

# Sustainable One-Pot Synthesis of 5-(Hydroxymethyl)furfural from C6-Sugars by Enhanced H<sup>+</sup> Exchange Heterogeneous Catalysis

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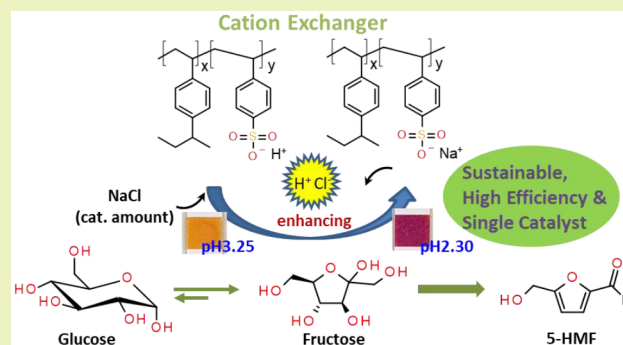
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**ABSTRACT:** This study focuses on the characterization of NaCl-induced enhancement of H<sup>+</sup> exchange catalysis and preparation of the renewable C6 platform chemical, 5-(hydroxymethyl)furfural (5-HMF), through dehydration of fructose and glucose, C6-sugars, utilizing a heterogeneous catalyst. The effect of a catalytic amount of NaCl was explored to enhance the H<sup>+</sup> exchange of cation exchangers, characterized on the distortion of tetrahedral sulfonates due to the formation of direct ionic bonds with Na<sup>+</sup>, as observed by FT-IR. Dehydration of high concentrations of C6-sugars (24%, w/v) was carried out as a one-pot multistep reaction to synthesize 5-HMF in DMSO/MIBK (0.35/0.65) at temperatures ranging from 110 to 120 °C under ambient pressure. Cation exchangers (hydrogen form) were employed as catalysts in amounts ranging from 2.5% to 10% (w/w). The addition of NaCl resulted in a decrease in the pH of both water and organic solvents, leading to improved H<sup>+</sup> exchange on cation exchangers. Consequently, this facilitated a reduction in catalyst quantity and significantly enhanced the dehydration of fructose and glucose to 5-HMF. At 110 °C, fructose achieved a 99% conversion rate with an 81% 5-HMF yield within 1 h, while at 120 °C, glucose conversion reached 92.2% with a 36.1% 5-HMF yield over 11 h. Furthermore, the catalyst exhibited consistent activity across at least five consecutive fructose dehydration batches. The NaCl-induced enhancement of H<sup>+</sup> exchange catalysis was first proposed and successfully demonstrated for the dehydration of C6-sugars in the organic phase. This concept can be extended to various organic synthesis reactions using cation exchangers in both aqueous and organic systems, with the aim of reducing the catalyst amount and facilitating the reaction rate.

**KEYWORDS:** 5-(hydroxymethyl)furfural, dehydration of glucose and fructose, one-pot multistep heterogeneous catalysis, cation exchange catalysis, NaCl-induced enhancement of H<sup>+</sup> exchange catalysis, characterization of H<sup>+</sup> exchange catalysis



## INTRODUCTION

Fossil-derived resources are currently the main feedstock of carbon building blocks for fuels, chemicals, and polymers. The sustainable production of these materials from biobased renewable resources using environmentally friendly routes has encouraged academia and industry to focus on more biobased alternatives with green processes.<sup>1–4</sup> 5-(Hydroxymethyl)furfural (5-HMF) is a widely studied bioplatform chemical owing to its versatile chemical reactivity and functionality.<sup>2–4</sup> Various valuable chemicals, such as dimethylfuran (DMF), alkyl levulinate, levulinic acid, 2,5-furandicarboxylic acid (FDCA), 5-(hydroxymethyl)furan-2-carboxylic acid (HMFCA), 2,5-diformylfuran (DFF), 2,5-bis(hydroxymethylfuran), 5-hydroxy-4-keto-2-pentenoic acid,  $\gamma$ -valerolactone, 1,6-hexanediol, and adipic acid, can be derived through oxidation, reduction, esterification, and hydrogenation of HMF. These compounds are important building blocks for the polymer industry.<sup>3–9</sup>

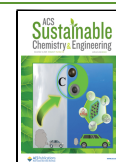
Currently, the production of 5-HMF on an industrial scale is limited, with the majority of HMF being marketed and utilized as a specialty chemical for research and laboratory purposes.<sup>10–12</sup> Most of the studies on 5-HMF preparation are focused on finding new synthesis procedures or efficient catalytic systems, and only limited studies have focused on the development of large-scale synthesis and purification of HMF.<sup>10</sup> Several studies on the production of 5-HMF using various homogeneous and heterogeneous acid catalysts in different solvent systems have been reported.<sup>4,11–14</sup> The reactions conducted using HCl or H<sub>2</sub>SO<sub>4</sub> as catalyst with 0.5–10 wt % substrates in various solvent systems under

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pressure and in a temperature range of 120–200 °C mostly resulted in moderate fructose conversion and HMF yields ranging from 40% to 90%.<sup>13,14</sup> Purification of 5-HMF from dilute product streams is also challenging in large scale due to its instability at high temperature for distillation, solubility in both water and organic solvents for liquid–liquid extraction, containing black humins.<sup>10</sup> We have recently reported a high yield of 5-HMF (89%) from a high concentration (30 wt %) of fructose by acid catalysis at 180 °C in a water-dimethyl carbonate two-phase system.<sup>3</sup> Drawbacks associated with the use of mineral acids (HCl or H<sub>2</sub>SO<sub>4</sub>) as catalysts, such as equipment and human tissue corrosion, and difficulty in recovery and recyclability of catalysts, have prompted the development and use of heterogeneous acid catalysts.<sup>15,16</sup>

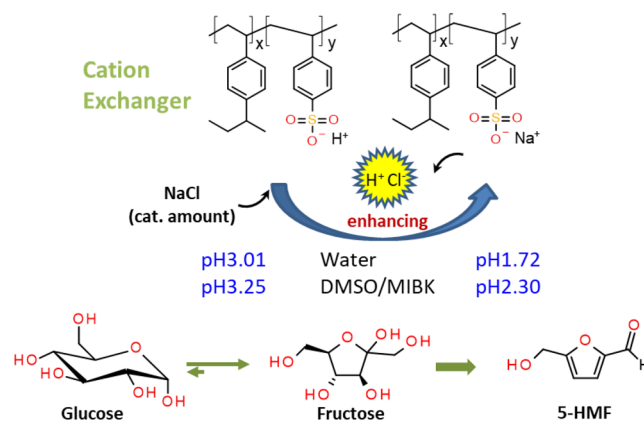
Generally, cation-exchange resins, such as DR-2030 and Amberlyst 15, are commonly used as commercially available heterogeneous catalysts in various chemical reactions, including dehydration, esterification, and hydrolysis, and are also employed for the dehydration of fructose to 5-HMF.<sup>12,16</sup> The catalytic dehydration of high-concentration fructose (300 g/L) to 5-HMF has been demonstrated using the acidic ion exchanger DR-2030 in DMSO at 110 °C in batch and continuous modes.<sup>12</sup> Amberlyst 15 was also used for fructose dehydration to 5-HMF in water/acetone, yielding 78% yield at 120 °C.<sup>17</sup> However, the processes have certain drawbacks, such as the requirement for a high catalyst-to-substrate ratio (0.1–1.0 equiv, w/w), low substrate concentration (mostly 1–10%), longer reaction time, and need for high temperature under pressured conditions.

