lignin [1–6]. The most abundant type of linkage, the  $\beta$ -O-4 bond, is cleaved by acidolysis, resulting in depolymerization and removal of lignin to achieve the above-described applications. We have reinvestigated the detailed reaction mechanism of the  $\beta$ -O-4 bond cleavage during acidolysis using non-phenolic lignin model compounds, and already published several papers [7–12], adding to earlier literature [2, 13–22].

Figure 1 shows the acknowledged mechanism of the  $\beta$ -O-4 bond cleavage proposed by Lundquist and Lundgren

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[13]. A  $\beta$ -O-4-type substructure of lignin **i** is primarily converted to the benzyl cation intermediate **ii**, which progresses via routes **A** and **B** to cleave the  $\beta$ -O-4 bond and is hence a branching point [2, 10–13, 22]. The type of acid applied determines which of route **A** or **B** predominates. When HCl or HBr is applied, route **A** predominates. An enol ether substructure **iii**, which is considerably labile under acidic conditions, is presumed to form and then be acid-hydrolyzed to form the Hibbert's ketone-type substructure **iv** and a new phenolic moiety **v**. When  $\text{H}_2\text{SO}_4$ , as well as most other acids, is applied, route **B** predominates. Benzyl cation intermediate **ii** liberates the HCHO molecule from the  $\gamma$ -position to convert to a  $\text{C}_6$ - $\text{C}_2$ -type enol ether substructure **vi**, which is then acid-hydrolyzed



to form a  $\text{C}_6$ - $\text{C}_2$ -type Hibbert's monomer-type substructure **vii** and the phenolic moiety **v**. Because route **A** predominates only in acidolyses using HBr and HCl, the counter anions,  $\text{Br}^-$  and  $\text{Cl}^-$ , must characteristically act in the acidolyses. Clarifying this action has been one of our key objectives.

In our two primary reports [7, 8], we employed a common non-phenolic  $\text{C}_6$ - $\text{C}_2$ -type lignin model compound with the  $\beta$ -O-4 bond, 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol (veratrylglycol- $\beta$ -guaiacyl ether, **I**, Fig. 2), which does not have the  $\gamma$ -hydroxymethyl group, because compound **I** seemed to react simply owing to the lack of the  $\gamma$ -hydroxymethyl group limiting the acidolysis reaction to the only remaining route. Since this limitation did not motivate us to focus on the type of applied acid, we used only HBr in these reports. However, our subsequent reports, in which  $\text{C}_6$ - $\text{C}_3$ -type model compounds were employed, showed that type of applied acid determines not only the predominance of the reaction routes, **A** and **B** (Fig. 1), but also the acidolysis rate [9–12]. This finding has motivated us to focus on the type of applied acid even in acidolyses using  $\text{C}_6$ - $\text{C}_2$ -type model

compounds, because the above-described limitation may explain the effect of applying different types of acid on the acidolysis rate and the participation of  $\text{Br}^-$  and  $\text{Cl}^-$  in the  $\beta$ -O-4 bond cleavage.

In this study, we acidolyzed compound **I** as well as others using HBr, HCl, or  $\text{H}_2\text{SO}_4$ , to examine the differences between the acidolyses using these acids. As expected, the obtained results enabled us to propose a characteristic action of  $\text{Br}^-$  and  $\text{Cl}^-$ .

## Materials and methods

### Materials

All chemicals used in this study except for the compounds and reagents described below were purchased from FUJIFILM Wako Pure Chemical Co. (Osaka, Japan), Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), or Sigma-Aldrich Japan K. K. (Tokyo, Japan) and used without further purification.  $\text{H}_2\text{O}$  and 1,4-dioxane (Diox) were deionized and roughly distilled in an evaporator, respectively, and thoroughly degassed before use. HCl and  $\text{H}_2\text{SO}_4$  were purchased as solutions with specifically certified concentrations. A purchased solution of HBr was titrated with a purchased NaOH solution with a specifically certified concentration before use, to determine the exact concentration.

Compound **I** was synthesized according to a previous report [23], and purified by recrystallization from ethanol. The structure and purity were confirmed by  $^1\text{H-NMR}$  (JNM-A500, 500 MHz, JEOL Ltd., Tokyo, Japan) using acetone- $d_6$  and an aliquot of  $\text{D}_2\text{O}$  as solvents. The spectral data are shown in our previous reports [7, 24].

The major reaction products in an acidolysis of compound **I**, the *cis*- and *trans*-isomers of 1-(2-methoxyphenoxy)-2-(3,4-dimethoxyphenyl)ethene (**IIc** and **IIt**, respectively, Fig. 2) and 3,4-dimethoxyphenylacetaldehyde (**III**, Fig. 2), were isolated from an acidolysis solution of compound **I** by flash chromatography using a mixture of  $\text{EtOAc}/n\text{-C}_6\text{H}_{14}$  as the eluent. The structures and purities of compounds **IIc** and **IIt** were confirmed by  $^1\text{H-NMR}$  using acetone- $d_6$  and an aliquot of  $\text{D}_2\text{O}$  as solvents. Those of compound **III** were confirmed by GC/MS (GC2010/PARVUM2, Shimadzu Co., Kyoto, Japan). The spectral data of these compounds are shown in our previous report [7]. Because compound **III** is too unstable to undergo dimerization to be a naphthalene derivative when attempting to isolate by removal of solvent [7, 22], it was acetalized with ethylene glycol and an aliquot of  $\text{H}_2\text{SO}_4$  to form 2-(3,4-dimethoxybenzyl)-1,3-dioxolane before removing the solvents. These isolated compounds were used as the starting compounds for acidolysis or as authentic compounds for quantification. The other major reaction product, 2-methoxyphenol (guaiacol, **IV**, Fig. 2), and a minor reaction product,

3,4-dimethoxybenzaldehyde (veratraldehyde, **V**, Fig. 2), were purchased and purified for use as authentic compounds for quantification.

The  $\alpha$ -methyl-etherified derivative of compound **I**, 1-methoxy-2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethane (**VI**, Fig. 2), was synthesized from compound **I** by the method described in our previous report [8] for use as a starting compound in acidolysis and as an authentic compound for quantification. The structure and purity were confirmed by GC/MS. The spectral data are shown in our previous report [8].

