Conversion of *N*-acetyl-D-glucosamine to nitrogen-containing chemicals in high-temperature water

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Abstract

To demonstrate the conversion of renewable biomass to platform chemicals, we previously reported the noncatalytic conversion of *N*-acetyl-D-glucosamine (GlcNAc), which is obtained from chitin, to nitrogen-containing chemicals; however, various aspects of this process were not clarified. Herein, we reported updated and expanded results for the synthesis of nitrogen-containing chemicals from GlcNAc in high-temperature water at 180–280 °C and 25 MPa with a reaction time of 5–34 s. The main products were 2-acetamido-2,3-dideoxy-D-erythro-hex-2-enofuranose (Chromogen I) and 3-acetamido-5-(1',2'-dihydroxyethyl)furan (Chromogen III) with the maximum yields of 37.0% and 34.5%, respectively. Although 3-acetamido-5-acetylfuran was expected to form by the dehydration of Chromogen III, a yield of only <1% was obtained, likely because the dehydration of Chromogen III is difficult in the absence of a catalyst. The evaluation of the effects of acid and base catalysts on the dehydration of GlcNAc revealed that the acid catalyst suppressed the transformation of GlcNAc to Chromogen I and promoted the transformation of Chromogen I to Chromogen III, whereas the base catalyst had the opposite effects on these processes. The synthesis of nitrogen-containing chemicals from GlcNAc in high-temperature water is an environmentally benign method for utilizing renewable chitin biomass.

Keywords: biomass, chitin, glucosamine, subcritical water, hydrothermal treatment

1. Introduction

The efficient conversion of renewable biomass to platform chemicals that are applicable as raw materials or synthetic intermediates for higher-value chemicals has been actively pursued in the field of green chemistry. *N*-Acetyl-D-glucosamine (GlcNAc) is an important unit of chitin and can be obtained by acidic hydrolysis or enzymatic degradation of this polysaccharide [1–7]. Chitin is the second most abundant biomolecule on Earth (after cellulose) and a major component of fungi cell walls and the exoskeletons of insects and crustaceans [1], which makes GlcNAc an abundant monosaccharide. In contrast to glucose, GlcNAc has an acetoamide group at C-2, which endows it with versatile functions as a skin moisturizer, an analgesic for joint pain, and an antitumoral and antimicrobial agent. These functions differ greatly from those of glucose, which contains only hydroxy groups. In addition, many GlcNAc derivatives, namely, nitrogen-containing chemicals such as 2-acetamido-2,3-dideoxy-D-erythro-hex-2-enofuranose (Chromogen I), 3-acetamido-5-(1',2'-dihydroxyethyl)furan (Chromogen III), and 3-acetamido-5-acetylfuran (3A5AF) also exhibit potent biological activities and have attracted recent attention as new functional food additives and medicines [8–13].

To date, acid or base catalysts, organic solvents, and ionic liquids have been used to synthesize nitrogen-containing chemicals from GlcNAc via dehydration reactions [14–16]. Ogata et al. have reported the synthesis of Chromogen I in aqueous boric acid, achieving a yield of 50% [17], while Chen et al. obtained 3A5AF in a very low yield (0.03%) by pyrolysis of GlcNAc at 200 °C in the presence of Na_2HPO_4 [18]. Furthermore, Omari et al. synthesized 3A5AF from GlcNAc in an organic solvent in 62% yield [19], while Chen et al. reported its synthesis from GlcNAc in an ionic liquid

in 56% yield [20]. However, these synthesis methods are problematic, as the strict elimination of organic solvents and ionic liquids is needed to apply the obtained nitrogen-containing chemicals in the fields of food and medicine.

The realization of truly green chemistry requires not only the use of renewable biomass resources as raw materials, but also eco-friendly conversion methods. High-temperature water is recognized as a green chemical medium for biomass conversion [21–25]. We have reported the noncatalytic synthesis of Chromogen I and Chromogen III from GlcNAc with maximum yields of 23.0% and 23.1%, respectively, in high-temperature water at 120–220 °C and 25 MPa with a reaction time of 7–39 s [26]. The use of high-temperature water allowed the dehydration reaction of GlcNAc to progress under catalyst-free conditions, as the ion product of water ($K_w = [H^+][OH^-]$) at high temperature and high pressure exceeds that at ambient temperature and pressure [27]. Advantageously, the high-temperature water method provides a shorter reaction time and uses only water. However, despite our previous report, three aspects of this method require further clarification. First, it is uncertain whether 3A5AF, which is the main product in ionic liquids or organic solvents, is synthesized in high-temperature water. Second, while the ion product of high-temperature water is higher than that of ambient temperature water, the effects of H^+ and OH^- as catalysts on the dehydration reaction of GlcNAc are not clear. Third, the role of steric effects during the dehydration of GlcNAc is unknown.

In this study, we investigated whether 3A5AF was synthesized in high-temperature water without catalysts. We expanded the range of experimental conditions beyond those used in our earlier work and redetermined the kinetic parameters of GlcNAc dehydration. In addition, acid or base catalysts were added deliberately to the reaction

system to reveal the effects of H^+ and OH^- originating from high-temperature water on the dehydration reaction of GlcNAc. Furthermore, the steric effect was investigated by comparing the reactions of GlcNAc and *N*-acetyl-D-mannosamine (ManNAc).