Glucose is preferred over fructose due to its higher abundance and lower cost. However, the dehydration of glucose is more challenging, necessitating the integration of glucose isomerization to fructose and subsequent fructose dehydration, which mandates the presence of both Brønsted and Lewis acid sites.<sup>18</sup> Consequently, dual catalytic systems, such as H-ZSM-5 zeolite<sup>18</sup> and Cu–Cr/ZSM-5 zeolite,<sup>19</sup> have been utilized. Nonetheless, these methods demand low glucose concentrations and high catalyst ratios to achieve a substantial 5-HMF yield from glucose.

In general, commercial ion-exchange resins, such as DR-2030 and Amberlyst 15, are advised to be employed at temperatures below 120–130 °C for long-term reactions. This is due to the risk of thermal inactivation and decomposition of the polymer matrix, which hampers their reusability.<sup>12,21</sup> For these reasons, cation exchange has not been effectively employed in glucose dehydration. For instance, a recent report highlighted that the cation exchanger DIAION RCP160 M (used at a ratio three times that of glucose) catalyzed the dehydration of glucose (at a concentration of 1%) to 5-HMF, yielding only 7% of 5-HMF in a biphasic system.<sup>20</sup> Consequently, reaction and process designs should consider these limitations, especially for high substrate concentrations that generally require longer reaction times and higher temperatures.

In this study, a facile green synthetic approach was developed to produce 5-HMF from biomass-derived C6-sugars (glucose and fructose). This was achieved through NaCl-induced enhancement of H<sup>+</sup> exchange catalysis by using a cation exchanger in an organic solvent (Scheme 1). The NaCl-induced enhancement of H<sup>+</sup> exchange catalysis was first proposed and evaluated based on the pH changes and FT-IR characteristics of the sulfonate groups on the cation exchanger. The catalytic performance of the heterogeneous catalysts was

**Scheme 1. One-Pot Synthesis of 5-HMF from Glucose and Fructose by Enhanced H<sup>+</sup> Exchange Catalysis Using Cation Exchanger**



significantly enhanced, facilitating the reaction, reducing the required catalyst amount, and enabling the use of ambient pressure for the dehydration of both fructose and glucose to 5-HMF.

## EXPERIMENTAL SECTION

**Materials.** 5-HMF (99% purity), (D)-fructose (99% purity), dimethyl sulfoxide, methyl isobutyl ketone (MIBK), Amberlite IR120, Dowex DR-2030, and Amberlyst 15 were procured from Sigma-Aldrich. Amberlyst 15 hydrogen form, a strong cation ion-exchange resin, is a macroporous styrene–divinylbenzene resin functionalized with sulfonic acid groups, acid sites with concentration  $\geq 4.7$  eq/kg, and a surface area of 53 m<sup>2</sup>/g. The upper temperature limit for safe operation of Amberlyst 15 is 120 °C. All chemicals were used without further treatment.

**Dehydration of Fructose to 5-HMF Using an Ion-Exchange Resin.** A solvent or solvent mixture at a certain ratio was prepared with a volume of 20 mL. In a 4 mL glass vial, 300 mg of fructose and 1 mL of solvent were placed, and then the ion-exchange resin Amberlyst 15, Amberlite IR120, or Dowex DR-2030 was added. The solution was heated and shaken at 110 °C using a thermomixer (HTMR 131; HLC BioTech, Germany). The catalyst-to-fructose ratio was varied between 0.025 and 0.2 (w/w), and the effect of salt (NaCl) on dehydration of 300 mg fructose in 1 mL solvent at 110 °C was also investigated. Effects of salt (NaCl) on Amberlyst 15 catalysis for fructose dehydration and on the pH changes of deionized water and DMSO/MIBK (1/1) without fructose were investigated.

To verify the reaction conditions in a larger volume, 60 g of fructose in 200 mL of a solvent mixture was placed in a 500 mL flask (final volume of 240 mL). Then, 3 g of ion-exchange resin (0.05 (w/w) equivalent to fructose) and 2 g of NaCl were added to the mixture. The mixture was shaken in an oil bath at 110 °C. Samples (50  $\mu$ L each) were collected at different time intervals and analyzed for the concentrations of fructose and products.

**Dehydration of Glucose to 5-HMF Using an Ion-Exchange Resin.** In a 4 mL glass vial, 200–400 mg of glucose and a mixture of 1 mL of MIBK and 1 mL of DMSO were placed. Subsequently, the ion-exchange resin Amberlyst 15 (ranging from 0 to 40 mg) and NaCl (ranging from 0 to 40 mg) were added. The solution was then heated and shaken at temperatures between 110 and 130 °C using a thermomixer (HTMR 131; HLC BioTech, Germany). The ratios of catalyst-to-glucose and NaCl-to-glucose were varied between 0.05 and 0.2 (w/w) under different conditions of temperature and substrate concentration.

**Regeneration and Recycling of the Ion-Exchange Resin in Dehydration of Fructose and Glucose.** For fructose dehydration, in a 4 mL glass vial, 300 mg of fructose, 1 mL of a mixture of DMSO and MIBK (0.5/0.5), 15 mg of resin, and 10 mg of NaCl were placed,

heated, and shaken at 110 °C and 600 rpm in a thermomixer. After 1 h of reaction, the resin was separated, washed with 0.3 mL of DMSO, regenerated in 0.3 mL of 1 N HCl for 1 h, washed with deionized water until a neutral pH was reached, and then washed with DMSO. The resin was recycled for four consecutive runs under identical conditions. Samples (50  $\mu$ L each) were collected at 1, 2, and 3 h of reaction and analyzed for concentrations of fructose and products.

For glucose dehydration, in a 4 mL glass vial, 400 mg of glucose, 2 mL of a mixture of DMSO and MIBK (0.5/0.5), 40 mg of resin, and 40 mg of NaCl were placed, heated, and shaken at 120 °C and 600 rpm in a thermomixer. After 11 h of reaction, the resin was separated, washed, and regenerated as the same method with the above fructose reaction. The resin was recycled for four consecutive runs under identical conditions. Samples (50  $\mu$ L each) were collected at 11 h of reaction and analyzed for concentrations of glucose and products.

**Purification of the Prepared 5-HMF.** The final product solution obtained from 60 g of fructose in 200 mL of a solvent mixture of DMSO and MIBK (0.35/0.65, v/v) was used to evaluate the purification process and to prepare samples for further experiments. The solution was concentrated to remove MIBK at 70 °C under reduced pressure, followed by the evaporation of DMSO at 100 °C under reduced pressure. After adding 200 mL of a saturated NaHCO<sub>3</sub> and NaCl aqueous solution, the resulting solution was decanted into a 500 mL separation funnel for liquid–liquid extraction, which was performed using 50 mL of ethyl acetate. This liquid–liquid extraction was repeated four more times, after which all collected organic phases were pooled. The crude dark solution was dried using anhydrous Na<sub>2</sub>SO<sub>4</sub> and treated with 30 g of activated carbon at 50 °C to remove colored materials. The resulting solution was treated with 15 g of silica, filtered, and concentrated by simple evaporation. Finally, 32.6 g of partially purified 5-HMF (deep purple color, 96% purity by <sup>1</sup>H NMR) was obtained in 81% reaction yield (mol/mol) and 92% recovery yield (mol/mol). The recovered solvents MIBK, DMSO, and ethyl acetate were reused in the next runs of the reaction and purification. The isolated 5-HMF was confirmed by H<sup>1</sup>-NMR (DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub>) using a 400 MHz NMR (Bruker, UltraShield Plus 400, Germany).