The  $\alpha$ -bromo-substituting derivative of compound **I**, 1-bromo-2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethane (**VII**, Fig. 2), was synthesized from compound **I** in chloroform-*d* by adding bromotrimethylsilane, following the method described in our previous report [25], for use as a starting compound in an acidolysis. The obtained chloroform-*d* solution was analyzed by  $^1\text{H-NMR}$  to confirm its formation, disappearance of compound **I**, and absence of compound **II**.  $^1\text{H-NMR}$ :  $\delta$  3.78, 3.85, 3.86 (s (each), 9H,  $-\text{OCH}_3$ ), 4.50 (m, 2H,  $\text{C}_\beta\text{-H}_2$ ), 5.26 (t, 1H,  $J=6.9$  Hz,  $\text{C}_\alpha\text{-H}$ ), 6.80–7.02 (7H, aromatic  $\text{C-H}_7$ ).

### Acidolysis reaction

A stock solution of aqueous 82% Diox (vol%) containing HCl, HBr, or  $\text{H}_2\text{SO}_4$  with a concentration of 2/9 mol/L was prepared in advance as follows. Density of the purchased solution of each acid was primarily determined. To a volumetric flask (1000 mL) was added a portion of the acid solution whose volume was regulated by its density and weight to contain 2/9 mol of the acid. To the flask was added 820 mL of Diox followed by addition of  $\text{H}_2\text{O}$  to adjust the whole volume to the marked line.

All reactions were conducted in a three-necked round-bottom glass flask (50 mL) equipped with a condenser, thermometer, and magnetic stirrer. The air in the flask was primarily replaced with nitrogen. To the flask was added 27 mL of the stock solution, and the flask was soaked into a water bath at 85 °C. After establishing equilibrium at 85°C, 3.0 mL of another 82% Diox solution containing 30  $\mu\text{mol}$  of compound **I**, a mixture of compounds **IIc** and **IIt** (67/33), or compound **VI** was added to the flask to initiate the reaction. In some acidolyses, the latter 3.0 mL of the 82% Diox solution also contained 15  $\mu\text{mol}$  of an internal standard compound, 5-acetyl-1,2,3-trimethoxybenzene. The initial concentrations of the acid and model compound were 0.20 mol/L and 1.0 mmol/L, respectively.

A portion of the above-described chloroform-*d* solution containing synthesized compound **VII** was added to aqueous 82% Diox containing HBr or  $\text{H}_2\text{SO}_4$  with a

concentration of 0.20 mol/L and the internal standard compound at 85 °C to initiate the reaction.

### Quantification

At prescribed reaction times, about 1.5 mL of the reaction solution was withdrawn, added to a small glass tube, and quickly soaked in a cold water bath for 30 s. Then, 1.0 mL of the cooled reaction solution was withdrawn and added to another glass tube containing 300  $\mu$ L of the saturated NaHCO<sub>3</sub> solution for neutralization. To the glass tube was added 1.0 mL of CH<sub>3</sub>OH containing 0.50  $\mu$ mol of the internal standard compound or just 1.0 mL of CH<sub>3</sub>OH depending on whether the acidolysis solution had contained it. A portion of the mixture was filtered with a membrane filter and injected to HPLC (LC-10A, Shimadzu Co.) equipped with a photodiode array detector (SPD-M10A, Shimadzu Co.).

A portion of the reaction solution of compound **VII** was withdrawn about 10 s after adding the above-described chloroform-*d* solution, and added to a glass tube containing an amount of the saturated NaHCO<sub>3</sub> solution for neutralization and CH<sub>3</sub>OH. A portion of the mixture was filtered with a membrane filter and injected to HPLC.

In HPLC analyses, a column of Luna 5 u C18(2) 100 Å (length: 150 mm, inner diameter: 4.6 mm, particle size: 5.0  $\mu$ m, Phenomenex, Inc., Torrance, CA, USA) was used at an oven temperature of 40 °C and a flow rate of 1.0 mL/min. The CH<sub>3</sub>OH/H<sub>2</sub>O ratio of 15/85 (v/v) was adjusted

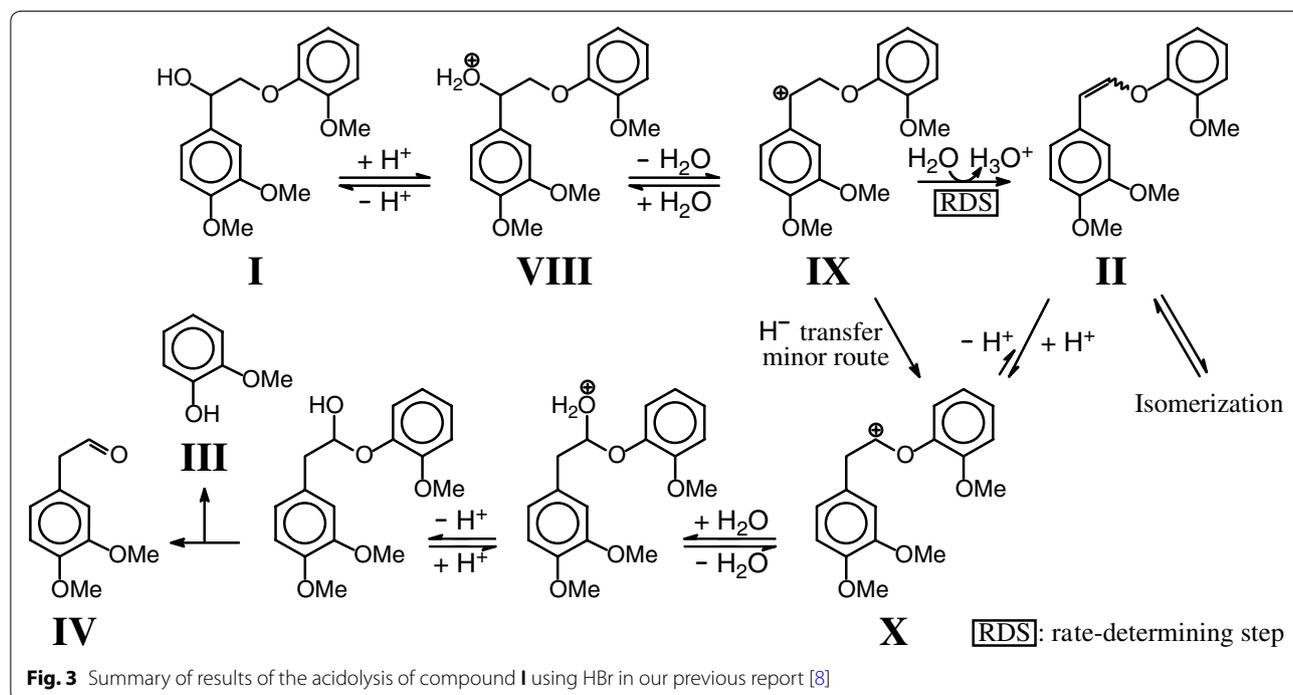
to 40/60 in 30 min, maintained at 40/60 for 15 min, and then readjusted to 85/15 in 10 min and maintained at 85/15 for 15 min, for a total of 70 min. Quantification was based on absorbances at 280 nm.

