

Reactions of β -O-4-type Non-phenolic Lignin Model Compounds in Various Basic Systems using *tert*-Butoxide and Other Bases under Mild Conditions

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Abstract

Non-phenolic C₆-C₂- and C₆-C₃-type lignin model compounds with the β -O-4 bond were treated in *tert*-butyl alcohol (*t*BuOH) or dimethyl sulfoxide (DMSO) containing potassium *tert*-butoxide (KOtBu) or various other bases under mild conditions (at a base concentration of 0.5 mol/L and 30°C) to examine how the reactions differ between these systems. The β -O-4 bond cleavage in KOtBu/*t*BuOH was slower than that in KOtBu/DMSO owing to the greater solvation of *t*BuO[−] in *t*BuOH than in DMSO. The β -O-4 bond cleavage of the *erythro* isomer of the C₆-C₃-type compound was slower than that of the *threo* isomer in all the reactions. This is explained by the preferred formation of a strong hydrogen bond between the α -hydroxy and the dissociated γ -alkoxy groups (or *vice versa*) of the former, which interferes with the cleavage. The rates of the β -O-4 bond cleavages in DMSO were in the order of the systems containing: NaOtBu > KOtBu >> LiOtBu, which seems to relate to whether each base dissolves as an ion pair or free ions in DMSO. Those in DMSO were in the order of the systems containing KOtBu >> potassium hydride (KH) >> potassium *iso*-propoxide > potassium ethoxide, which is consistent with their basicities except for KH.

Keywords: Alkali; Methylsulfinylmethylide; Neighboring group participation

INTRODUCTION

It is highly desirable to comprehensively utilize all the components of woody biomass, to reduce the impact of industry on the environment. This requirement will mainly be achieved by establishing methods for the practical utilization of lignin. Chemical removal of lignin (delignification) is the most common strategy, and is most commonly advanced by cleaving the β -O-4 bond, the most abundant type of linkage between monomeric units of lignin.

Given this importance of β -O-4 bond cleavage, we developed a system for cleaving the β -O-4 bond using potassium *tert*-butoxide (KOtBu) and a C₆-C₂-type non-phenolic lignin model compound with the β -O-4 bond, 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol (**I**, Fig. 1), in various solvents under relatively mild conditions ^{1,2}. This development was based on a previous finding that the β -O-4 bond of the phenolic analogue of compound **I**, 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)ethanol, is cleaved in a KOtBu/dimethyl sulfoxide (DMSO) system at room temperature ³. Our previous report confirmed that the β -O-4 bond of compound **I** is sufficiently cleaved in a DMSO, *tert*-butyl alcohol (*t*BuOH), 1,4-dioxane, or tetrahydrofuran solution containing KOtBu with a concentration of 0.5 mol/L at 30°C ². This was rather surprising, because the β -O-4 bond cleavage requires harsh conditions, such as both a concentration of sodium hydroxide (NaOH) of 1.0 mol/L or higher and a temperature of 130°C or higher, in the common pulping process for paper making.

We further examined the reaction mechanisms of the *erythro* and *threo* diastereomers of a C₆-C₃-type non-phenolic lignin model compound with the β -O-4 bond, 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)propane-1,3-diol (**IIe** and **II_t**, respectively, Fig. 1), in the KOtBu/DMSO system, and compared them with that of compound **I** to examine the effects of the γ -hydroxymethyl group and

diastereomerism, in our recent report ⁴⁾. The β -O-4 bond cleavage was accelerated by the presence of the γ -hydroxymethyl group, since the rates of the cleavage were in the order: compound **II**t > **II**e > **I**. Because this order was different from that observed in the common alkaline pulping process, *i.e.*, compound **II**e > **I** > **II**t, we could show how the diastereomers' effects appears on the rates are dependent on the applied reaction system, and hence that the mechanism of the β -O-4 bond cleavage differs between different reaction systems.

In this paper, we examined the differences in reactions and rates of the β -O-4 bond cleavage between various basic systems using compounds **I**, **II**e, and/or **II**t, and *tert*-butoxide (*t*BuO⁻) as well as other bases in *t*BuOH or DMSO.