**Analytical Procedures.** Quantitative analysis of 5-HMF was performed using gas chromatography–mass spectrometry (GC–MS, 431-GC and 210-MS, Varian, U.S.A.) equipped with a FactorFour Capillary column, VF-1 ms (Varian, 15 M  $\times$  0.25 mm). The initial column oven temperature was increased from 50 to 250 °C at a rate of 20 °C/min. The samples, diluted with acetonitrile to a sample concentration of 0.1–0.5 mg/mL, were injected in split injection mode of 10% at 275 °C. The conversion and concentration of the substrates and the ratios of the products formed were calculated from the calibration curves of the standard materials on the chromatograms.

The concentrations of fructose and glucose were determined using an HPLC system (JASCO, Tokyo, Japan) equipped with an Aminex HPX-87H chromatographic column connected to a guard column (Bio-Rad, Richmond, CA, U.S.A.), an RI detector (ERC, Kawaguchi, Japan), a JASCO UV detector operating at 215 nm, and a JASCO intelligent autosampler. The column temperature was maintained at 65 °C in a chromatography oven (Shimadzu, Tokyo, Japan). The samples were diluted with a 0.5 mM H<sub>2</sub>SO<sub>4</sub> sulfuric acid solution and then filtered. A 40  $\mu$ L aliquot was injected in 0.5 mM H<sub>2</sub>SO<sub>4</sub> mobile phase flowing at a rate of 1.0 mL min<sup>-1</sup>. The peaks of different compounds were confirmed and quantified by using external standards.

The conversion of the substrates and the concentrations of the products formed were calculated from the standard curves of the GC and HPLC chromatograms. The calculated reaction parameters were the percent substrate conversion (mol/mol) and the percent product yield (mol/mol). The isolated product yields were calculated according to the molar ratio of the isolated products to the substrates used for the representative reactions. All data were obtained from two independent experiments and are presented as the average of replicates  $\pm$  the standard deviation.

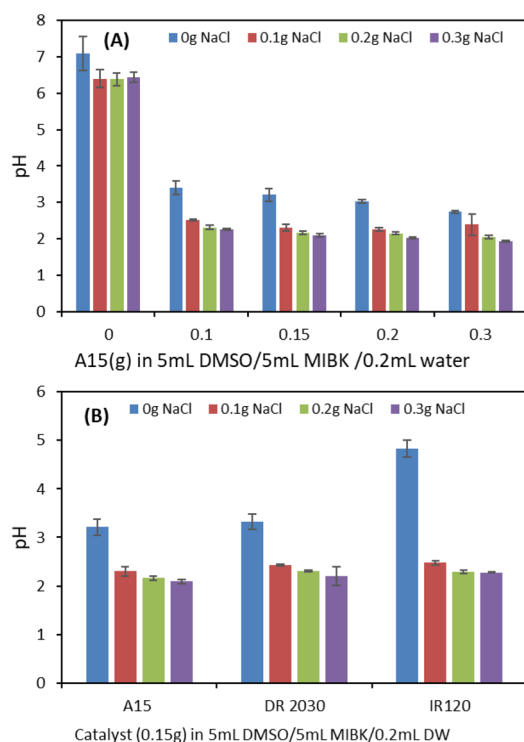
Amberlyst 15 samples treated under various conditions were characterized for their sulfonate groups through FT-IR analysis. The spectra of the samples were obtained in the region of 600–4000 cm<sup>-1</sup> using a Nicolet-iS5 instrument (Thermo Scientific, U.S.A.). An air background spectrum was collected before analysis of each sample, and it was subtracted from the spectrum of each corresponding sample. The samples were prepared by mixing 40 mg of Amberlyst 15 with 1 mL of deionized water, 1 mL of MIBK, and 1 mL of MIBK/deionized water (with water contents of 2% and 6%), both with and without NaCl (40 mg). Subsequently, the resulting samples were dried at 120 °C for 2 h prior to analysis.

## RESULTS AND DISCUSSION

**Enhancement and Characterization of Catalytic Performance of Acidic Ion Exchangers by Exchange of Na<sup>+</sup> and H<sup>+</sup>.** For building a sustainable and efficient synthetic process for 5-HMF from C6 sugars requires consideration of energy efficiency, waste amount, and reaction conditions including types and amounts of solvent and catalyst. The dehydration of fructose and glucose to 5-HMF is generally accompanied by many side reactions, generating humins and organic acids. Moreover, the dehydration can be divided into pathways involving cyclic or acyclic intermediates.<sup>12,22</sup> Environmentally friendly heterogeneous catalysts with adequate separation efficiency are preferred over homogeneous catalysts. Therefore, new or known heterogeneous catalysts based on zeolites, ion-exchange resins, functional silica, and surface-functionalized carbon materials have been continuously used for dehydration of C6 sugars to 5-HMF. However, high catalyst-to-substrate ratios or low substrate concentration were required to obtain high substrate conversion and product yield.

In this study, to enhance the catalytic performance of acidic ion exchangers, the effects of salts at a minimal (catalyst) amount (0–3% (w/v)) in water and the mixture of DMSO/MIBK (5/5, v/v) were investigated for the dehydration of fructose and glucose under similar conditions (Figure 1). The pH changes in deionized water and the mixture of MIBK, DMSO, and water, with and without the presence of a catalyst, Amberlyst 15, were measured before and after the addition of an inorganic salt, NaCl (Figure 1).

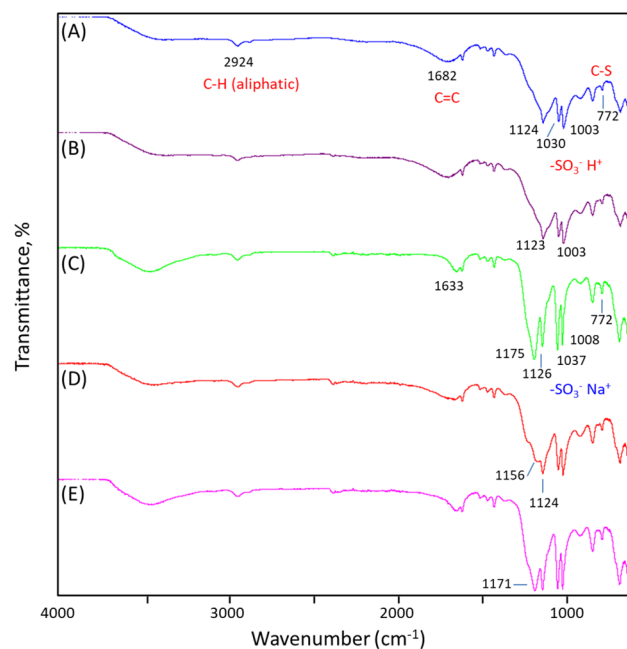
The presence of Amberlyst 15 decreased the pH of the solutions from neutral to 3.5, and the addition of 1 wt % NaCl accelerated the reduction in pH from 3.5 to 1.5 in aqueous solution (Figure S1A) and to 2.3 in DMSO/MIBK/water (Figure 1A). This difference was expected because NaCl is poorly soluble in various solvents. Increasing the amount of Amberlyst 15 caused a slight change in the pH of the solution; however, this was not significant. In aqueous solution, acid ion exchanger Amberlyst 15 (hydrogen form, dry) decreased pH from neutral to approximately 3.2, which was further decreased to 1.7 by adding catalytic amount (1%) of NaCl (Figure S1), whereas under the same conditions, the pH of the DMSO/MIBK solution was decreased only to 2.3 (Figure 1A). In addition, various inorganic salts, such as NaCl, CaCl<sub>2</sub>, KCl, and FeCl<sub>3</sub> were compared in a mixture of DMSO and MIBK (Figure S1B). Although there were slight differences between the different salts, the strongest pH reduction (to approximately pH 1) occurred with the addition of Fe<sup>3+</sup>, followed by the addition of Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup>. This is because the cation exchangeability of different cation metals is different. In particular, Fe<sup>3+</sup> can react with the Amberlyst 15 (H) to form a complex that releases H<sup>+</sup>; the pH in this case decreased rapidly. Furthermore, Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup> in DMSO/MIBK behave differently in terms of ion mobility; that is, Na<sup>+</sup> is more mobile