In these quantifications, a calibration curve for each compound was created by analyzing four samples, each of which contained a specific amount of the internal standard compound and a different amount of an authentic compound. Compound **III** was generated in situ from the acetalized derivative in the creation.

## Results and discussion

### Summary of acidolysis of compound **I** using HBr in our previous reports

Compound **I** had been acidolyzed using HBr in our previous reports [7, 8]. The results are summarized in Fig. 3. The primary elementary reaction is protonation at the oxygen of the  $\alpha$ -hydroxy group, rapidly establishing an equilibrium with the conjugate acid **VIII**. The H<sub>2</sub>O molecule reversibly leaves, and the benzyl cation intermediate **IX** forms. A base (probably H<sub>2</sub>O as well as Diox) abstracts a proton from the  $\beta$ -carbon of benzyl cation **IX** to afford compound **II** (shows **IIc** and **IIt** undistinguishably), which is the irreversible rate-determining step. The detected amount of compound **II** increases up to the maximum yield of about 40% at a reaction time of about 2 h. Compound **IIc** forms more than compound **IIt**. Protonation at the double bond of compound **II** affords the  $\beta$ -cation intermediate **X**, whose reverse reaction is rather



slow. Because the isomerization between compounds **IIc** and **III** is rather fast despite this slow reverse reaction, discrete  $\beta$ -cation **X** does not form in the isomerization. A  $\text{H}_2\text{O}$  molecule adds to  $\beta$ -cation **X** to be hydrolyzed to compounds **III** and **IV**. A hydride transfers from the  $\beta$ - to  $\alpha$ -carbon of benzyl cation **IX**, resulting in direct conversion to  $\beta$ -cation **X** as a minor route.

#### Verification of the reaction system in this study

Compound **I** was acidolyzed using HBr in this study under the above-described conditions, which were intended to replicate those employed in our previous reports [7, 8]. The disappearance was approximated well to a pseudo-first-order reaction in this study. However, the rate constant  $k_{\text{obs}}$ ,  $0.637 \text{ h}^{-1}$  (Table 1), was not exactly the same as  $0.512 \text{ h}^{-1}$  ( $0.00854 \text{ min}^{-1}$ ) observed in our previous reports. Some conditions employed in this study must have slightly been different from those in our previous reports. Because the above-described procedures for preparing the stock solution of HBr in this study were not exactly the same as those in our previous reports, the contents of HBr and Diox may have slightly been different. A purchased solution of Diox commonly contains small amounts of peroxides generated from itself by oxygen oxidation, so the distillation may not have been sufficient for the complete removal of peroxides that oxidize  $\text{Br}^-$ . The degas level may not have been sufficient for complete removal of dioxygen, which slowly oxidized  $\text{Br}^-$ . There may have been other differences in the employed conditions.

Although differences were observed in the rates between this study and our previous reports, all the standard deviations were small enough to show rather high reproducibility in this study (Table 1). Therefore, the following results are based only on acidolyses conducted in this study.

#### Acidolyses of compound **I** using three acids

Compound **I** was acidolyzed using HBr, HCl, or  $\text{H}_2\text{SO}_4$ . Because reproducibility was not high enough in a preliminary acidolysis using  $\text{H}_2\text{SO}_4$ , the internal standard compound was added together. It was stable and did not react with any organic compound under the employed conditions. Figure 4 illustrates the time courses of the changes in the recovery yield of compound **I** and yields of all the major reaction products, compounds **II**, **III**, and **IV**, and a minor reaction product, compound **V**. The disappearances of compound **I** were approximated well to pseudo-first-order reactions in the acidolyses using HBr or HCl (Table 1), while the approximations were slightly worse in those using  $\text{H}_2\text{SO}_4$ . All the approximations were based on data points observed before the recovery yield of compound **I** reached 15 mol%. The observed rate constants

**Table 1 Pseudo-first-order reaction rate constants ( $k_{\text{obs}}$ ) observed in this study and squared correlation coefficients ( $R^2$ ) in each run**

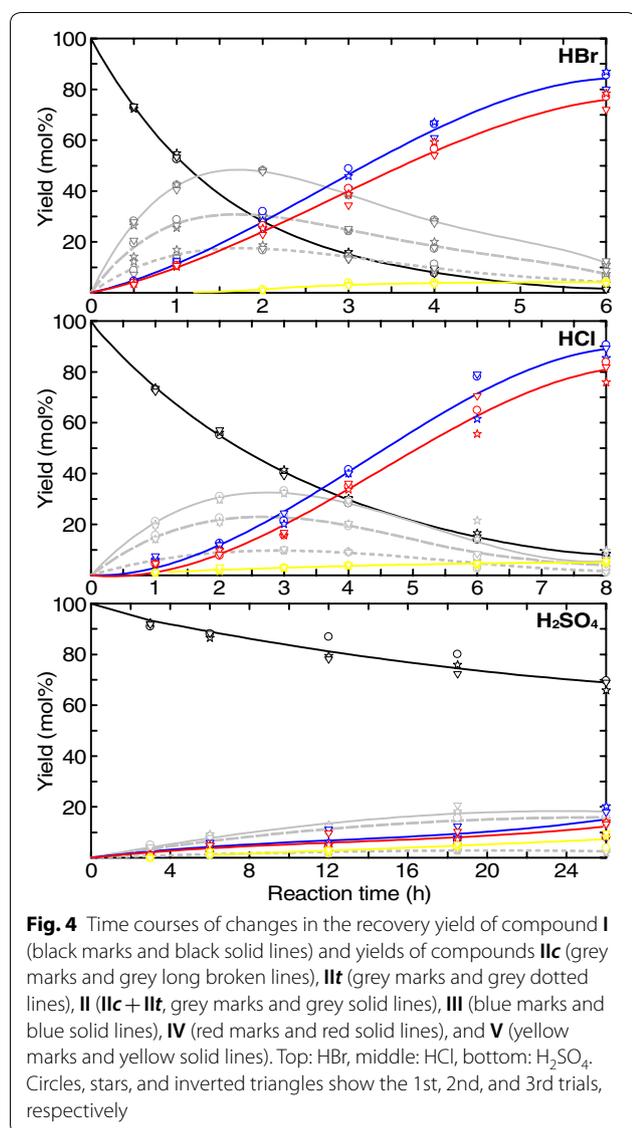
Compound	Acid	$k_{\text{obs}} (\text{h}^{-1})^a$	$R^2$
<b>I</b>	HBr	$0.637 \pm 0.022$	1.00
			1.00
			0.999
	HCl	$0.310 \pm 0.010$	0.998
			1.00
			0.997
	$\text{H}_2\text{SO}_4$	$0.0154 \pm 0.0013$	0.918
			0.954
			0.926
<b>II</b>	HBr	$0.552 \pm 0.027$	0.999
			0.997
			0.990
	HCl	$0.395 \pm 0.019$	0.989
			0.988
			0.986
	$\text{H}_2\text{SO}_4$	$0.191 \pm 0.003$	0.987
			0.995
			0.999
<b>VI</b>	HBr	$2.88 \pm 0.09$	1.00
			0.997
			0.998
	HCl	$1.72 \pm 0.09$	0.997
			0.999
			0.995
	$\text{H}_2\text{SO}_4$	$1.50 \pm 0.03$	0.999
			0.997
			0.998