2. Experimental

GlcNAc, acetic acid, and acetonitrile were purchased from Wako Pure Chemicals Industries Ltd. ManNAc was purchased from Tokyo Chemical Industry Co., Ltd. Sodium hydroxide was obtained from Kanto Industry Co., Ltd. All chemicals were used without further purification. Chromogen I, 2-acetamido-3,6-anhydro-2-deoxy-D-glucofuranose (3,6-anhydro-GNF), 2-acetamido-3,6-anhydro-2-deoxy-D-mannofuranose (3,6-anhydro-MNF), Chromogen III, and 3A5AF were synthesized by previously reported methods [17,18] and used as the standard samples for high-performance liquid chromatography (HPLC) analysis in this study.

The employed experimental flow reactor has been described elsewhere [26]. The concentration of GlcNAc and ManNAc aqueous solutions equaled 0.045 mol L^{-1} (1.0 wt%). The reaction temperature was varied from 180 to 280 °C. The reaction time in the reactor was varied from 5 to 34 s. To examine the effects of acid and base catalysts, the GlcNAc aqueous solution was mixed with acetic acid or sodium hydroxide. The final concentrations of acetic acid and sodium hydroxide after mixing were 0.1 and 0.01 mol L^{-1}, respectively.

HPLC analysis was performed using a Shimadzu Intelligent System liquid chromatograph equipped with a Unison UK-Amino column (4.6 × 250 mm, Imtakt) or a Unison US-C18 column (4.6 × 250 mm, Imtakt) with detection at 210 nm. The eluent was 95 wt% CH_3CN and 5 wt% water for the former column and 10 wt% CH_3CN and 90 wt% water for the latter column. The sample was eluted at a flow rate of 1.0 mL min^{-1} at 40 °C.

The product yield of components *i* (Y_i) was defined as

$$Y_i\ (\%) = C_i / C_{0,\ \mathrm{GlcNAc}} \times 100, \qquad (1)$$

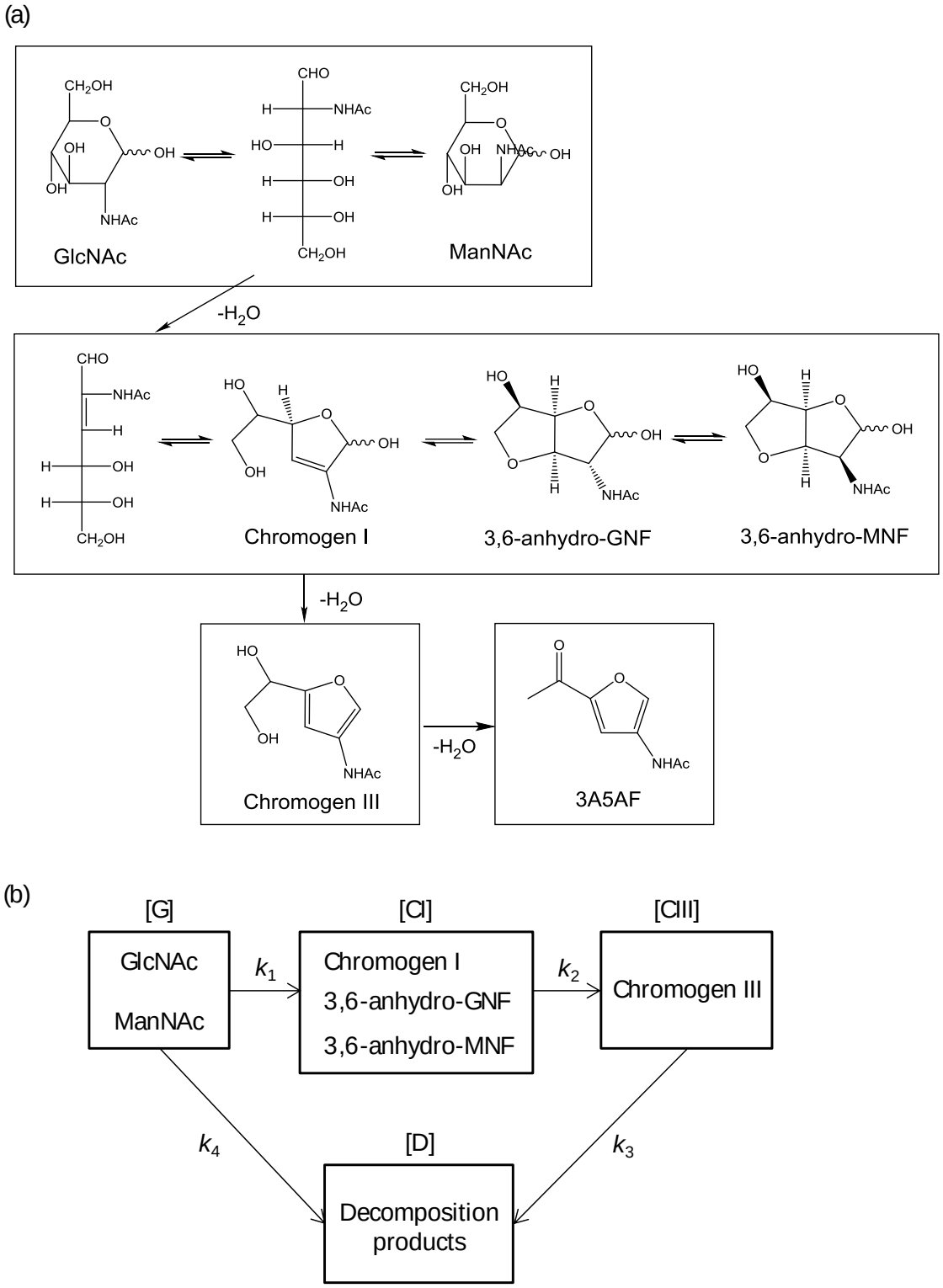
where $C_{0,\ \mathrm{GlcNAc}}$ is the concentration of GlcNAc at the reactor inlet [mol L^{-1}] and C_i is the concentration of product *i* at the reactor outlet [mol L^{-1}].