EXPERIMENTAL

Materials

All chemicals except for compounds **I**, **II**e, and **II**t, which were synthesized according to our recent report ⁴⁾, 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. Lithium *tert*-butoxide (LiO*t*Bu), sodium *tert*-butoxide (NaO*t*Bu), KO*t*Bu, and DMSO were of semiconductor grades. Potassium *iso*-propoxide (KO*i*Pr) and potassium ethoxide (KOEt) were prepared by adding potassium hydride (KH, dispersion in mineral oil) to propan-2-ol (*iso*-propyl alcohol) and ethanol, respectively, followed by concentration in an evaporator, filtration, and dryness under vacuum.

Reaction of Model Compound

The following three reaction series were conducted in this study: i) To a round-bottom Teflon flask (50 mL) was added 2.5 mmol of KO*t*Bu and successively 2.5 mL of *t*BuOH. Then, 2.5 mL of another *t*BuOH solution containing compound **I**, **II**e, or **II**t was added to the Teflon flask to initiate the reaction, and the flask was sealed with the Teflon lid. ii) To the round-bottom Teflon flask was added 2.5 mmol of KO*t*Bu, NaO*t*Bu, or LiO*t*Bu and successively 2.5 mL of DMSO. The obtained suspension was stirred for 1 or 3 h to completely dissolve NaO*t*Bu or LiO*t*Bu, respectively, into DMSO except for KO*t*Bu, which dissolved in a minute. Then, 2.5 mL of another DMSO solution containing compound **II**e or **II**t was added to the Teflon flask to initiate the reaction, and the flask was sealed with the Teflon lid. iii) To the round-bottom Teflon flask was added 2.5 mmol of KO*t*Bu, KO*i*Pr, KOEt, or KH and successively 2.5 mL of DMSO. Then, 2.5 mL of another DMSO solution containing compound **II**e or **II**t was added to the Teflon flask to initiate the reaction, and the flask was sealed with the Teflon lid.

The initial concentrations of each base and the model compound were almost 0.50 mol/L and 3.0 mmol/L, respectively. The solution was maintained at 30°C to the end of the reaction with stirring in a water bath. Before adding the second *t*BuOH or DMSO solution, all the prepared solutions were thoroughly degassed under reduced pressure and immediately flushed with nitrogen gas. At prescribed reaction times, 0.5 mL of the reaction solution was withdrawn and added to a glass tube containing 25 μ L of acetic acid for neutralization and an internal standard compound, 5-acetyl-1,2,3-trimethoxybenzene, as the *t*BuOH or DMSO solution, respectively. The obtained mixture was filtered with a membrane filter, and then subjected to identification and quantification of the model compounds and reaction products as described below.

Identification and Quantification of Model Compounds and Reaction Products

Five reaction products identified and quantified in our recent report ⁴⁾, 2-methoxyphenol (guaiacol, **V**, Fig. 1), 1,2-dimethoxybenzene (veratrol, **VI**, Fig. 1), 3,4-dimethoxybenzaldehyde (veratraldehyde, **VII**, Fig. 1), 4-acetyl-1,2-dimethoxybenzene (acetoveratrone, **VIII**, Fig. 1), and 3,4-dimethoxybenzoic acid (veratric acid, **IX**, Fig. 1), were also quantified in this study. Compounds **III** and **IV** do not appear and are not referred to in this study, to maintain correspondence of compound names between this study and our previous report ⁴⁾.

The procedures for the identification and quantification were as described in our recent report ⁴⁾.