<sup>a</sup> The approximation to a pseudo-first-order reaction was based on data points observed before recovery yield reached 15% in each compound. The values after the '±' marks are standard deviations obtained from three duplicated runs

$k_{\text{obs}}$  and squared correlation coefficients  $R^2$  are listed in Table 1.

The total yield of compounds **I** (recovery yield), **II**, and **IV** was always close to 100 mol% in most cases. This result indicates the following two reactions as possible routes: i) compound **I** primarily converts to compound **II** followed by the acidolytic  $\beta$ -O-4 bond cleavage to afford compounds **III** and **IV**; ii) the  $\beta$ -O-4 bond is directly cleaved to afford compounds **III** and **IV** without the primary formation of compound **II**. It is discussed below which route is predominant in acidolysis using each acid, although our previous report showed the former to be almost the exclusive route in acidolysis using HBr [7]. The yield of compound **IV** was slightly higher than that of compound **III**, which is discussed in the next section.

A remarkable difference was observed in the disappearance rates of compound **I** between the acidolyses



using three acids, although the same molar concentration of 0.2 mol/L was applied when using not only HBr or HCl, but also a diprotic acid of H<sub>2</sub>SO<sub>4</sub>. H<sub>2</sub>SO<sub>4</sub> behaves as a monoprotic acid under the employed conditions owing to the  $pK_a$  value of HSO<sub>4</sub><sup>-</sup> (1.99). The order of the rates was: HBr > HCl >> H<sub>2</sub>SO<sub>4</sub>. This rate difference can originate from an effect of the acid not only on the rate-determining step (Fig. 3), but also on proton activity, because high proton activity shifts the equilibrium between compound I and conjugate acid VIII to the latter and consequently increases the concentration of benzyl cation IX to accelerate the rate-determining step. Although a possible explanation for the above-described rate order is that the proton activities are considerably different between the acidolyses

using these acids, those activities should be similar because the same molar concentrations of the acids were used. Another possible explanation for the order is that the rates of the rate-determining step are very different between the acidolyses using these acids, which was proposed in a previous study [21]. This explanation would be correct, if Br<sup>-</sup> or Cl<sup>-</sup> readily abstracted, but HSO<sub>4</sub><sup>-</sup> hardly abstracted, a  $\beta$ -proton from benzyl cation IX. However, not Br<sup>-</sup>, Cl<sup>-</sup>, and HSO<sub>4</sub><sup>-</sup> but the solvents, H<sub>2</sub>O and Diox, must abstract the proton owing to the weak basicity of these anions and their amounts being much smaller than those of the solvents. Because Br<sup>-</sup> and Cl<sup>-</sup> have high nucleophilicity while HSO<sub>4</sub><sup>-</sup> is inert as a nucleophile, Br<sup>-</sup> and Cl<sup>-</sup> must participate in the rate-determining step not as a base but as a nucleophile to consequently accelerate it. This participation is further discussed in next sections.

Another noticeable difference was the amounts of compound II detected when a specific amount of compound I disappeared. When the recovery yield of compound I was about 70 mol%, the yield of compound II was 25–30 mol%, 20–25 mol%, or 15–20 mol% in the acidolysis using HBr, HCl, or H<sub>2</sub>SO<sub>4</sub>, respectively. A possible explanation for this result is that most molecules of compound I primarily convert to compound II in the acidolysis using HBr while some molecules directly undergo the  $\beta$ -O-4 bond cleavage without the formation of compound II in that using HCl or H<sub>2</sub>SO<sub>4</sub>. It was shown in our previous report that most molecules of compound I primarily convert to compound II in the acidolysis using HBr [7]. Another possible explanation is that the lability of compound I is dependent on the acid types more decisively than that of compound II. These phenomena are further discussed in the next section.

Thermodynamically less-stable compound IIc was detected more than compound II in any acidolysis, regardless of the acid-type. These compounds gradually equilibrated. The same phenomenon was observed in the acidolysis using HBr in our previous report [8]. This phenomenon may possibly suggest that discrete benzyl cation IX does not form; instead, two elementary steps, the H<sub>2</sub>O liberation from conjugate acid VIII and subsequent  $\beta$ -proton abstraction from benzyl cation IX, are actually a concerted step, because the two  $\beta$ -protons of benzyl cation IX are no longer diastereotopic and hence the abstraction of a  $\beta$ -proton from benzyl cation IX should afford thermodynamically stable compound II more than compound IIc. In spite of this possibility, the following discussion in this study is on the basis of the formation of discrete benzyl cation IX. The predominant formation of compound IIc over II may seem greater in the acidolysis using H<sub>2</sub>SO<sub>4</sub> than in those using the other two. It is one of our key objectives in future studies to

clarify whether or not discrete benzyl cation forms in acidolysis.