3. Results and discussion

3.1 Effect of reaction conditions on the yields of nitrogen-containing chemicals

Scheme 1a shows the products obtained from GlcNAc in this work in high-temperature water. The products detected were ManNAc, Chromogen I, 3,6-anhydro-GNF, 3,6-anhydro-MNF, Chromogen III, and 3A5AF. As 3,6-anhydro-GNF and 3,6-anhydro-MNF are isomers of Chromogen I and were obtained in yields of less than 5%, they were grouped with Chromogen I in this work. HPLC analysis revealed numerous weak signals corresponding to the unknown species, which indicated that GlcNAc was also converted to products other than those shown in Scheme 1a. Fig. 1 shows the yields of the products obtained from GlcNAc at temperatures of 180–280 °C as a function of the reaction time. Although we expected to obtain 3A5AF through dehydration of Chromogen III, the yield of 3A5AF was less than 1% at all temperatures; therefore, the yield of 3A5AF is not shown in Fig. 1. Very little 3A5AF was produced in high-temperature water, whereas 3A5AF was one of the main products in organic solvents or ionic liquids with catalysts [19,20]. In these previous studies on the catalytic process in organic solvents or ionic liquids, two possible reaction pathways have been proposed for the formation of 3A5AF: (1) simultaneous removal of three water molecules from GlcNAc with subsequent ring closure and/or (2) the dehydration between H-5 and OH-6 of Chromogen III. However, in high-temperature water, pathway (1) will not proceed because the catalytic effect of high-temperature water molecules is not strong; therefore, the dehydration of GlcNAc progresses sequentially through Chromogen I and III. In addition, pathway (2) will not proceed because the dehydration of the ethanediol structure of H-5 and OH-6 in Chromogen III is difficult in high-temperature water at temperatures below 250 °C. It

has been reported that ethylene glycol, which has a structure similar to that of the ethanediol in Chromogen III, is stable in high-temperature water at temperatures below 250 °C without a catalyst [28]. Therefore, the degradation of Chromogen III via removal of the acetyl group may occur more easily than dehydration between H-5 and OH-6. As a result, although the yield of Chromogen III decreased at temperatures below 250 °C, the production of 3A5AF was not observed. These results reveal that the formation of 3A5AF is difficult in high-temperature water.



Scheme 1. (a) Reaction pathway of GlcNAc in high-temperature water and (b) reaction pathway for kinetic calculations.