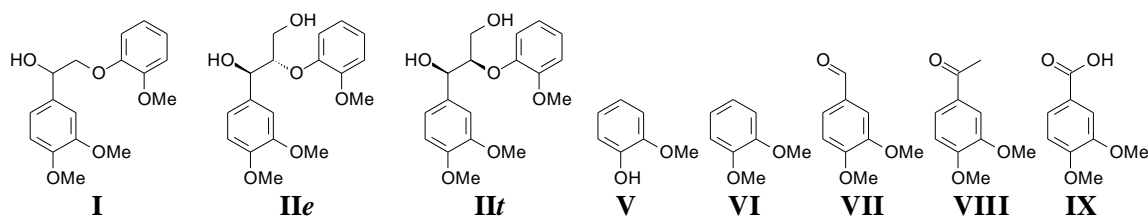


Fig. 1. Chemical structure of compounds **I**, **IIe**, and **IIIt** used as starting materials and compounds **V**, **VI**, **VII**, **VIII**, and **IX** quantified as reaction products.

RESULTS AND DISCUSSION

Reaction of Compounds **I**, **IIe**, and **IIIt** in the KO t Bu/ t BuOH System

Although compound **I** had been treated in the KO t Bu/ t BuOH system in our previous report ³⁾, t BuOH was not used in our recent report ⁴⁾, leaving the comparison of the reactions in this system between compounds **I**, **IIe**, and **IIIt** unfinished. This time, compound **I**, **IIe**, and **IIIt** were individually treated in the KO t Bu/ t BuOH system to compare their reactions.

The disappearance of compound **I** in this study was slower than that in our previous report ³⁾, although the conditions were intended to be exactly the same. This inconsistency must have resulted from a difference in the amount of H₂O contaminating the systems between our previous report and this study. A relatively large amount of H₂O contamination in this study, due to utilizing the most common commercially available t BuOH, must have slowed the disappearance of compound **I**. In contrast, a semiconductor grade solution of KO t Bu in t BuOH had been used in our previous report ³⁾. Our recent report showed that a relatively high level of H₂O contamination in DMSO decelerates the disappearance of compound **I** in the KO t Bu/DMSO system ⁴⁾.

Fig. 2 shows the time courses of the changes in the disappearances of compounds **I**, **IIe**, and **IIIt** and formations of compounds **V** and **IX** when compound **I**, **IIe**, or **IIIt** was individually treated in the KO t Bu/ t BuOH system. No reaction products including compounds **VI**, **VII**, and **VIII** other than compounds **V** and **IX** were detected in any reaction. The total of the remaining yield of compound **I**, **IIe**, or **IIIt** and yield of compound **V** was always at least 96%, and commonly more than 98%, in any reaction, indicating that the disappearance accompanied the β -O-4 bond cleavage. The total of the remaining yield of compound **I**, **IIe**, or **IIIt** and yield of compound **IX** was always at least 95%, and commonly more than 97%, in any reaction, indicating that the 3,4-dimethoxyphenyl nucleus portion of compound **I**, **IIe**, or **IIIt** was converted almost entirely to compound **IX**. The mechanism of the β -O-4 bond cleavage is common neighbouring γ - or α -hydroxy group participation to afford compound **V** and the corresponding epoxide intermediates, as shown in our recent report ⁴⁾. Because compound **VII** or **VIII** can readily form from the epoxides *via* the alkali-catalysed rearrangements ⁴⁾, compounds **VII** and **VIII** were treated in the KO t Bu/ t BuOH system as starting compounds to examine whether or not once-produced compound **VII** or **VIII** would convert to compound **IX** in the reaction of compound **I**, **IIe**, or **IIIt**. The remaining yields of compounds **VII** and **VIII** were 82% and 95%, respectively, at a reaction time of 2 h. Compound **IX** formed only from compound **VIII**, with a yield of less than 1% at this reaction time. This confirmed that compound **IX** does not originate from once-produced compound **VII** or **VIII** in the reaction of compound **I**, **IIe**, or **IIIt**. The formation mechanism of compound **IX** is thus unclear. Compound **VIII** was not detected in this study, despite its formation in our previous report ³⁾. The relatively large amount of H₂O contamination may have resulted in the formation of compound **IX** as the only reaction product from the 3,4-dimethoxyphenyl nucleus portion.