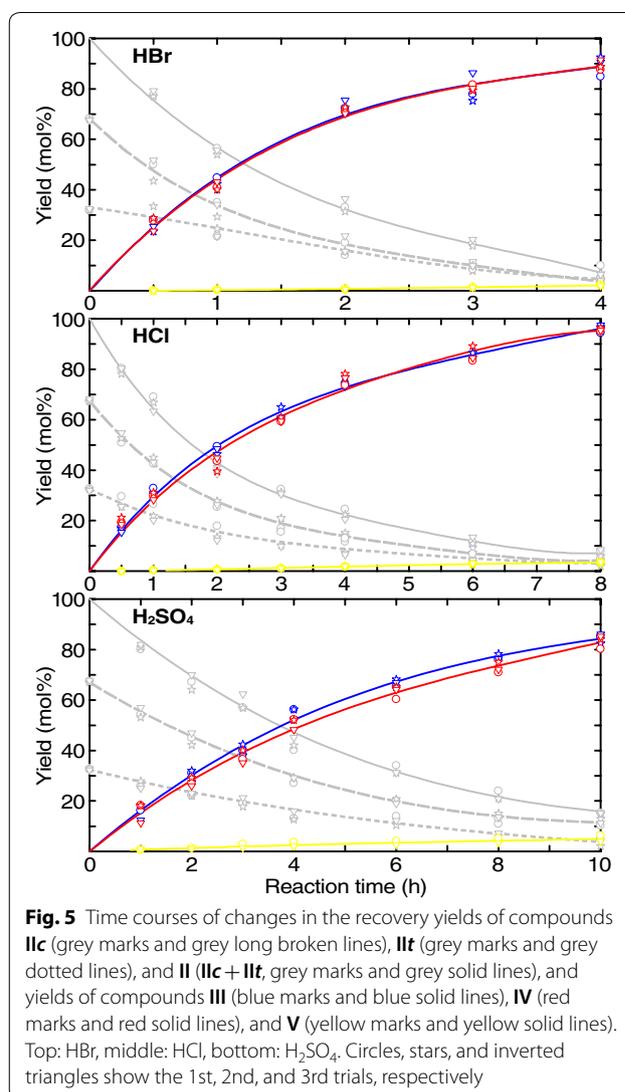
It was thus confirmed that compound **I** as a C<sub>6</sub>-C<sub>2</sub>-type reacts differently between the acidolyses using three acids, probably accompanying some unknown action of Br<sup>-</sup> and Cl<sup>-</sup>, although compound **I** was considered to progress to the only available reaction route owing to the lack of the  $\gamma$ -hydroxymethyl group.

In our previous report, a C<sub>6</sub>-C<sub>3</sub>-type non-phenolic lignin model compound with the  $\beta$ -O-4 bond, 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)propane-1,3-diol (veratrylglycerol- $\beta$ -guaiacyl ether, **VG**), was acidolyzed using HBr or HCl under the same conditions as those employed in this study, and disappeared with a  $k_{\text{obs}}$  value of 0.0765 or 0.0361 h<sup>-1</sup>, respectively [10]. Therefore, compound **I** disappeared 8.3 or 8.5 times, respectively, more rapidly than **VG**. The  $k_{\text{obs}}$  value was 0.00808 h<sup>-1</sup> in the acidolysis of **VG** using a H<sub>2</sub>SO<sub>4</sub> concentration of 0.1 mol/L under otherwise the same conditions [10]. Compound **I** thus disappeared 1.9 times more rapidly than **VG**, although the concentration of H<sub>2</sub>SO<sub>4</sub> was 0.2 mol/L in the acidolysis of the former, indicating that their disappearance rates were not largely different. These comparisons suggest that Br<sup>-</sup> and Cl<sup>-</sup> show their high nucleophilicity more strongly in the acidolyses of compound **I** than in those of **VG**, which can originate from the presence of two or one  $\beta$ -protons in the former or latter, respectively, and/or the steric factor of the former being smaller than that of the latter.

#### Acidolyses of compound **II** using three acids

The intermediate in the acidolysis of compound **I**, compound **II** (**IIc**:**IIt**=67:33), was acidolyzed as a starting compound using HBr, HCl, or H<sub>2</sub>SO<sub>4</sub> under the same conditions. Because reproducibility was not high enough in preliminary acidolyses using HCl or H<sub>2</sub>SO<sub>4</sub>, the internal standard compound was added together. Figure 5 illustrates the time courses of the changes in the recovery yield of compound **II** and yields of the major reaction products, compounds **III** and **IV**, and a minor reaction product, compound **V**. The disappearance of compound **II** was approximated well to a pseudo-first-order reaction in any acidolysis reaction (Table 1). All the approximations were based on data points observed before the recovery yield of compound **II** reached 15 mol%. The observed rate constants  $k_{\text{obs}}$  and squared correlation coefficients  $R^2$  are listed in Table 1.

When a mixture of compounds **IIc** and **IIt** with a ratio of about 60/40 or 90/10 had been acidolyzed using HBr under the same conditions in our previous report, the difference in the observed  $k_{\text{obs}}$  values was small enough to say that the disappearance rate of compound **II** is not dependent on the ratio [8]. This result indicates that the



**Fig. 5** Time courses of changes in the recovery yields of compounds **IIc** (grey marks and grey long broken lines), **IIt** (grey marks and grey dotted lines), and **II** (**IIc** + **IIt**, grey marks and grey solid lines), and yields of compounds **III** (blue marks and blue solid lines), **IV** (red marks and red solid lines), and **V** (yellow marks and yellow solid lines). Top: HBr, middle: HCl, bottom: H<sub>2</sub>SO<sub>4</sub>. Circles, stars, and inverted triangles show the 1st, 2nd, and 3rd trials, respectively

isomerization is more rapid than the progress of the acidolytic  $\beta$ -O-4 bond cleavage.

The total yield of compound **II** (recovery yield) and **IV** was close to 100 mol% in most cases, which indicates that most molecules of compound **II** undergo the acidolytic  $\beta$ -O-4 bond cleavage to afford compounds **III** and **IV** with the formation of a minor product, compound **V**. The yields of compounds **III** and **IV** were closer to each other than those in the acidolyses of compound **I**. This observation suggests that a small amount of compound **I** directly undergoes the  $\beta$ -O-4 bond cleavage not via the formation of compound **II**, which may afford compound **V**. Compound **I** was not detected at all in any of acidolyses, which had also been indicated in our previous report using HBr [7, 8]. This important observation confirms, as described in our previous reports [7, 8], that not benzyl

cation **IX** but only  $\beta$ -cation **X** forms accompanying protonation at the double bond of compound **II**, regardless of the acid type, because compound **I** forms once when benzyl cation **IX** is generated as shown in our previous report [8] and the next section.