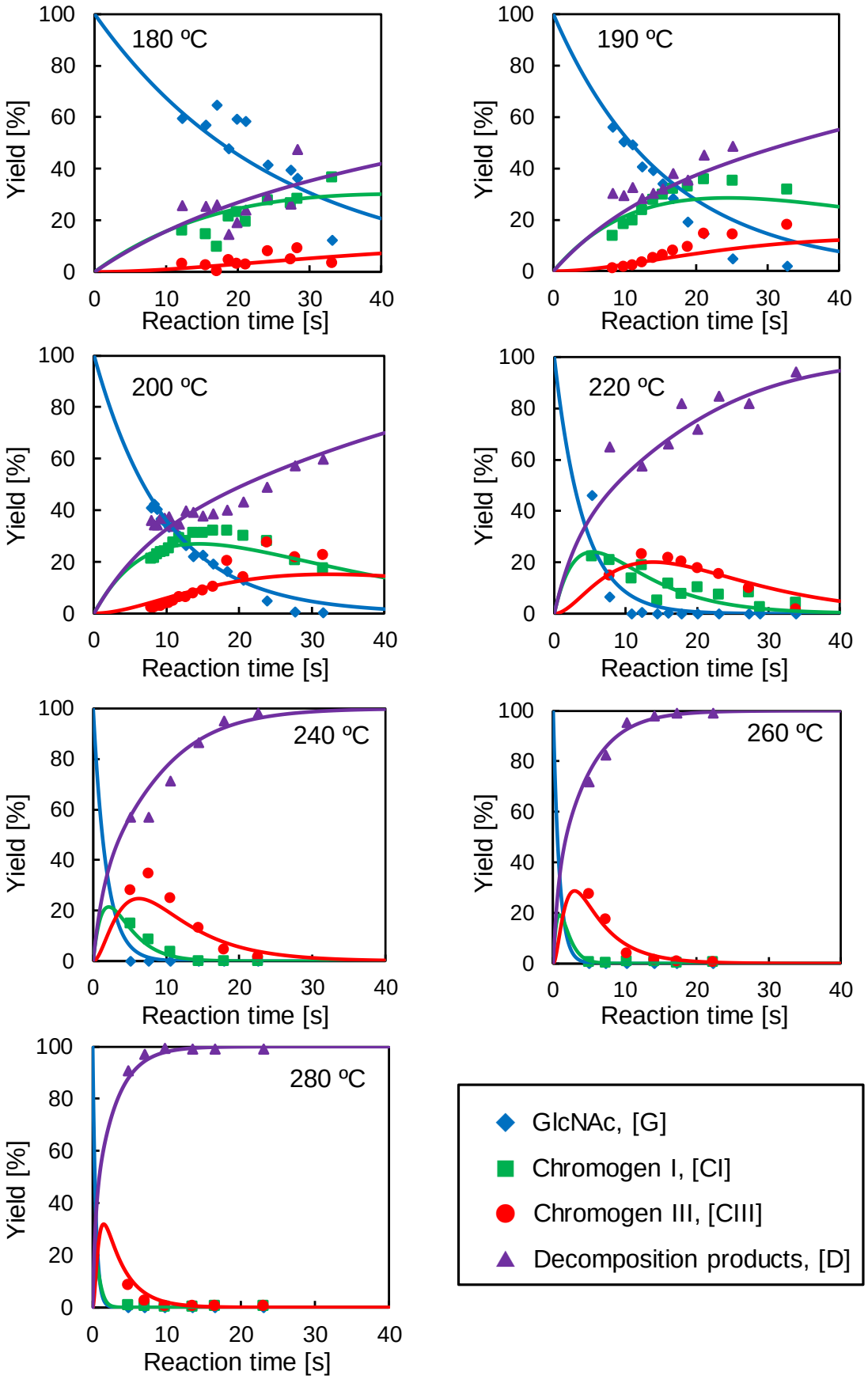

180 ºC
190 ºC
200 ºC
220 ºC
240 ºC
260 ºC
280 ºC
Yield [%]
Reaction time [s]
0
10
20
30
40
0
20
40
60
80
100
GlcNAc, [G]
Chromogen I, [CI]
Chromogen III, [CIII]
Decomposition products, [D]

Fig. 1. Comparison of experimental and calculated product yields for GlcNAc dehydration in high-temperature water.

Fig. 1 shows that the GlcNAc yield decreased with increasing reaction time at all the reaction temperatures. The yield of Chromogen I increased continuously with reaction time at 180 °C, but maxima were observed at 190 and 200 °C. The yield of Chromogen I decreased as it was dehydrated to Chromogen III, as observed at 220 and 240 °C. The maximum yields of Chromogen I at 180, 190, and 200 °C were 37.0%, 35.7%, and 32.1%, respectively. The yield of Chromogen III increased continuously with reaction time at 180 and 190 °C, but maxima were observed at 200, 220, and 240 °C. The yield of Chromogen III decreased as it was decomposed to other products. The maximum yields of Chromogen III at 200, 220, 240, and 260 °C was 27.5%, 23.1%, 34.5%, and 27.4%, respectively.

3.2 Kinetic analysis of GlcNAc dehydration in high-temperature water

We have previously reported a kinetic model for GlcNAc dehydration in the temperature range of 180–220 °C [26]. In this work, we redetermined the preexponential factor A and activation energy E_a of the reaction by fitting additional experimental data in the temperature range of 180–280 °C to obtain more accurate values of kinetic parameters. To simplify the kinetic model, we grouped GlcNAc and ManNAc as [G] and Chromogen I, 3,6-anhydro-GNF, and 3,6-anhydro-MNF as [CI] (Scheme 1b). In our previous study, we confirmed that the GlcNAc reaction obeys first-order kinetics by probing the effects of initial GlcNAc concentration on the reaction rate [26]. The kinetic parameters in eq. (2), A_n and E_{an}, were evaluated by

fitting the experimental results by nonlinear regression using Microsoft® Excel Solver [28, 29].

$$k_n = A_n \exp(E_{an}/RT) \quad (2)$$

The preexponential factor and activation energy values obtained in this study were slightly different from those in our previous report, as shown in Table 1 [26].

Table 1 Comparison of the kinetic parameters for GlcNAc dehydration in high-temperature water obtained in this work and in previous studies [26,31].

	This work		Previous work [26]		Previous work [31]	
n	A_n (s^{-1})	E_{an} (kJ mol^{-1})	A_n (s^{-1})	E_{an} (kJ mol^{-1})	A_n (s^{-1})	E_{an} (kJ mol^{-1})
1	$10^{7.95}$	83.6	$10^{8.17}$	85.7	–	–
2	$10^{10.8}$	110	$10^{10.2}$	105	–	–
3	$10^{4.38}$	51.2	$10^{6.74}$	73.5	–	–
4	$10^{8.29}$	86.9	$10^{9.28}$	95.6	–	–
Apparent rate of GlcNAc degradation						
k	$10^{11.7}$	115	–	–	$10^{12.5}$	126

Analysis of the residuals between the kinetic model and the experimental data gave standard deviations of 5.3%, 3.6%, 4.6%, and 7.7% for the yields of [G], [CI], [CIII], and [D], respectively. The calculated product yields given by the solid lines in Fig. 1 show that good agreement with the experimental data could be obtained.