The disappearance rates of compounds **I**, **IIe**, and **IIIt** corresponded to those of their β -O-4 bond cleavages, and were in the order: compound **IIIt** > **IIe** > **I**, as shown in Fig. 2. This is the same order as in the KO t Bu/DMSO system ⁴⁾, and different from that in the common alkaline pulping process, *i.e.*, compound **IIe** > **I** > **IIIt** ⁵⁾. This observed order shows that the presence of the γ -hydroxy group accelerates the β -O-4 bond cleavage. An explanation for this order is, as described in our recent report ⁴⁾, that the strong hydrogen bond exists in the most preferred staggered conformation of



compound **IIe** between the α -hydroxy and dissociated γ -alkoxy groups (or *vice versa*) and interferes with the β -O-4 bond cleavage, for which the α - or γ -alkoxide must attack the β -carbon from the opposite side of the β -O-4 bond after breaking the strong hydrogen bond. Consequently, compound **IIe** mostly undergoes β -O-4 bond cleavage in other, less preferable conformations, which results in slower cleavage. Because the strong hydrogen bond does not conformationally exist in the preferred conformation of compound **II_t**, it can undergo β -O-4 bond cleavage in this conformation. Furthermore, compound **IIe** or **II_t** can undergo β -O-4 bond cleavage in any staggered conformation, owing to the participation of the achiral γ -hydroxy group. We confirmed that the order of the β -O-4 bond cleavage rates of compounds **I**, **IIe**, and **II_t** in the KO t Bu/ t BuOH system is the same as that in the KO t Bu/DMSO system, and that the presence of the γ -hydroxy groups also accelerates the β -O-4 bond cleavages in the KO t Bu/ t BuOH system.

The β -O-4 bond cleavages in the KO t Bu/ t BuOH system were much slower than those in the KO t Bu/DMSO system. Because DMSO is known to mainly solvate the cations of salts without strongly solvating the anions when the salts dissolve in DMSO ⁶⁾, the faster cleavage in DMSO must result from the weak solvation of t BuO⁻, allowing it to express its original strong basicity.

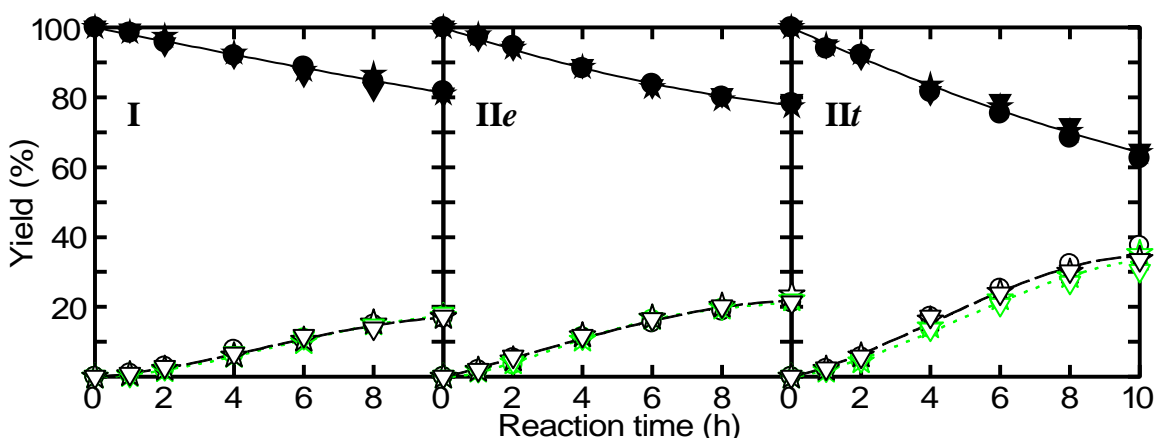


Fig. 2. Time course of the changes in the remaining yields of compounds **I**, **IIe**, and **II_t** (black marks and solid lines) and yields of compounds **V** (white marks with black contours and long broken lines) and **IX** (white marks with green contours and dotted lines) when compound **I**, **IIe**, or **II_t** was individually treated in the KO t Bu/ t BuOH system (left: **I**, middle: **IIe**, right: **II_t**). Circles, stars, and inverted triangles show the 1st, 2nd, and 3rd trials, respectively.