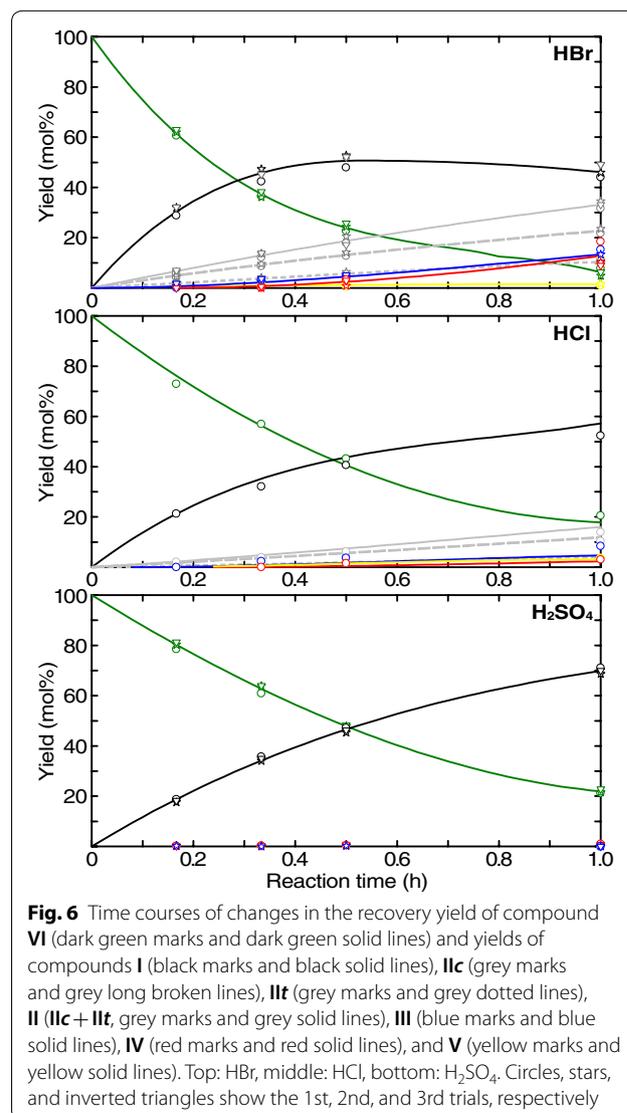
The disappearance rates of compound **II** in the acidolyses using three acids were in the order of:  $\text{HBr} > \text{HCl} > \text{H}_2\text{SO}_4$ , which is the same order as for compound **I**. However, the difference in the rates was much smaller than for compound **I**. The ratios of the  $k_{\text{obs}}$  values were calculated to be 1.4 and 2.9 in the acidolyses of compound **II** using HBr and HCl ( $k_{\text{obs}(\text{HBr})}/k_{\text{obs}(\text{HCl})}$ ) and using HBr and  $\text{H}_2\text{SO}_4$  ( $k_{\text{obs}(\text{HBr})}/k_{\text{obs}(\text{H}_2\text{SO}_4)}$ ), respectively. These ratios were 2.1 and 41.4 in the acidolyses of compound **I** using the same two acids, respectively. Consequently, the disappearance of compound **II** was slower than that of compound **I** in the acidolysis using HBr, while the reverse was observed in the acidolyses using the other two acids. Compound **II** disappeared much faster than compound **I** in the acidolysis using  $\text{H}_2\text{SO}_4$ . These phenomena explain why compound **II** accumulated in different amounts in the acidolyses of compound **I** using the three acids, as shown in the previous section ( $\text{HBr} > \text{HCl} > \text{H}_2\text{SO}_4$ ). Because the proton activities must be similar in the acidolyses using the three acids, it is suggested that highly nucleophilic  $\text{Br}^-$  and  $\text{Cl}^-$  participate in the acidolysis reactions of compounds **I** and **II** and the degrees of their participations are much greater in the former acidolysis than in the latter. The participation of  $\text{Br}^-$  is greater than that of  $\text{Cl}^-$ . It is discussed in the following sections how these anions participate in the acidolysis reaction. In contrast,  $\text{HSO}_4^-$  must be inert in the acidolyses.

A differential equation,  $d[\text{II}]_t/dt = k_{\text{obs}(\text{I})}[\text{I}]_t - k_{\text{obs}(\text{II})}[\text{II}]_t$ , where the terms  $[\text{I}]_t$  and  $[\text{II}]_t$  are the concentrations of compounds **I** and **II**, respectively, at reaction time  $t$ , is established with respect to the formation of compound **II** in the acidolysis of compound **I**, when all the molecules of compound **I** primarily convert to compound **II** accompanied by the acidolytic  $\beta$ -O-4 bond cleavage to afford compounds **III** and **IV**. The solution of the equation is in good agreement with the observed formation of compound **II** in the acidolysis of compound **I** using HBr or HCl, similarly to our previous report using HBr [7]. However, compound **II** accumulated in an amount larger than that expected from the solution in the acidolysis using  $\text{H}_2\text{SO}_4$ . This suggests that the disappearance of compound **II** was slower when it formed as the intermediate in the acidolysis of compound **I** than when it was acidolyzed as a starting compound, although no rational explanation can be proposed. It is thus confirmed that most molecules of compound **I** primarily convert to compound **II** followed by the acidolytic  $\beta$ -O-4 bond cleavage

to afford compounds **III** and **IV** regardless of the acid type.

#### Acidolyses of compound **VI** using three acids

The  $\alpha$ -methyl-etherified derivative of compound **I**, compound **VI**, was acidolyzed as a starting compound using HBr, HCl, or  $\text{H}_2\text{SO}_4$  under the same conditions. The internal standard compound was added together. Figure 6 illustrates the time courses of the changes in the recovery yield of compound **VI** and yields of the major reaction products, compounds **I**, **II**, **III**, and **IV**, and a minor reaction product, compound **V**. The disappearance of compound **VI** was approximated well to a pseudo-first-order reaction in any acidolysis reaction (Table 1). All the approximations were based on data points observed before the recovery yield of compound **VI** reached



15 mol%. The observed rate constants  $k_{\text{obs}}$  and squared correlation coefficients  $R^2$  are listed in Table 1.

Compound **VI** is initially protonated at the oxygen of the  $\alpha$ -methoxy group to afford the conjugate acid that liberates the  $\text{CH}_3\text{OH}$  molecule to be benzyl cation **IX** without the reverse  $\text{CH}_3\text{OH}$  addition. Because of the absence of this reverse addition, it can be examined which route benzyl cation **IX** undergoes (Fig. 3), i.e., the addition of a  $\text{H}_2\text{O}$  molecule to afford conjugate acid **VIII** and further compound **I** (the reserve of the formation of benzyl cation **IX** from compound **I**) or the  $\beta$ -proton abstraction to afford compound **II**.