Next, we applied the enthalpy–entropy compensation to the kinetic parameters in Table 1. The enthalpy–entropy compensation is known to be extra thermodynamic or empirical correlations [32]. Specifically, the compensation effect refers to the behavior of a series of closely related chemical reactions that feature kinetic parameters exhibiting a linear relationship. The enthalpy–entropy compensation phenomenon can be described as

$$\ln A = \alpha + E_a/R\beta, \quad (3)$$

where α is a constant, and β is a parameter called the isokinetic temperature, which gives the temperature at which the rate constants are identical for all concerned reactants. When E_a is varied, a related change in A is observed. Specifically, an increase in E_a tends to compensate for an increase in A, which is why this phenomenon is termed the compensation effect.

The preexponential factors A_n and activation energies E_{an} of the GlcNAc reaction obtained in this work (Table 1) are plotted in Fig. 2. We also calculated the apparent reaction rate constant, k, of GlcNAc degradation from the time profiles of GlcNAc disappearance (Table 1). The A and E_a values obtained for this apparent rate constant were slightly different from those determined previously [31]. A linear relationship between the A and E_a values of the apparent rate constant of monosaccharide degradation in high-temperature water has been reported [33], as shown by the solid line in Fig. 2. The monosaccharides are glucose, mannose, fructose, galactose, and sorbose, which have hydroxy groups.

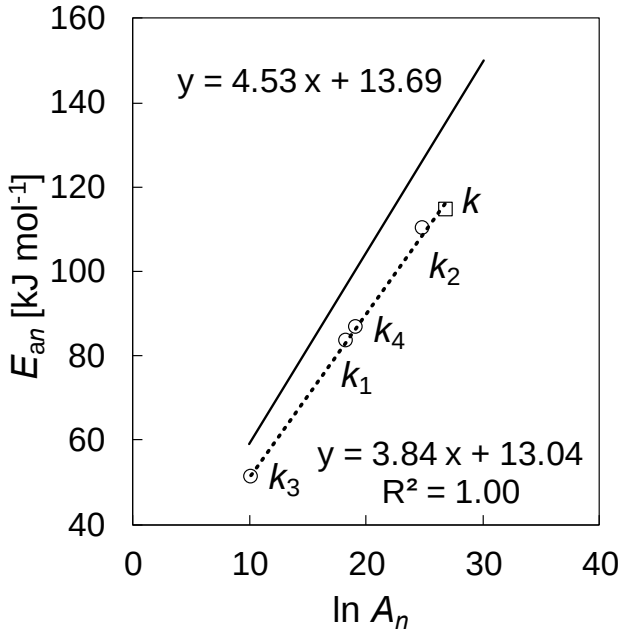


Fig. 2. Enthalpy–entropy compensation for GlcNAc dehydration and monosaccharide degradation in high-temperature water. The solid line shows the relationship reported for monosaccharide degradation reported in the literature [33].

Interestingly, k_1–k_4 and k show a linear relationship, and this is the first example where not only k but also the elementary rate constants k_1–k_4 for GlcNAc degradation show a linear relationship. Thus, the enthalpy–entropy compensation effect held for the reaction of GlcNAc in high-temperature water. In general, a linear relationship indicates that each step of the reaction of GlcNAc proceeds through essentially the same mechanism. Although the steps with rate constants k_1 and k_2 are dehydration reactions, the detailed reactions involved in steps with rate constants k_3, k_4, and k are not clear. The line obtained for GlcNAc is different from that of the previously reported monosaccharides, which is probably due to the presence of the acetoamide group in GlcNAc.

3.3 Effects of catalysts on the yields and selectivity of nitrogen-containing chemicals

Fig. 3 shows the effects of the acid and base catalysts on the yields of GlcNAc, Chromogen I, and Chromogen III at temperatures of 190 and 200 °C as a function of the reaction time. The yield of GlcNAc with the acid catalyst decreased slower than that without a catalyst, whereas that with the base catalyst decreased faster. For Chromogen I, a slight decrease was observed with the base catalyst and the yield showed a maximum without a catalyst. In addition, the yields of Chromogen I with the acid catalyst were less than 5%. For Chromogen III, the yields with the acid catalyst were lower than those with the base catalyst and the yields without a catalyst were higher. For both Chromogen I and Chromogen III, the maximum yields were obtained without a catalyst within the experimental conditions examined in this work.