**Figure 1.** Effects of inorganic salts and acid ion exchangers on the pH change of water and the mixture of DMSO and MIBK (5/5). Changes in the pH of (A) DMSO/MIBK/water (5 mL/5 mL/0.2 mL (2%)) using Amberlyst A15 and 0, 0.1, 0.2, and 0.3 g of NaCl, (B) DMSO/MIBK/water (5 mL/5 mL/0.2 mL (2%)) using Amberlyst A15, Dowex DR-2030, and Amberlite IR120, and 0, 0.1, 0.2, and 0.3 g of NaCl, respectively.

than  $K^+$  and  $Ca^{2+}$ , which are restricted by their larger ionic radii and lattice energies, respectively (Figure S1). Considering the availability, environmental factors, and similar reaction profiles from the use of these salts, we chose NaCl as the pH-decreasing accelerator for further upscaling trials. The same salt effects were also observed using other cation exchangers, such as Dowex DR-2030 ( $H^+$ ) and Amberlite IR120 ( $H^+$ ; Figure 1B).

The cation exchanger, including Amberlyst 15, comprises a copolymer of styrene as a cross-linking agent with a sulfonate functional group.<sup>23</sup> Amberlyst 15 was treated by the addition of NaCl in both water and an organic solvent and subsequently dried at 120 °C for 2 h. The chemical structural characteristics of the dried Amberlyst 15 samples were confirmed and compared in terms of functional groups using FT-IR spectroscopy (Figure 2). The distinctive bands corresponding to the aromatic  $C=C$  stretching and aliphatic  $C-H$  vibrations were observed at 1682 and 2924  $cm^{-1}$ , respectively. The stretching vibrations of the sulfonate group in its  $H^+$  form (dry), without NaCl treatment, were evidenced by peaks at 1124 (broad), 1030, and 1003  $cm^{-1}$ . Additionally, the  $C-S$  vibration was identified at 772  $cm^{-1}$  (Figure 2A). Upon treatment in water without NaCl, the FT-IR characteristics of dried Amberlyst 15 remained identical to those of the original dried sample (Figure 2A,B). In contrast, dried Amberlyst 15 subjected to treatment in water containing NaCl exhibited changes in the stretching vibrations of the sulfonate group, as evidenced by peaks at 1124 and 1175  $cm^{-1}$ , implying that the tetrahedrons of sulfonate are substantially distorted due to the



**Figure 2.** FT-IR spectra of (A) Amberlyst A15 ( $H^+$  form), (B) Amberlyst A15 after treatment in deionized water, (C) Amberlyst A15 after treatment with NaCl in deionized water, (D) Amberlyst A15 after treatment with NaCl in MIBK/deionized water (99.8/0.2, 2%), and (E) Amberlyst A15 after treatment with NaCl in MIBK/deionized water (99.4/0.6, 6%). All samples were dried at 120 °C for 2 h before analysis.

formation of direct ionic bonds with  $Na^+$  (Figure 2C). This alteration closely resembled the characteristics of the sulfonate group in its  $Na^+$  form (dry).<sup>23</sup> For the dried Amberlyst 15 after treatment in the organic solvent (MIBK), with a minimal amount of water and NaCl, the intensity of stretching vibrations of the sulfonate group at 1175  $cm^{-1}$  significantly increased with increasing amount of water (1%, 3%), as shown in Figure 2D,E. This observation indicates that the exchange of  $Na^+$  and  $H^+$  in the catalytic system resulted in the formation of the free  $H^+$  form, which is capable of serving as an acidic catalyst. This phenomenon was enhanced in the presence of minimal water amount. In contrast, the spectra of dried Amberlyst 15 after treatment in MIBK without water or NaCl were identical, showing no changes in the characteristic stretching vibrations of the sulfonate group at 1124 (broad), 1030, and 1003  $cm^{-1}$  (Figure S2).

The aforementioned observations regarding the alteration of pH and FT-IR characteristics upon the introduction of NaCl suggest that even a small quantity of salt facilitates the exchange of cations, consequently releasing free  $H^+$  from the ion exchanger (Scheme 1). Consequently, the reduction of the solvent system's pH can potentially intensify the dehydration process of fructose and glucose, which occurs via acid catalysis. Moreover, the dehydration of glucose and fructose into 5-HMF results in the liberation of three water molecules. These molecules may play a role in the exchange of  $Na^+$  and  $H^+$  using the catalytic system.

In comparison to the aforementioned observations, earlier investigations have demonstrated that the dehydration of C6-sugars using a modified acid zeolite and Nb-MMT catalyst exhibited enhancements in a biphasic solvent system composed of a high concentration of NaCl aqueous solution

Table 1. Fructose Dehydration to 5-HMF Using Heterogeneous Catalysts<sup>a</sup>

run	fructose conc. <sup>b</sup> (wt %)	catalyst	catalyst ratio <sup>c</sup> (wt %)	solvent system	time (min)	temp (°C)	fructose conversion (%)	5-HMF yield (%)	year (refs)
1	10	TPA/ZSM-5 (20:10)	10	DMSO	120	140		80.7	2022 (22)
2	2.5	SCS	40	DMSO	5	70 (MW)	97.8	89.2	2022 (28)
3	10	LDMCC	10	DMSO	120	180		96	2022 (29)
4	5	Pt-WO <sub>3</sub> /TiO <sub>2</sub>	continuous	H <sub>2</sub> O	gas phase	350	100	21	2022 (30)
5	18	TiO <sub>2</sub> -imi-PW12	1	H <sub>2</sub> O	180	165	83	43	2022 (31)
6	10	IL-zeolite ZSM-5	10	[BMIm][Cl]	90	110	95	67.2	2021 (32)
7	2	H-USY zeolites	100	H <sub>2</sub> O/MIBK (1/10)	300	120		65	2019 (33)
8	30	DR-2030	20	DMSO	120	110	99.7	82.2	2019 (34)
9	10	Purolite CT275DR	10	DMC/TEAB	180	110		75	2022 (15)
10	9	Lewatit K2420	22	H <sub>2</sub> O/HFIP (12.6/87.4)	137	105	98	71	2018 (35)
11	2.7	Amberlyst 70	continuous	H <sub>2</sub> O/dioxane/MIBK	1.6 (RT)	120	90	84	2023 (36)
12	10	Amberlyst 70	80	H <sub>2</sub> O	20	180 (MW)		45.6	2017 (37)
13	1	Amberlyst 15	62.5	H <sub>2</sub> O/acetone (2/8)	120	120	79.6	78	2019 (17)
14	9	Amberlyst 15	22	H <sub>2</sub> O/HFIP (12.6/87.4)	180	105	98	70	2018 (35)
15	24	Amberlyst 15/NaCl	5/5	DMSO/MIBK (3.5/6.5)	60	110	99	81	this study
16	24	Dowex DR2030/NaCl	5/5	DMSO/MIBK (3.5/6.5)	60	110	99	81.5	this study

<sup>a</sup>SCS: Acid-functionalized spherical carbon superstructure. LDMCC: Lignin-derived mesoporous carbon solid acid catalyst. IL-zeolite ZSM-5: Dicationic ion liquid-assisted zeolite ZSM-5. RT: Residence time in packed column. MW: Microwave assisted. DMSO: Dimethyl sulfoxide. MIBK: Methyl isobutyl ketone. DMC: Dimethyl carbonate. TEAB: Tetraethylammonium bromide. HFIP: Hexafluoroisopropanol. <sup>b</sup>Fructose concentration in reaction media (organic and aqueous solution). <sup>c</sup>Catalyst ratio to substrate.