Reactions of Compounds **IIe** and **II_t** in DMSO Using KO t Bu, NaO t Bu, and LiO t Bu

Compound **IIe** or **II_t** was individually treated in DMSO containing KO t Bu, NaO t Bu, or LiO t Bu as a base to examine the differences in reactions between these three systems. The data for the reactions in the KO t Bu/DMSO system were taken from our recent report ⁴⁾. It took 1 h or 3 h to completely dissolve NaO t Bu or LiO t Bu in DMSO, respectively, which was different from dissolving KO t Bu. The reactions were initiated after complete dissolution.

Fig. 3 shows the time courses of the changes in the disappearances of compounds **IIe** and **II_t** and formations of compounds **V**, **VI**, **VII**, **VIII**, and **IX** in these systems when compound **IIe** or **II_t** was individually treated in each system. The data for the reactions in the KO t Bu/DMSO system were taken from our recent report ⁴⁾. These five were the only major reaction products, although small peaks appeared on the chromatograms showing the formation of many minor reaction products. The total of the remaining yield of compound **IIe** or **II_t** and yield of compound **V** was always close to 100% in all the systems, indicating that the disappearance accompanied the β -O-4 bond cleavage.

The β -O-4 bond cleavage of compound **IIe** was slower than that of compound **II_t** in all the systems, which can also be explained by the above description for the KO t Bu system from our recent report ⁴⁾.



In the LiOtBu system, either compound **IIe** or **II_t** disappeared only slightly. The remaining yields were 96% and 92%, respectively, at a reaction time of 60 min. Dissolution of a salt of *t*BuO[−] (MO*t*Bu) in DMSO comprises first solid MO*t*Bu to the ion pair of *t*BuO[−] and M⁺, and followed by the ion pair to the free ions ⁷⁾. It is also known that LiOtBu exists as an ion pair in DMSO ⁸⁾. Li⁺ carrying the large positive charge density must have a strong electrostatic interaction with the negatively charged oxygen of *t*BuO[−], and be too small to be sufficiently solvated by the relatively large molecule of DMSO. LiOtBu must thus be rather inert as a base in the LiOtBu/DMSO system. The only detected reaction product was compound **VII** in the reaction of compound **IIe**. Compounds **VII** and **VIII** were produced in the reaction of compound **II_t**.