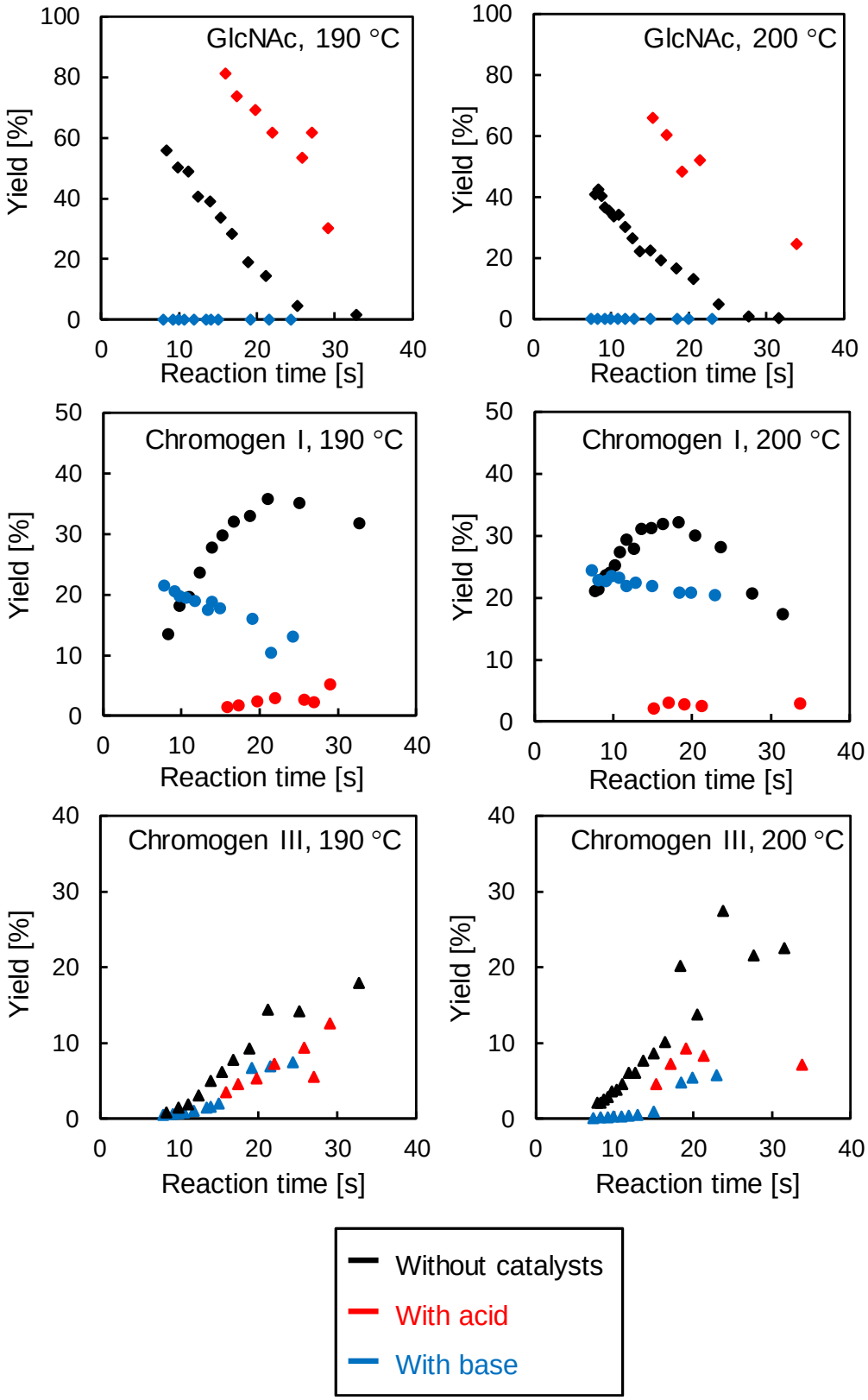
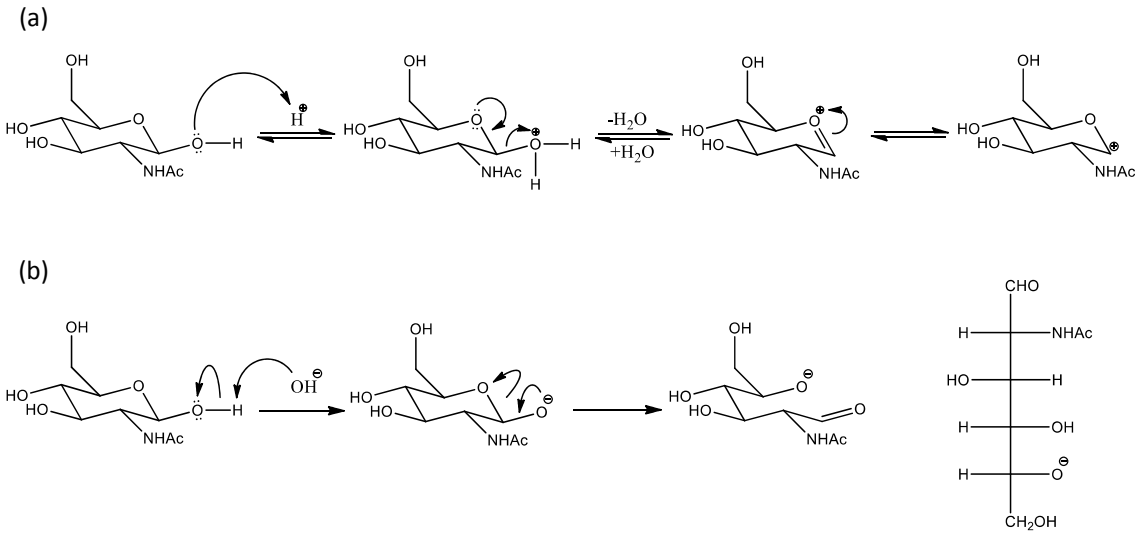


Fig. 3. Effect of acid and base catalysts on the yields of GlcNAc, Chromogen I, and Chromogen III in high-temperature water.