The disappearance of compound **VI** was much faster than those of compounds **I** and **II**. The rates were in the order of:  $\text{HBr} > \text{HCl} > \text{H}_2\text{SO}_4$ , which is the same tendency as those of compounds **I** and **II**. However, the difference in the disappearance rates was much smaller than that for compound **I**. The ratios of the  $k_{\text{obs}}$  values were calculated to be 1.7 and 1.9 in the acidolyses of compound **VI** using  $\text{HBr}$  and  $\text{HCl}$  ( $k_{\text{obs}(\text{HBr})}/k_{\text{obs}(\text{HCl})}$ ) and using  $\text{HBr}$  and  $\text{H}_2\text{SO}_4$  ( $k_{\text{obs}(\text{HBr})}/k_{\text{obs}(\text{H}_2\text{SO}_4)}$ ), respectively; those were 2.1 and 41.4, respectively, in the acidolyses of compound **I**. These results show that benzyl cation **IX** sufficiently forms but mostly progresses to the reverse addition of a  $\text{H}_2\text{O}$  molecule rather than to the  $\beta$ -proton abstraction in the acidolysis of compound **I** using  $\text{H}_2\text{SO}_4$ , although the disappearance of compound **I** is apparently quite slow, as shown in Fig. 4. Therefore, the difference observed in the rates of compound **I** between the acidolyses using the three acids mainly results not from that in the formation rates of benzyl cation **IX** but from that in the rates of the  $\beta$ -proton abstraction. This fact is apparent in the remarkable difference observed in the formations of compounds **I** and **II** between the acidolyses of compound **VI** using the three acids. Although compound **I** formed more than compound **II** in all the acidolyses, moderate or smaller amounts of compound **II** formed in the acidolysis using  $\text{HBr}$  or  $\text{HCl}$ , respectively, while almost no compound **II** was detected in that using  $\text{H}_2\text{SO}_4$  at least until a reaction time of 1 h. Because the proton activities must be almost the same in the acidolyses using the three acids, the observed phenomena are apparently explained by the assumption that  $\text{Br}^-$  or  $\text{Cl}^-$  readily abstract while  $\text{HSO}_4^-$  hardly abstracts a  $\beta$ -proton from benzyl cation **IX**, as described in the previous section. Because  $\text{Br}^-$  and  $\text{Cl}^-$  are quite weak bases, this explanation is not agreeable. It is discussed in the next section how  $\text{Br}^-$  or  $\text{Cl}^-$  can participate in the acidolysis.

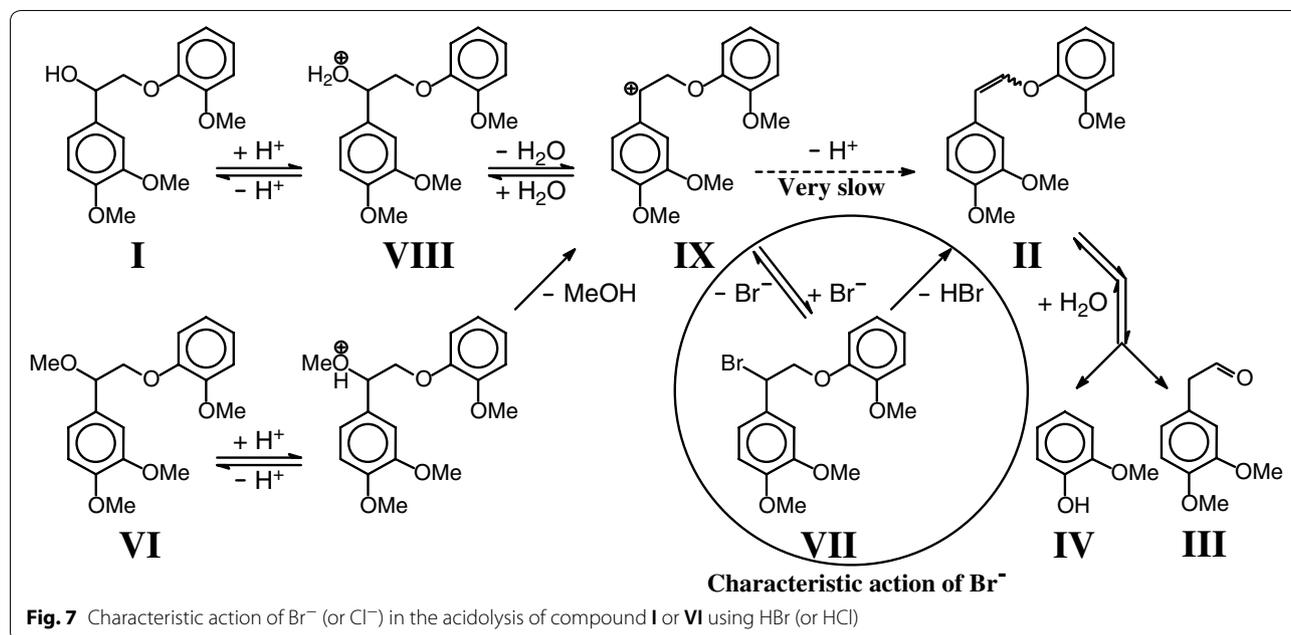
Because the disappearance rates of compound **VI** were in the order of the acidolyses using:  $\text{HBr} > \text{HCl} > \text{H}_2\text{SO}_4$ , despite the proton activities being similar,  $\text{Br}^-$  or  $\text{Cl}^-$  must also participate in the formation of benzyl cation **IX** from compound **VI** (also from compound **I**). A

possible mechanism is that these anions assist in the liberation of the  $\text{CH}_3\text{OH}$  ( $\text{H}_2\text{O}$ ) molecule via the  $\text{S}_{\text{N}}2$ -type mechanism.

#### Acidolysis of compound **VII** and characteristic action of $\text{Br}^-$ and $\text{Cl}^-$

The only readily conceivable mechanism for explaining the frequent  $\beta$ -proton abstraction from benzyl cation **IX** to afford compound **II** in the acidolysis using  $\text{HBr}$  or  $\text{HCl}$  is that highly nucleophilic  $\text{Br}^-$  or  $\text{Cl}^-$  primarily adds to the cation center of benzyl cation **IX** to afford compound **VII** or the  $\alpha$ -chloro derivative, respectively, which can then undergo the elimination reaction of  $\text{HBr}$  or  $\text{HCl}$ , respectively, at the  $\alpha$ - and  $\beta$ -positions to afford compound **II**. To confirm whether or not this mechanism is active, compound **VII** was synthesized and acidolyzed as a starting compound using  $\text{HBr}$  under the same conditions. If this mechanism is active, a certain amount of compound **II** must form. The relative amount of afforded compound **I** to **II** was examined about 10 s after the chloroform-*d* solution containing compound **VII** was added to the acidolysis solution containing  $\text{HBr}$ . Because compound **VII** is unstable under the employed conditions, and immediately disappears from the acidolysis solution, the conversion of compound **VII** to compound **I** or **II** must complete before a reaction time of about 10 s. The internal standard compound was added together.