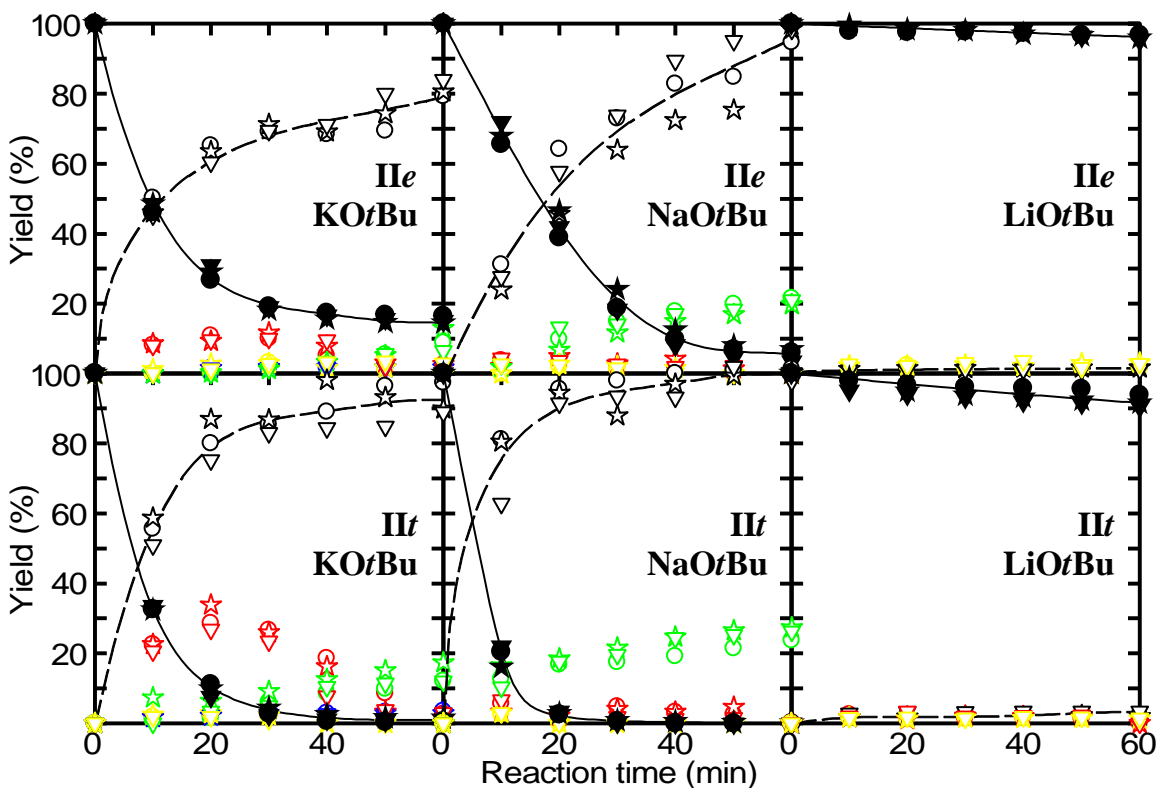


Fig. 3. Time course of the changes in the remaining yields of compounds **IIe** and **II_t** (black marks and solid lines) and yields of compounds **V** (white marks with black contours and long broken lines), **VI** (white marks with blue contours), **VII** (white marks with yellow contours), **VIII** (white marks with red contours), and **IX** (white marks with green contours and dotted lines) when compound **IIe** or **II_t** was individually treated in the KO*t*Bu/DMSO, NaOtBu/DMSO, or LiOtBu/DMSO system (upper three: **IIe**, lower three: **II_t**, left two: KO*t*Bu/DMSO system, middle two: NaOtBu/DMSO system, right two: LiOtBu/DMSO system). Circles, stars, and inverted triangles show the 1st, 2nd, and 3rd trials, respectively.

The difference in disappearance observed between compounds **IIe** and **II_t** in the NaOtBu system was larger than that in the KO*t*Bu system. The disappearance of compound **IIe** in the NaOtBu system was initially slower than that in the KO*t*Bu system. Because it did not decelerate much during the reaction, however, the amount of disappearance in the NaOtBu system overtook that in the KO*t*Bu system at the middle stage. In contrast, the disappearance of compound **II_t** in the NaOtBu system was faster than that in the KO*t*Bu system from the initial stage, although the yields were not examined before a reaction time of 10 min. Fig. 4 shows logarithmic plots for the disappearances of compounds **IIe** and **II_t** in these systems until a reaction time of 40 min, to illustrate these phenomena more clearly. The disappearance of compound **IIe** in the NaOtBu system seems suppressed in the initial stage, after which it gradually accelerated, compared with a pseudo-first-order reaction. In the KO*t*Bu system, it gradually decelerated from the initial stage, compared with a pseudo-first-order reaction, although the degree was

small until the middle stage. The disappearance of compound **II***t* in the NaO*t*Bu system was in accordance with a pseudo-first-order reaction, while in the KO*t*Bu system it gradually decelerated from the initial stage. These phenomena cannot be fully explained.