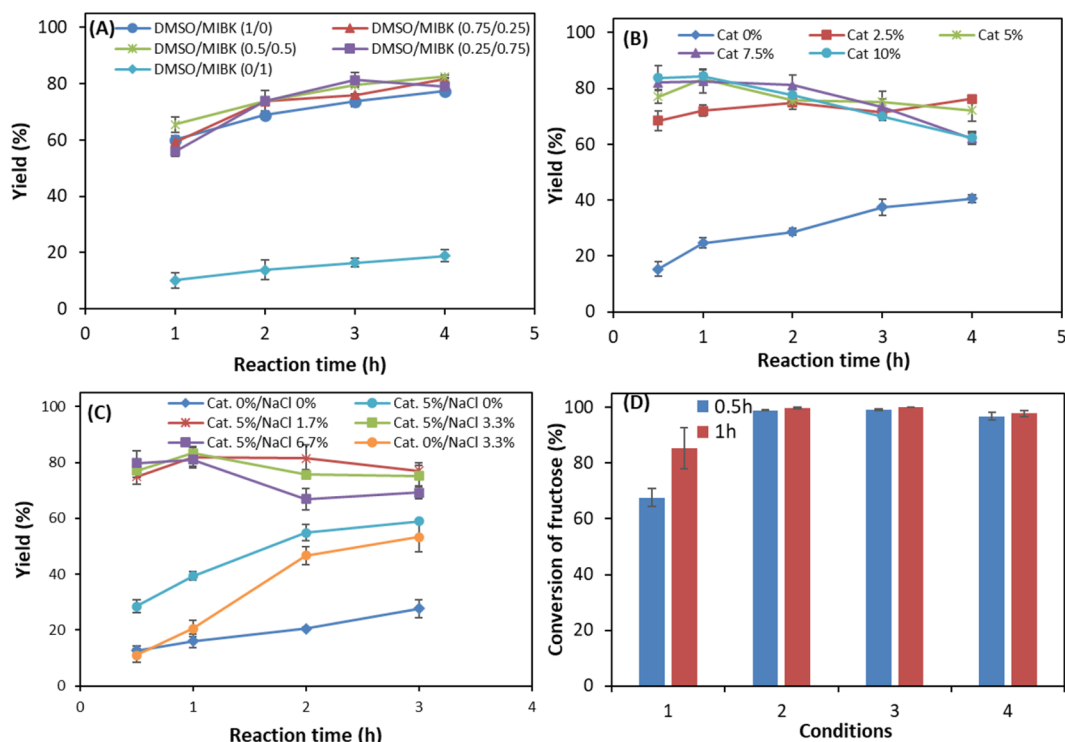
(e.g., 20%) and an organic solvent (MIBK), operating at temperatures of 180 and 170 °C, respectively.<sup>18–20,24</sup> This enhancement was attributed to the salting-out effect of Cl<sup>−</sup> in the solution, which led to a partitioning of the reaction to the organic phase and subsequently improved the reaction rate toward 5-HMF formation.<sup>24,25</sup> Consequently, the approach taken in those studies involved separating the resulting product through a salting-out process from the biphasic solvent system rather than employing NaCl as a catalyst enhancer.

**Dehydration of High-Concentration Fructose by Cation Exchangers.** Although water is preferable as solvent to minimize the environmental impact, it is inefficient for fructose dehydration because 5-HMF is easily rehydrated into levulinic acid, formic acid, and other byproducts in acidic aqueous solutions, resulting in a low product yield.<sup>17</sup> Different solvent systems were employed for the dehydration of fructose to 5-HMF. DMSO exhibits good solubility of fructose, provides high 5-HMF yields, and even good stability without high vapor pressure has been reported during the reaction at high temperatures.<sup>12</sup> However, DMSO and 5-HMF have high boiling points, which makes product recovery from the system by distillation significantly challenging owing to the formation of humins and other byproducts.<sup>17,26,27</sup> To overcome these problems, various mono- and biphasic solvent systems using lower boiling solvents, such as water, acetone, hexafluoroisopropanol (HFIP), and THF have been employed. However, the dehydration requires relatively high temperatures (above

the boiling point of the solvent used) and pressures (usually 0.3–2 MPa), as well as long reaction times (several hours, even days), which are energy intensive (runs 4, 5, 7, 9, and 14 in Table 1). In addition, in previous reports, the concentration of fructose ranged mostly between 1 and 10 wt % (Table 1).

Therefore, the process with high substrate concentration and high product yield in a recoverable and recyclable solvent system can be one of the approaches to reduce solvent usage, energy consumption, reactor/reaction volume, and operating cost. Hence, a highly efficient and sustainable process design for the recovery of 5-HMF that results in a high volumetric productivity, product yield, and concentration is of significant interest.

Based on the above results, Dowex DR-2030 was used as the heterogeneous acid catalyst and NaCl as the catalytic enhancer for the dehydration of fructose to 5-HMF in a mixture of DMSO and MIBK. Figure 3 shows the dehydration of fructose (300 mg) in a mixture (1 mL) of DMSO and MIBK using Dowex DR-2030 as the catalyst at 110 °C. The dehydration was performed at a high fructose concentration (24% w/w) in a solvent system at ambient pressure. Using 10% catalyst amount without salt in different ratios of DMSO and MIBK, the reaction resulted in approximately 80% yield of 5-HMF in 3 to 4 h (Figure 3A) as in a previous report.<sup>30</sup> Meanwhile, using an even lower catalyst amount (5%) with salt, the reaction significantly progressed and was completed within 1 h (Figure 3B). The increase in the amount of NaCl (from 1.7 to



**Figure 3.** Dehydration of fructose (300 mg) in a mixture (1 mL) of DMSO and MIBK using Dowex DR-2030 as a catalyst at 110 °C. (A) Effect of solvent at the ratio of DMSO and MIBK by Dowex DR-2030 at 10% (w/w) ratio to fructose. (B) Effect of catalyst amount at 0, 2.5, 5, 7.5, and 10% (w/w) with 3.3% NaCl (w/w) ratio to fructose. (C) Effect of NaCl amount at 0, 1.7, 3.3, and 6.7% (w/w) to fructose with 0 or 5% catalyst. (D) Conversion of fructose; Condition 1: DMSO/MIBK (0.5/0.5), 5% DR-2030, without NaCl; Condition 2: DMSO/MIBK (0.5/0.5), 5% DR-2030, 3.3% NaCl; Condition 3: DMSO/MIBK (0.5/0.5), 10% DR-2030, 3.3% NaCl; Condition 4: DMSO/MIBK (0.35/0.65), 5% DR-2030, 3.3% NaCl.

3.3 to 6.7%) could slightly increase the reaction rate while significantly increasing the 5-HMF yield from 40% without salt to approximately 80% (Figure 3C). However, the 5-HMF content exhibited a continual decline throughout the reaction process after reaching its peak at 1 h (as illustrated in Figure 3B,C). This observed decline can likely be attributed to the occurrence of various side reactions, resulting in the formation of humins and organic acids. Consequently, it became imperative to closely monitor the reaction profile and interrupt the process at the point of maximum 5-HMF content without compromising the product yield.