The observed relative amount of compound **I** to **II** was  $4.5 \pm 0.3$  in three duplicated acidolyses of compound **VII** (0.3: standard deviation). This confirmed that compound **II** forms from compound **VII**, and hence the above conceived mechanism is active and explains why compound **II** frequently forms from benzyl cation **IX** in the acidolysis of compound **VI** or **I** using  $\text{HBr}$ . This addition is a characteristic action of  $\text{Br}^-$  in acidolysis affecting the acidolysis reaction and rate (Fig. 7). The observed relative amount of compound **I** to **II** was  $10.4 \pm 1.9$  in three duplicated acidolyses of compound **VII** using  $\text{H}_2\text{SO}_4$ , in which  $\text{Br}^-$  still exists with the amount being smaller than that in the acidolysis using  $\text{HBr}$ . This result confirmed that the above conceived mechanism is active and the absence of  $\text{Br}^-$  must quench the progress of benzyl cation **IX** to the formation of compound **II**. In contrast, a ratio of the initial formation rates between compounds **I** and **II** in the acidolysis of compound **VI** using  $\text{HBr}$  indicates how benzyl cation **IX** reacts to be distributed to compounds **I** and **II**. This ratio can be obtained from that of the initial slopes between the curves corresponding to these compounds drawn in Fig. 6. This ratio was calculated to be 5.6, which is not largely different from but larger than the above ratio of 4.5. If the ratio of the initial formation rates were also calculated to be 4.5, an equilibrium would be established between benzyl cation **IX** and compound **VII**



more rapidly than the conversions of benzyl cation **IX** and compound **VII** to compounds **I** and **II**, respectively. Therefore, the rates of these conversions would not be largely different from those of the forward and reverse reactions of the equilibrium. Additionally, the ratio of the initial formation rates between compounds **I** and **II** in the acidolysis of compound **VI** using HCl was calculated to be 11.9, which suggests that benzyl cation **IX** combines with Cl<sup>-</sup> less frequently than with Br<sup>-</sup>.

It should be discussed why compound **VII** produced by the addition of Br<sup>-</sup> to benzyl cation **IX** progresses to the HBr elimination reaction to afford compound **II**, although a H<sub>2</sub>O (or Diox) molecule must abstract a β-proton from either compound **VII** or benzyl cation **IX**. Possible explanations are as follows: i) Compound **VII** must revert to benzyl cation **IX** to progress to the H<sub>2</sub>O addition to afford compound **I**. Because this reaction is naturally slower than the H<sub>2</sub>O addition to benzyl cation **IX**, the formation of compound **I** must be slower from compound **VII** than from benzyl cation **IX**. However, this must not be the main reason, because the formation of compound **I** from compound **VII** is still rather faster than that of compound **II**, as shown by the above-described ratio of 4.5; ii) Compound **VII** has a stereoelectronic effect at the α- and β-positions in which the electron pair present in the bonding orbital of either of the two C–H bonds at the β-position delocalizes to the antibonding orbital of the C–Br bond at the α-position, when compound **VII** exists as a conformer where the C–H bond at the

β-position locates at the antiperiplanar of the C–Br bond at the α-position. Owing to this stereoelectronic effect, compound **VII** is ready to undergo the HBr elimination from the α- and β-positions. Because H<sub>2</sub>O as well as Diox, which is a weak base, must abstract a β-proton from benzyl cation **IX**, the abstraction is quite slow and hence benzyl cation **IX** mostly undergoes the H<sub>2</sub>O addition to afford compound **I**.

The addition of Br<sup>-</sup> or Cl<sup>-</sup> to benzyl cation can also explain which of route **A** or **B** predominates in an acidolysis of the common C<sub>6</sub>-C<sub>3</sub>-type β-O-4 substructure **i** in lignin, and why the reaction is fast in an acidolysis using HBr (or HCl) (Fig. 1). Route **A** is the major route when HBr or HCl is used. Route **B** is the major route when H<sub>2</sub>SO<sub>4</sub> or another acid is applied. In acidolyses using the former two acids, Br<sup>-</sup> or Cl<sup>-</sup> adds to the cation center of benzyl cation intermediate **ii**, which leads to the formation of acid labile enol ether substructure **iii** and acceleration of the acidolysis. In an acidolysis using H<sub>2</sub>SO<sub>4</sub>, nucleophilically inert HSO<sub>4</sub><sup>-</sup> does not add to benzyl cation intermediate **ii**, which frequently reproduces the initial substructure **i**, decelerating the reaction. However in an acidolysis of a C<sub>6</sub>-C<sub>3</sub>-type substructure **i**, route **B** exists for benzyl cation intermediate **ii** to release the HCHO molecule and convert to a C<sub>6</sub>-C<sub>2</sub>-type enol ether substructure **vi**. Route **B** is initiated by the proton abstraction from the γ-hydroxy group of benzyl cation intermediate **ii**, which seems easier to progress than route **A** in which a proton is abstracted from the β-carbon. This comprehensively indicates that a highly nucleophilic anion with high

leaving ability leads the acidolysis reaction to route A and accelerates it. Only Br<sup>-</sup> and Cl<sup>-</sup> as well as I<sup>-</sup> can be such anions.

## Conclusions

C<sub>6</sub>-C<sub>2</sub>-type lignin model compounds **I**, **II**, and **VI** with the β-O-4 bond were individually acidolyzed using HBr, HCl, and H<sub>2</sub>SO<sub>4</sub> as acids. Although the disappearance rates of all the compounds were in the order of the acidolyses using: HBr > HCl > H<sub>2</sub>SO<sub>4</sub>, those of compound **I** in the acidolyses using HBr and HCl were remarkably greater than that using H<sub>2</sub>SO<sub>4</sub>, which was different from those in the acidolyses of compound **II** or **VI**. The acidolyses of compound **VI** using these three acids indicated that benzyl cation **IX**, which is also derived from compound **I**, mostly undergoes H<sub>2</sub>O addition to convert to compound **I** in the acidolysis using H<sub>2</sub>SO<sub>4</sub> while in those using the other two acids benzyl cation **IX** additionally progresses to β-proton abstraction to convert to compound **II** followed by the acidolytic β-O-4 bond cleavage. These results explain why the disappearance of compound **I** was remarkably slower in the acidolysis using H<sub>2</sub>SO<sub>4</sub> than in those using the other two. The acidolysis of compound **VII** using HBr confirmed that not only compound **I** but also compound **II** forms from compound **VII**, with the relative yield of the former 4.5 times that of the latter.

All of these results clarified a characteristic action of Br<sup>-</sup> (or Cl<sup>-</sup>) in the acidolysis of compound **I** using HBr (or HCl). Br<sup>-</sup> (or Cl<sup>-</sup>) adds to benzyl cation **IX** to afford compound **VII** (or the α-chloro derivative), resulting in the frequent formation of compound **II** followed by acidolytic β-O-4 bond cleavage and acceleration of the disappearance of compound **I**.

## Abbreviation

Diox: 1,4-Dioxane.

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## Authors' contributions

QY conducted the experiments, analyzed the data, and wrote the draft of this manuscript under the supervision of TM. TM completed the final manuscript. QY and TM read and approved the final manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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