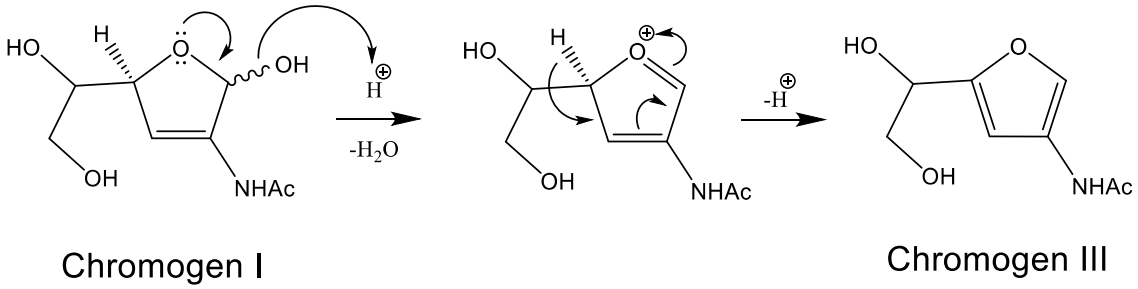
The selectivity for GlcNAc, Chromogen I, and Chromogen III was changed by the addition of catalysts. The data shown in Fig. 3 reveal that the dehydration of GlcNAc to Chromogen I was promoted by the base catalyst but suppressed by the acid catalyst. As shown in Scheme 1a, the dehydration of GlcNAc proceeded between H-2 and OH-3 after the ring opening reaction. However, the ring opening reaction is suppressed by the acid catalyst, as shown in Scheme 2a. In the presence of the acid catalyst, OH-1 gives an electron to H^+. Subsequently, H_2O is dissociated from C-1, and a lone pair on the oxygen in the pyranose ring moves to the bond between oxygen and C-1. Thus, a double bond is formed between the oxygen atom in the pyranose ring and C-1, and C-1 is cationized by electron movement from the double bond to oxygen. As a result, GlcNAc does not undergo ring opening and the dehydration of GlcNAc is suppressed by the acid catalyst.



Scheme 2. Effect of (a) acid and (b) base catalysts on the ring opening of GlcNAc in high-temperature water.

In contrast, the ring opening reaction of GlcNAc is promoted by the base catalyst, as shown in Scheme 2b. In the presence of the base catalyst, OH^- removes H^+ from OH-1, and the electron of O-1 moves to the oxygen in the pyranose ring. Then, the ring opening reaction occurs and O-5 is anionized. As a result, the dehydration between H-2 and OH-3 in the open ring proceeds easily. Therefore, the degradation rate of GlcNAc is greater in the presence of the base catalyst than in the presence of the acid catalyst. As a result, the formation rate of Chromogen I with the base catalyst is faster than that with the acid catalyst.

Although the yield of Chromogen I with the acid catalyst was low and remained almost constant, the yield of Chromogen III with the acid catalyst was almost the same as that with the base catalyst and without a catalyst. This behavior is probably due to the promotion of the dehydration of Chromogen I to Chromogen III by the acid catalyst, as shown in Scheme 3. The electron of the oxygen in the pentose ring moves to the bond between C-1 and OH-1, and OH-1 is removed by H^+. Subsequently, H-4 is eliminated as H^+, and the electron moves to the cationized oxygen in the pentose ring. As a result, Chromogen III is formed more easily in the presence of the acid catalyst. In contrast, the elimination of OH-1 is unlikely to occur with the base catalyst. Thus, the dehydration of Chromogen I to Chromogen III is suppressed in the presence of the base catalyst.



Chromogen I

Chromogen III

Scheme 3. Effect of the acid catalyst on the dehydration of Chromogen I to Chromogen III.

In summary, the acid catalyst suppresses the dehydration step from GlcNAc to Chromogen I and promotes the dehydration step from Chromogen I to Chromogen III. On the contrary, the base catalyst promotes the dehydration step from GlcNAc to Chromogen I and suppresses the dehydration step from Chromogen I to Chromogen III.

3.4 Steric effect on the yields of nitrogen-containing chemicals

To understand how the dehydration of GlcNAc via the opening of the pyranose rings (Scheme 1a) is influenced by steric factors, the reaction was studied using ManNAc, an epimer of GlcNAc, as a starting reactant. Fig. 4 shows a comparison of the product yields from ManNAc and GlcNAc as a function of the reaction time. When ManNAc was used as the starting reactant, the yield of ManNAc decreased with increasing reaction time and GlcNAc was obtained in approximately 10% yield. The yield of Chromogen I increased and then reached a maximum, whereas the yield of Chromogen III increased continuously with increasing reaction time. In contrast, when GlcNAc was used as a starting reactant, the yield of ManNAc was less than 5%. However, the sum of the yields of ManNAc and GlcNAc was similar with both starting reactants. Furthermore, the yields of Chromogen I and Chromogen III showed identical tendencies, irrespective of which starting reactant was used.