Furthermore, the fructose dehydration to 5-HMF without using catalyst was performed in the presence of DMSO and NaCl, and showed a higher reaction rate and 5-HMF yield than those without NaCl (Figure 3C). Among the monophasic systems, DMSO has provided high fructose conversion and 5-HMF yields with relatively lower content of undesired byproducts including humins. This outstanding performance can be attributed to stronger binding of DMSO to both the hydroxyl and carbonyl groups of 5-HMF, which reduces its susceptibility to nucleophilic attack and undesirable side reactions including humin formation.<sup>38</sup>

Meanwhile, the conversion of fructose to 5-HMF with or without salt showed similar trends (Figure 3D). Complete conversion of fructose was achieved within 1 h of the reaction with salt, while 83% fructose conversion was obtained in the reaction without salt, suggesting a significantly enhanced catalytic performance for dehydration of fructose in the presence of a very low salt concentration.

In a previous report, an incorporated catalyst, 10% Fe/AR prepared from  $\text{Fe}^{3+}$  ( $\text{FeCl}_3$ ) and Amberlyst 15 significantly

enhanced the yield and selectivity of 5-HMF compared to the unmodified Amberlyst 15 resin.<sup>39</sup> The results indicated that  $\text{Fe}^{3+}$  acted as a highly active Lewis acidic site that not only contributed to the formation of 5-HMF, but also accelerated the reaction rate. However, the mere substitution of NaCl with  $\text{FeCl}_3$  did not lead to an enhancement in the 5-HMF yield in this study (data not shown).

**Recovery and Purification of 5-HMF Produced from Fructose Dehydration.** Only a limited number of studies on the large-scale synthesis and purification of 5-HMF from reaction mixtures have been reported. Furthermore, in most studies on 5-HMF conversion, mostly purified form of 5-HMF or commercial high-purity products have been used to produce value-added chemicals.<sup>25,40</sup> Since the recovery of 5-HMF in a pure form is challenging due to its highly reactive nature, instability at high temperature, and high solubility in polar solvents, it is more attractive in terms of cost and energy efficiency to transform the partially pure 5-HMF to other value-added products, which are more stable and can be easily purified to avoid expensive and inefficient purification of 5-HMF. We have previously demonstrated that crude 5-HMF obtained by liquid–liquid extraction could be directly used for microbial oxidation to 5-hydroxymethyl-2-furancarboxylic acid.<sup>7</sup>

Dehydration of 60 g of fructose was performed in the mixture containing 70 mL of DMSO and 130 mL of MIBK using 30 mg of A15 and 20 mg of NaCl at 110 °C for 1 h (Figure S3). After cooling to room temperature, MIBK and DMSO were fractionally evaporated at 80–100 °C under reduced pressure. The removal of MIBK and DMSO improved the extraction efficiency of 5-HMF in the subsequent liquid–

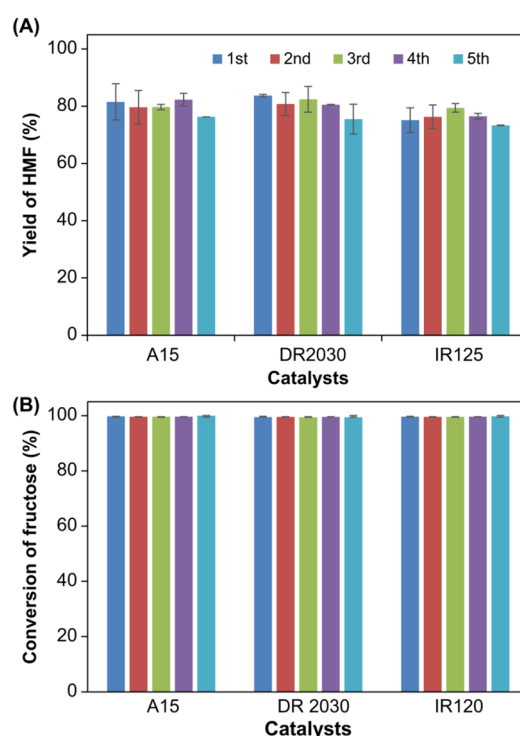
liquid extraction by phase separation between ethyl acetate and the aqueous salt solution, and the recovered MIBK and DMSO could also be recycled for dehydration of fructose in the next run. Over 95% of 5-HMF was recovered after four cycles of extraction, which could remove most of black humins. The colored material in the ethyl acetate extract was efficiently removed by treating it with activated carbon, followed by treatment with silica powder. After simple evaporation of ethyl acetate, partially purified 5-HMF was obtained with an overall recovery yield of 90% and 95% purity, as determined by  $^1\text{H-NMR}$  (Figures S3–S5). Since the reaction was performed at a high fructose concentration (25%, w/w) in the solution of DMSO/MIBK (0.35/0.65), the amount of DMSO required for reaction, not a preferable solvent, could be significantly reduced by approximately 14.3 times, compared to the reactions at lower fructose concentration (5%, w/w) in DMSO. This separation process can also be completed without using low-yield, high-cost, and time-consuming unit operations, such as recrystallization, distillation, and column chromatography, which are not recommended for large-scale production. The resulting purified 5-HMF was used for further transformation to produce various functional furan derivatives.

**Recycling of Catalysts, Acidic Ion Exchangers, for the Dehydration of Fructose.** The stability and reusability of catalysts, particularly ion-exchange resins, are important factors because of the risk of thermal inactivation and decomposition of the polymer matrix at elevated temperatures.<sup>12,21</sup> Because the reaction was performed at elevated temperatures and produced many side products, particularly humins, the stability and reusability of the catalyst are important factors owing to the risk of thermal inactivation, decomposition, and blocking of the polymer matrix.

The reusability and stability of the three catalysts, Amberlyst 15 (A15), Dowex DR 2030, and Amberlite IR120, were investigated for fructose dehydration for five consecutive batch reactions after regeneration using 1 N HCl. The dehydration of fructose was performed using 300 mg of fructose in 1 mL of the DMSO/MIBK solution (0.5/0.5), 5% catalyst, and 3.3% NaCl at 110 °C.

In between the consecutive reactions, the heterogeneous catalyst was easily collected from the reaction medium and washed with 0.5 mL of DMSO, 1 N HCl, and deionized water to neutralize the pH. Then, the catalyst was reused in the next reaction with the fresh fructose solution. All reactions were monitored at 1 h, and the fructose conversion and 5-HMF yield were analyzed to compare the reaction rates and the catalyst stability in each consecutive batch reactions. In the first batch the conversion of fructose reached up to 98% within 1 h of the reaction with 5-HMF yield of approximately 81% (Figure 4) for all catalysts. The reaction rate with fructose conversion and 5-HMF yield showed an identical profile and trend without significant loss of catalytic activity in the consecutive batch reactions. Therefore, for all of the catalysts, the initial catalyst could be reused for at least five consecutive batches to obtain 5-HMF at an average yield of 80%. This indicates that the catalyst has significant stability against mechanical damages under the reaction conditions used, and was regenerated appropriately.<sup>17</sup> The good stability could also be caused by the short reaction time (1 h) provided by the high reaction rate obtained by the presence of salt in the reaction.