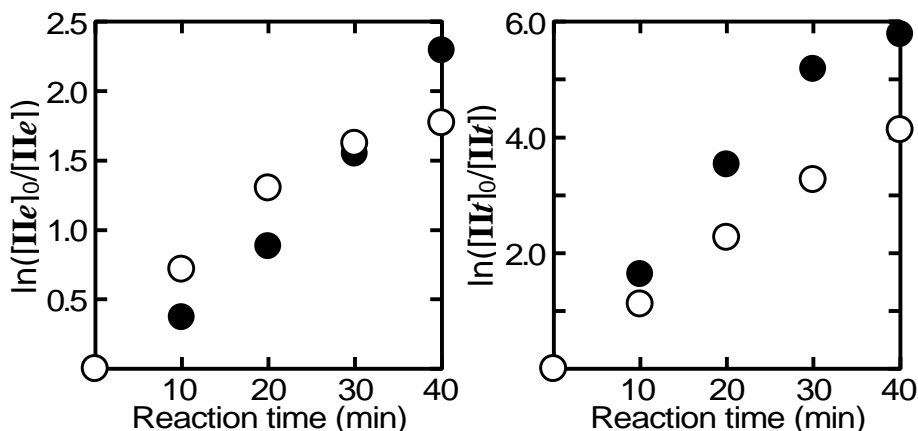


Fig. 4. Logarithmic plots for the disappearances of compounds **II***e* (left) and **II***t* (right) in the KO*t*Bu/DMSO and NaO*t*Bu/DMSO systems (white and black circles, respectively). $[\text{IIe}]_0$ and $[\text{IIIt}]_0$ show the initial concentrations of compounds **II***e* and **II***t*, respectively. $[\text{IIe}]$ and $[\text{IIIt}]$ show concentrations of compounds **II***e* and **II***t*, respectively.

Previous reports provide some hints: i) NaO*t*Bu dissolves in DMSO as an ion pair⁸⁾, although the interaction must be weaker than that of LiO*t*Bu due to the moderate positive charge density of Na⁺, and the ion pair must be able to gradually progress to free ions. ii) KO*t*Bu dissolves in DMSO mostly as free ions⁸⁾. iii) Free *t*BuO[−] abstracts a proton from DMSO to produce the conjugate base of DMSO, methylsulfinylmethide (CH₃SOCH₂[−]), and establishes an equilibrium (*t*BuO[−] + DMSO ⇌ *t*BuOH + CH₃SOCH₂[−]) shifting to the left^{9–11)}. iv) Aggregates of DMSO origin gradually form to decrease the basicity of the system when CH₃SOCH₂[−] is generated in DMSO^{7–9)}. A possible explanation for the phenomena described in the preceding paragraph may be described as follows, if it can also be assumed that the proton of the α-hydroxy group is not frequently abstracted by *t*BuO[−] of the ion pair with Na⁺ due to their large steric factors and the weakness as a base⁴⁾: The disappearance of compound **II***e* should initially be slow in the NaO*t*Bu system due to the presence of the ion pair, and gradually accelerate with the formation of free *t*BuO[−]. It should be fast from the initial stage in the KO*t*Bu system due to the dissolution as free ions, but decelerate gradually from the initial stage due to gradual formation of the aggregates. Indeed, aggregates gradually formed from the initial stage in the KO*t*Bu system. It is understandable that the disappearance of compound **II***t* is fast from the initial stage even in the NaO*t*Bu system, given the great contribution of the γ-hydroxy group with its low steric factor to the β-*O*-4 bond cleavage⁴⁾ without the deceleration caused by the formation of the aggregates, although the deceleration of the disappearance of compound **II***t* started from the initial stage in the KO*t*Bu system. Further investigation is needed to clarify the observed phenomena.

The profiles of the reaction products were not the same in the three systems (Fig. 3). Compound **VI** was detected only in the KO*t*Bu system. Only compound **VII** formed in all three systems. Compound **VIII** formed with the largest yield in the KO*t*Bu system. The yield of compound **IX** was higher in the NaO*t*Bu than in the KO*t*Bu system.

Reactions of Compounds **II***e* and **II***t* in DMSO Using KO*t*Bu, KO*i*Pr, KOEt, and KH

Compound **II***e* or **II***t* was individually treated in DMSO containing KO*t*Bu, KO*i*Pr, KOEt, or KH as a base to examine the differences in reactions between these systems. The data for the reactions in the KO*t*Bu/DMSO system were taken from our recent report⁴⁾, and are shown in Fig. 3 as described above. The reaction products were not analyzed in systems other than the KO*t*Bu/DMSO system.