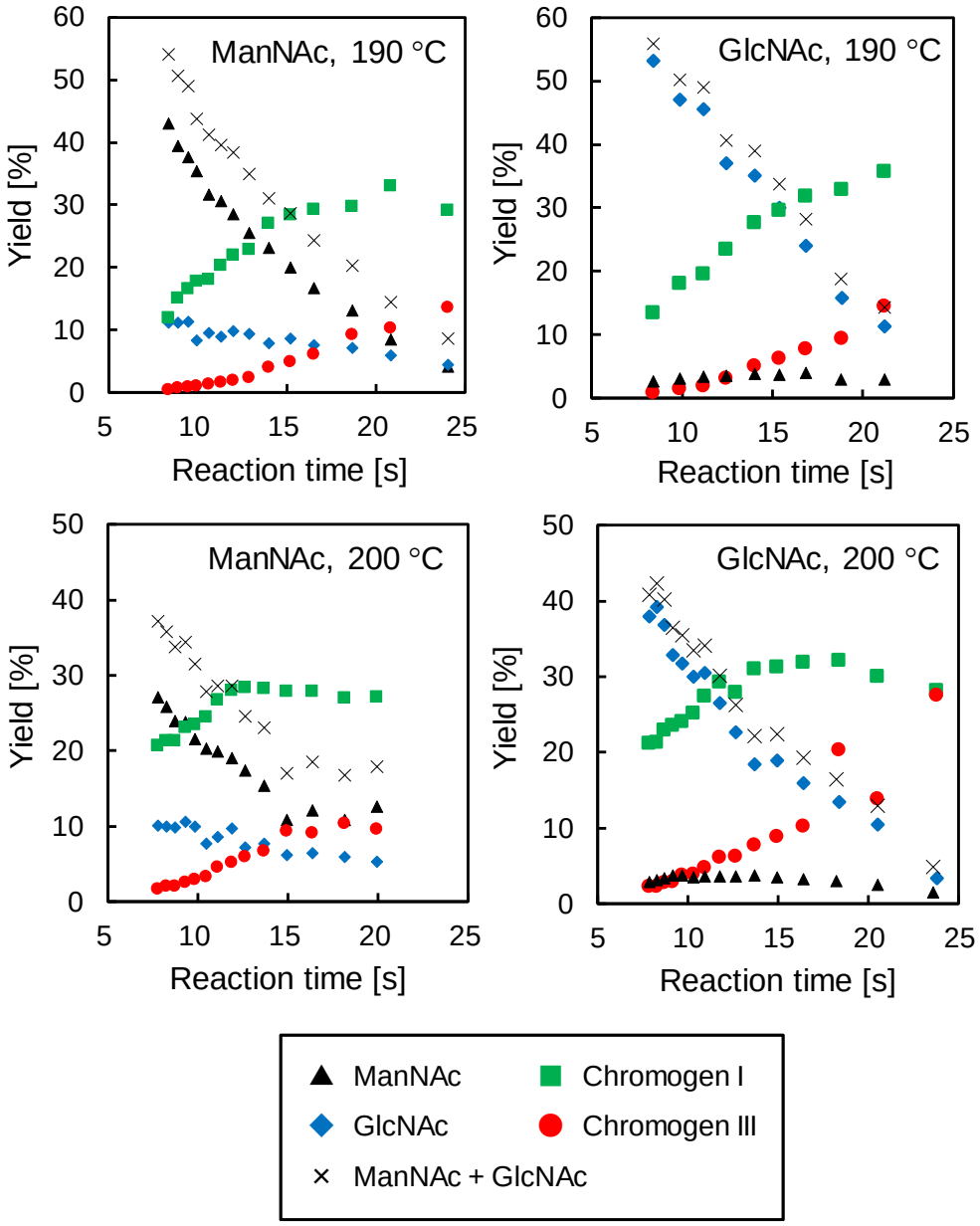


Fig. 4. Steric effects of ManNAc and GlcNAc dehydration in high-temperature water.

These results show that the steric effects on the dehydration of GlcNAc and ManNAc were not significant, indicating that the dehydration to Chromogen I proceeds through the opening of the pyranose rings of GlcNAc and ManNAc, as shown in Scheme 1a. The yield of GlcNAc from ManNAc as the starting reactant was higher than the yield of ManNAc from GlcNAc as the starting reactant because the GlcNAc

structure is more stable than the ManNAc structure.

4. Conclusions

We obtained updated and expanded results from a systematic study of the dehydration of GlcNAc in high-temperature water. The yield of 3A5AF was very low in high-temperature water (<1%). Although we expected to obtain 3A5AF in higher yields through the dehydration of Chromogen III, this process is likely difficult in the absence of a catalyst. The preexponential factor and activation energy values were redetermined using additional experimental data. We found, for the first time, that the elementary reactions of GlcNAc show a linear relationship between the preexponential factor and the activation energy. The enthalpy–entropy compensation held for each elementary reaction of GlcNAc in high-temperature water. The linear relationship of GlcNAc was different that of other monosaccharides containing only hydroxyl group, which is probably due to the presence of the acetoamide group in GlcNAc. The effect of addition of the acid and base catalysts on the dehydration of GlcNAc was revealed. The acid catalyst suppressed the dehydration from GlcNAc to Chromogen I and promoted the same from Chromogen I to Chromogen III. On the other hand, the base catalyst promoted the dehydration from GlcNAc to Chromogen I and suppressed the same from Chromogen I to Chromogen III. In addition, the steric effect on GlcNAc dehydration was studied by comparing the reaction using ManNAc as the reactant. The steric factor did not influence the yields of Chromogen I and III. We, therefore, successfully demonstrated that the noncatalytic conversion of GlcNAc in high-temperature water is an environmentally benign route to the nitrogen-containing chemicals.

Acknowledgments

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Competing interests:

The authors have no competing interests to declare.

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