**Dehydration of High-Concentration Glucose by Cation Exchangers.** Compared with fructose dehydration,



**Figure 4.** Reusability of catalysts (5% (w/w) with respect to fructose) for the dehydration of fructose (300 mg) with 3.3% NaCl (w/w with respect to fructose) in the mixture of DMSO/MIBK (0.5/0.5 mL) at 110 °C for 1 h: (A) Yield (%) of 5-HMF; (B) Conversion (%) of fructose. The catalysts were reused five times after regeneration using 1 N HCl.

the dehydration of glucose, a preferred feedstock, using a cation exchanger as a heterogeneous catalyst is more challenging and has not been successfully demonstrated. This is due to the necessity of integrating glucose isomerization to fructose and fructose dehydration in a one-pot reaction. The integration of glucose isomerization to fructose and subsequent glucose and fructose dehydration processes necessitates the presence of catalytic sites that encompass both Brønsted and Lewis acids.<sup>18,41,42</sup> Lewis acid sites play a pivotal role in enhancing glucose conversion, particularly by facilitating the isomerization of glucose to fructose. Cation exchangers are generally considered as Brønsted acids, functioning as proton donors. They can actively participate as Brønsted acids in glucose isomerization to fructose. Simultaneously, when HCl is generated from the cation exchanger with NaCl, it serves as a dual-purpose acid, exhibiting both Brønsted and Lewis acid characteristics, which can play a role in facilitating both the glucose isomerization and subsequent dehydration steps.

Table 2 summarizes the dehydration of glucose to 5-HMF under various conditions by using homogeneous and heterogeneous catalysis. In general, the results show lower yields and longer reaction times compared to fructose dehydration.

Although relatively high yields of 5-HMF from glucose were observed in dual catalytic systems such as H-ZSM-5 zeolite<sup>18</sup> and Cu–Cr/ZSM-5 zeolite,<sup>19</sup> they required low glucose concentrations and high catalyst ratios. On the other hand, homogeneous  $\text{H}_2\text{SO}_4$  and HCl at 130 and 120 °C, respectively, yielded only 13% of 5-HMF with 16% selectivity from glucose (Table 2, runs 1 and 2).<sup>43,44</sup>

Table 2. Glucose Dehydration to 5-HMF Using Homo- and Heterogeneous Catalysts<sup>a</sup>

run	glucose conc. (wt %)	catalyst	catalyst ratio (wt %)	solvent system	time (min)	temp. (°C)	conversion (%)	5-HMF yield (%)	year (refs)
1	3.1	H <sub>2</sub> SO <sub>4</sub>	5M	H <sub>2</sub> O/GVL	60	130		13	2014 (43)
2	18	HCl	0.25M	H <sub>2</sub> O	240	120	38	16(sel)	2017 (44)
3	1.2	Nb-MMT	66	H <sub>2</sub> O(NaCl)/MIBK (3/7)	180	170	99	70.5	2019 (24)
4	1	DIAION RCP160M/Al <sub>2</sub> O <sub>3</sub>	300	H <sub>2</sub> O/NMP/NaCl/MIBK	480	120	94	84.9	2020 (20)
5	1	DIAION RCP160M	300	H <sub>2</sub> O/NMP/NaCl/MIBK	360	120	25	7	2021 (20)
6	3	ZSM-5 zeolites	33	H <sub>2</sub> O(NaCl)/MIBK (3/7)	30	195	80	42	2016 (18)
7	10	Sn-Al-β zeolite	70	[C4mim]Cl	120	120	81	54	2023 (45)
8	2.5	Cu-Cr/ZSM-5 zeolite	20	DMSO	240	140	57.5	50.4	2020 (19)
9	2	P-VI-0/Amberlyst 15	100/50	THF-DMSO	600	100		58.1	2014 (46)
10	1.2	(Fe <sup>3+</sup> )Amberlyst 15	40	H <sub>2</sub> O(NaCl)/THF	40	160	97	68	2019 (47)
11	3.3	Amberlyst 15	100	DMF	180	100	69	0	2009 (48)
12	3.3	HT/Amberlyst 15	100/100	DMF	180	100	64	38(sel)	2009 (49)
13	17.6	Amberlyst 15	10	DMSO/MIBK (5/5)	660	120	83.1	8.6	this study
14	17.6	Amberlyst 15/NaCl	10/5	DMSO/MIBK (5/5)	660	120	92.2	36.1	this study
15	17.6	Amberlyst 15/NaCl	10/5	DMSO/MIBK (5/5)	540	130	94.8	34.9	this study

<sup>a</sup>(a) Glucose concentration in reaction media (organic and aqueous solution). (b) Catalyst ratio to substrate. (c) Selectivity of 5-HMF. DMSO: dimethyl sulfoxide; MIBK: methyl isobutyl ketone; HT: Mg–Al hydrotalcite; GVL:  $\gamma$ -valerolactone; DMF: *N,N*-dimethylformamide.

When using cation exchangers as single, unmodified catalysts, only 7% and 0% yields of 5-HMF were obtained from glucose dehydration using DIAION RCP160 M and Amberlyst 15 in biphasic solvent and DMF at 120 and 100 °C, respectively (Table 2, runs 5 and 11).<sup>20,48</sup>

Therefore, we employed enhanced H<sup>+</sup> exchange catalysis for glucose dehydration to 5-HMF, using Amberlyst 15 as the catalyst in an organic solvent. We investigated the effect of temperature on the dehydration of glucose (400 mg) in a mixture (2 mL) of DMSO and MIBK, using Amberlyst 15 (10 wt % to glucose) and NaCl (10 wt % to glucose) at 110, 120, and 130 °C, respectively (Figure 5A). The reaction rate was much slower than that of fructose dehydration; the yield of 5-HMF reached 35–36% at 120 and 130 °C after an 11 h reaction, while it was 17.2% at 110 °C after an 11 h reaction. Considering that Amberlyst 15 is recommended for use below 120–130 °C for long-term reactions due to the risk of thermal inactivation and polymer matrix desulfonation, we selected 120 °C as the limiting process temperature for further experiments.

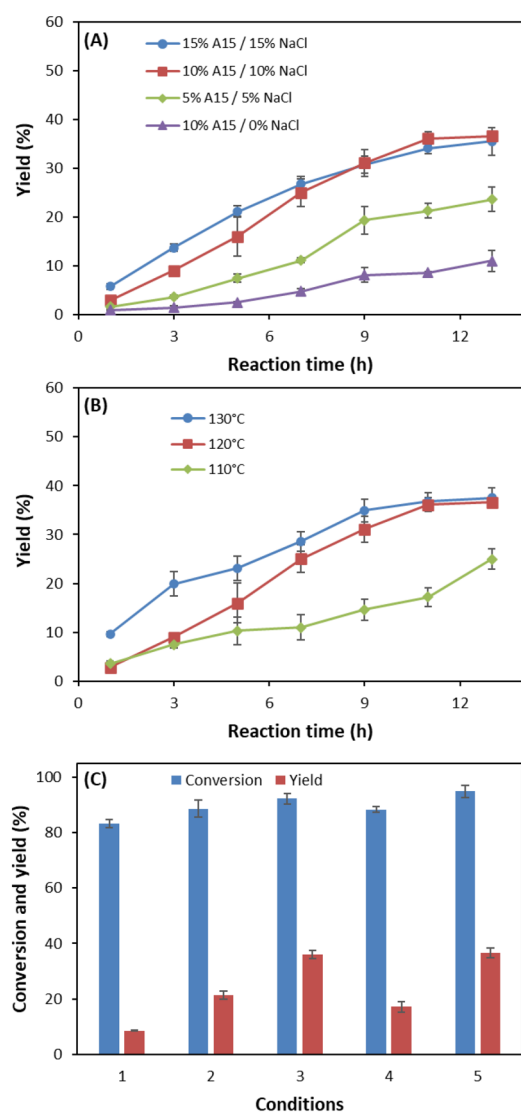
Figure 5B illustrates the dehydration of glucose (400 mg) in a mixture (2 mL) of DMSO and MIBK at different ratios of Amberlyst 15 to the substrate, both with and without NaCl, at 120 °C. When using a 10% catalyst amount without salt, the reaction resulted in only 8.6% yield of 5-HMF over 11 h (Figure 5B). However, when employing 10% and 15% catalyst amount with the same quantity of NaCl, the yields of 5-HMF were significantly improved, reaching 34.2% and 36.1%, respectively, under the same conditions. This confirms that the catalytic amount of NaCl can significantly enhance the yield of 5-HMF during glucose dehydration. While glucose

conversions remained consistent, approximately ranging from 82% to 95% under various conditions at an 11 h reaction time, the highest yield was achieved when using a 10% catalyst amount with NaCl at 120 and 130 °C (Figure 5C).