The disappearances of compound **II***e* and **II***t* were small in the KO*i*Pr and KOEt systems. The remaining yields were 95.9±0.2% and 92.9±0.5%, respectively, in the KO*i*Pr system, and 97.7±0.3%



and $95.6 \pm 0.1\%$, respectively, in the EtOK system (values \pm SD for 3 experiments) at a reaction time of 60 min. Because KO i Pr and KOEt must dissolve in DMSO as free ions similarly to KO t Bu, these observations indicate that the basicities of *iso*-propoxide (i PrO $^-$) and ethoxide (EtO $^-$) are not high enough to sufficiently cleave the β -O-4 bond under the employed mild conditions despite the basicity of i PrO $^-$ being higher than EtO $^-$ in accordance with the above-described remaining yields. The degree of the β -O-4 bond cleavage under the employed mild conditions is thus ordered by the basicity of the alkoxides: t BuO $^-$ (tertiary alkoxide) $>$ i PrO $^-$ (secondary alkoxide) $>$ EtO $^-$ (primary alkoxide). Thus, high basicity is necessary for the cleavage under the mild conditions. This necessity can also be suggested by the fact that sever conditions, such as those described in the introduction, are required for the cleavage in any aqueous alkaline system, where the levelling effect of water limits the maximum level to that not enough for the cleavage. Additionally, compound **IIe** always disappeared more than compound **II t** .

The remaining yields of compound **IIe** and **II t** were $63.4 \pm 1.7\%$ and $51.9 \pm 1.8\%$, respectively, in the KH system at a reaction time of 60 min. These yields were higher than those in the KO t Bu system, although the basicity of hydride (H $^-$) is higher than that of t BuO $^-$, and hence the disappearances in the KH system had been expected to be greater than those in the KO t Bu system. This observation results from CH $_3$ SOCH $_2^-$ being quantitatively produced from DMSO in the KH system to significantly form the aggregates discussed in the previous section from the initial stage, and consequently significantly decreasing the basicity. Because CH $_3$ SOCH $_2^-$ is not quantitatively formed in the KO t Bu system, the aggregates do not significantly form, and only a gradual decrease of the basicity is seen. Although the basicity of the KO t Bu system is weaker than that of the KH system, it is strong enough to advance the β -O-4 bond cleavage.

CONCLUSIONS

1. The β -O-4 bond cleavage of compound **I**, **IIe**, or **II t** was slower in the KO t Bu/ t BuOH system than in the KO t Bu/DMSO system, which is explained by the greater solvation of t BuO $^-$ in t BuOH than in DMSO. The order of the rates, compound **II t** $>$ **IIe** $>$ **I**, was observed in both systems and was different from that in an alkaline pulping process, compound **IIe** $>$ **I** $>$ **II t** , which shows the significant contribution of the γ -hydroxy groups of compounds **II** to the β -O-4 bond cleavage.
2. The β -O-4 bond cleavage of compound **IIe** was slower than that of compound **II t** in DMSO using KO t Bu, NaO t Bu, or LiO t Bu as a base. The rates of compound **IIe** or **II t** in these DMSO systems were mostly in the order of: NaO t Bu $>$ KO t Bu \gg LiO t Bu, although the rate of compound **IIe** was less in the NaO t Bu system than in the KO t Bu system at the initial stage. These phenomena cannot be fully explained but may be dependent on whether each base dissolves in DMSO as an ion pair or free ions, which affects the system basicity.
3. The disappearance rates of compound **IIe** or **II t** in DMSO containing bases were in the order of: KO t Bu \gg KH \gg KO i Pr $>$ KOEt, which shows that the rates are mostly dependent on the basicity of these bases except for KH. KH is too strong as a base to quantitatively produce the conjugate base of DMSO, and hence, an abundance of DMSO aggregates forms to consequently decrease the basicity and the disappearance rate.

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