We examined the effect of Al<sub>2</sub>O<sub>3</sub> in cation exchange catalysis under the optimum conditions (in Table 2, run 4), and compared it to the use of NaCl in glucose dehydration to produce 5-HMF. The catalysis using A15/NaCl exhibited significantly higher yields than the A15/Al<sub>2</sub>O<sub>3</sub> under the same conditions. A similar trend was observed when A15/NaCl/Al<sub>2</sub>O<sub>3</sub> was used (data not shown). This compelling evidence underscores the enhancing role of NaCl in the catalytic process.

Hence, it can be inferred that NaCl likely participates in both glucose isomerization and the dehydration of glucose and its resulting intermediates. Generally, a salt, NaCl, can exert a profound influence on the reaction through its ability to modulate ion solvation and local ion concentrations. The conversion of glucose to 5-HMF can be achieved through two distinct pathways: direct dehydration or a sequential route involving glucose-to-fructose isomerization followed by fructose dehydration.<sup>49</sup> Recent experimental findings showed that the overall yield of 5-HMF can be substantially influenced by the choice of solvents and the presence of halide anions.<sup>49</sup> Chloride ions, for instance, exhibit the ability to stabilize transition states in both fructose and glucose dehydration. However, it is important to note that chloride ions do not impact humin formation, as C–C addition reactions lack hydrophilic, positively charged binding sites at their reactive





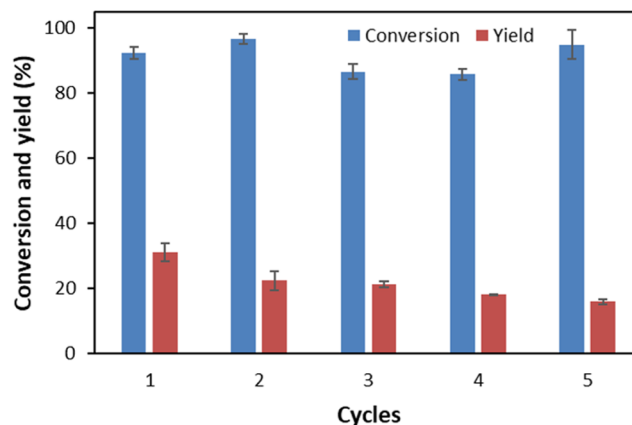
**Figure 5.** Dehydration of glucose (400 mg) in the mixture of 1 mL of DMSO and 1 mL of MIBK using Amberlyst A15 as a catalyst. (A) Effect of catalyst amount at 5, 10, 15% (w/w) with 0, 5, 10, 15% NaCl (w/w) ratio to glucose at 120 °C. (B) Effect of reaction temperature at 110, 120, 130 °C using 10% catalyst and 10% NaCl to glucose. (C) Conversion of glucose for 11 h; Condition 1: 10% catalyst, without NaCl, at 120 °C; Condition 2: 5% catalyst, 5% NaCl, at 120 °C; Condition 3: 10% catalyst, 10% NaCl, at 120 °C; Condition 4: 10% catalyst, 1% NaCl, at 110 °C; Condition 5: 10% catalyst, 1% NaCl, at 130 °C.

centers.<sup>49</sup> Consequently, chloride ions function to enhance the conversion process, with minimal effects on selectivity.

As shown in Table 2, most literature reports focus on the dehydration of glucose at relatively low concentrations (1–5%) with a high loading ratio of catalyst to glucose at high temperature and under pressure. We employed high-concentration reactions and minimized the catalyst amount, nevertheless, achieved improved reaction yields and fast reaction rates through a one-pot, multistep dehydration of glucose.

**Recycling of Catalysts, Acidic Ion Exchangers, In the Dehydration of Glucose.** The reusability and stability of Amberlyst 15 (10% ratio to glucose) were investigated for the

dehydration of 400 mg of glucose in a 2 mL DMSO/MIBK solution (1/1) with 5% NaCl at 120 °C. After washing, regeneration and recyclability of catalyst were tested for five consecutive batches of reaction run for 6 h (Figure 6).



**Figure 6.** Reusability of catalyst, Amberlyst A15 (10% (w/w) and 10% NaCl with respect to glucose) for the dehydration of glucose (400 mg) in the mixture of DMSO/MIBK (1 mL/1 mL) at 120 °C for 9 h. The catalyst was reused five times after regeneration by using 1 N HCl.

Glucose conversion and 5-HMF yield were analyzed to compare the reaction rates and catalyst stability in each consecutive batch. The conversion of glucose remained consistent at around 83% to 95% across the five batches, showing no significant decrease. In contrast, 5-HMF yields continuously decreased from 31.1% to 16.5%. As glucose dehydration necessitates higher temperatures and longer reaction times, it was anticipated that the heterogeneous catalyst would be more susceptible to damage and inactivation. This heightened susceptibility can be attributed to the increased risk of leaching of sulfonic acid groups and the excessive deposition of humins, which may lead to obstruction of the catalyst's surface or active sites.

## CONCLUSION

5-HMF has garnered significant attention due to its potential as a biobased platform chemical for the low carbon industry. However, most literature reports focus on the dehydration of fructose and glucose at relatively low concentrations (1–5%). Additionally, the purification of 5-HMF presents challenges. In this study, we employed high-concentration reactions and minimized the catalyst amount. Nevertheless, we achieved high reaction yields and fast reaction rates through a one-pot, multistep dehydration of fructose and glucose. This was accomplished by enhancing the H<sup>+</sup> exchange catalysis of cation exchangers. The enhancement of the H<sup>+</sup> exchange catalytic performance, achieved by adding a minimal amount of NaCl, was both proposed and evaluated through pH changes and FT-IR characterization.

This observation suggests that commercial cation exchangers, without catalytic modification, can be directly used for C6-sugars dehydration, and can potentially extend to other heterogeneous catalysts in general organic synthesis. Further investigations into the effects of salts such as KCl, CaCl<sub>2</sub>, and FeCl<sub>3</sub> could yield meaningful insights in future research on dehydration processes. Adhering to the principles of green

chemistry, the overall process demonstrates sustainability by utilizing renewable resources, enabling easy recovery and high reusability of heterogeneous acid catalysts, ensuring high catalytic efficiency, and proving cost-effectiveness. This is achieved through high substrate concentrations, short reaction times, and utilization of small and reusable catalyst amounts.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.3c05595>.

Effects of inorganic salts and acid ion exchangers on the pH change, FT-IR spectra, Representative GC chromatograms, Representative HPLC chromatograms, and <sup>1</sup>H NMR spectrum of 5-HMF (PDF)

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### Author Contributions

S.-H.P., J.C., N.R., and R.H.-K. conceived and designed the study. T.T.T.V., S.L., M.J., S.J., R.K., and S.-H.P. performed experiments and analyses. T.T.T.V., S.L., and S.-H.P. wrote the initial draft of the manuscript, and all authors revised the manuscript. All authors have read and approved the final manuscript for submission.

## Notes

The authors declare no competing financial interest.

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