

Organocatalytic Dehydration of Fructose-Based Carbohydrates into 5-Hydroxymethylfurfural in the Presence of a Neutral Inner Salt

Hao Ma,* Biao Yu, Chaochao Yue, Yanhui Qiao, Ning Li, Tao Cai, and Junjiang Teng*

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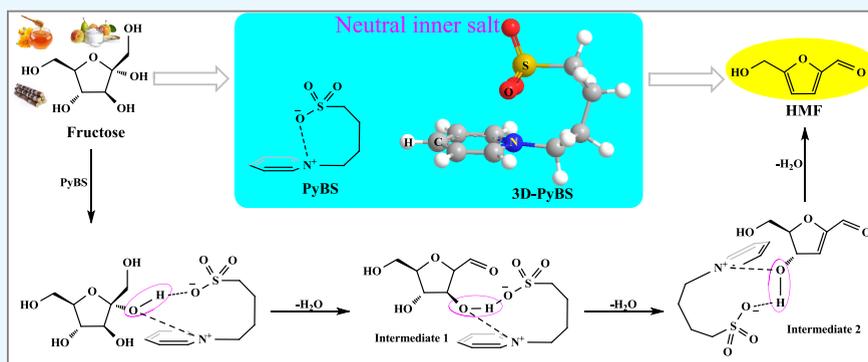
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ABSTRACT: A series of organic sulfonate inner salts, viz., aprotic imidazolium- and pyridinium-based zwitterions bearing sulfonate groups ($-\text{SO}_3^-$), were synthesized for the catalytic conversion of fructose-based carbohydrates into 5-hydroxymethylfurfural (HMF). The dramatic cooperation of both the cation and anion of inner salts played a crucial role in the HMF formation. The inner salts have excellent solvent compatibility, and 4-(pyridinium)butane sulfonate (PyBS) affords the highest catalytic activity with 88.2 and 95.1% HMF yields at almost full conversion of fructose in low-boiling-point protic solvent isopropanol (*i*-PrOH) and aprotic solvent dimethyl sulfoxide (DMSO), respectively. The substrate tolerance of aprotic inner salt was also studied through changing the substrate type, demonstrating its excellent specificity for catalytic valorization of fructose-moiety-containing C₆ sugars, such as sucrose and inulin. Meanwhile, the neutral inner salt is structurally stable and reusable; after being recycled four times, the catalyst showed no appreciable loss of its catalytic activity. The plausible mechanism has been elucidated based on the dramatic cooperative effect of both the cation and sulfonate anion of inner salts. The noncorrosive, nonvolatile, and generally nonhazardous aprotic inner salt used in this study will benefit many biochemical-related applications.

1. INTRODUCTION

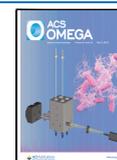
Acid-catalyzed dehydration of the renewable fructose-based carbohydrates into 5-hydroxymethylfurfural (HMF), a famous value-added platform chemical positioned in top 12 of high-potential bio-based products by the U.S. Department of Energy, is the most preferred route because of their much easier dehydration processes under acidic conditions.¹ Unfortunately, these reported acidic catalysts, such as mineral acids, metal chlorides, solid acids, etc., not only promote the formation of HMF through the dehydration of sugars but also accelerate the side reactions such as rehydration of formed HMF into levulinic acid (LA) and formic acid (FA) and condensations/degradative condensations of substrates, intermediates, products, and/or byproducts into humins, a brown polymer, inevitably resulting in the lower HMF selectivity and higher separation/purification cost for its production.² Therefore, designing a rational catalyst with weak acidity or neutrality might be a preferable strategy to promote the dehydration reaction of fructose into HMF while inhibiting the occurrence of other side reactions, as mentioned above.

So far, several efforts for the preparation of weak acidic catalysts have been made through introducing the organic base sites to the solid sulfonic acidic catalysts, weakening the acidic strength of the Brønsted acid site via hydrogen bonding between sulfonic acid groups ($-\text{SO}_3\text{H}$) and organic base sites,^{3–7} achieving the complete suppression on HMF rehydration as expected. For example, Dai et al. developed a sulfonated polyaniline (SPAN) as the novel acidic solid organocatalyst for the effective dehydration of fructose into HMF in the low-boiling water/1,4-dioxane cosolvent.⁴ The quinoid imine nitrogen ($-\text{N}=\text{C}_6\text{H}_4=\text{N}-$) from the polyaniline backbone could act as the basic center to neutralize the

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sulfonic acid groups of SPAN via the hydrogen-bonding effect, thus prohibiting its Bronsted acidity to catalyze the rehydration of HMF into LA and FA. The highest HMF yield of 71% is obtained from fructose with complete restriction of the HMF rehydration reaction in the presence of the SPAN catalyst.⁴ Furthermore, it was found that after deep sulfonation of polyaniline, the as-prepared catalyst (S-A-PAN-H) is mainly Lewis acidic with lower acidic strength. Its catalytic specificity for HMF production has also been improved, giving a maximum HMF yield of 88.8% in dimethyl sulfoxide (DMSO) or low-boiling 1,4-dioxane/water within 40–45 min, wherein the side reaction of HMF rehydration could also be completely restrained.⁶ Recently, encouraged by the performance of DMSO, such as dissolving hexoses, stabilizing HMF, and reducing side reactions as well as the catalytic activity in hexose dehydration,^{8–10} a DMSO-like polymeric solid organocatalyst (Au@polythiophene–polythiophene oxides, Au@PTh–PThO_x, $x = 1–2$) has been designed for neutral catalytic conversion of fructose into HMF.¹¹ It was strongly confirmed that both the sulfoxide (–SO) and sulfone (–SO₂) groups are responsible for the production of HMF from fructose, and the –SO group is more active than the –SO₂ group, giving the highest HMF yields of 72.6% by adjusting the molar ratio of –SO to –SO₂ groups in the Au@PTh–PThO_x catalyst.¹¹ Although these weak acidic or neutral solid catalysts could provide the good catalytic performance for HMF production, their preparation is time-consuming, tedious, complicated processes, and the use of highly active and corrosive reagents (e.g., H₂SO₄ and H₂O₂). Therefore, designing and preparing the novel weak acidic or neutral catalysts with good catalytic efficiency for fructose dehydration is highly desirable.

Ionic liquids (ILs) are a class of state-of-the-art task-specific chemical media with many unique properties including molecular designability, negligible volatility, and high thermal stability. ILs with the –SO₃H groups on cations (acidic ILs) are the robust Brønsted acids for the catalytic dehydration of carbohydrates into HMF. The proton (H⁺) of the –SO₃H group is the key active site for the catalytic dehydration of fructose into HMF undoubtedly, but the sulfone (–SO₂) moiety in the –SO₃H group may also give its contribution on HMF formation from the results reported by Guo et al.¹¹ The zwitterionic-type molten salts nominated as the inner salts with sulfonate groups (–SO₃[–]) are the essential intermediates that can be synthesized through the reactions of the various imidazoles or pyridines with 1,4-butane sultone/1,3-propane sultone for the preparation of the acidic SO₃H-functionalized ionic liquids. Zwitterions are neutral, polar, and designable molecules with nonvolatile, safe, and environmentally non-hazardous properties and have been employed successfully in catalysis.^{12,13} For example, Majee and co-workers use the aprotic imidazolium inner salts, such as 4-(3-methylimidazolium)butane sulfonate (MimBS) and 3-(1-methylimidazolium)propane sulfonate (MimPS), for a series of catalytic reactions including *syn*-selective *aza*-Henry reaction,¹⁴ multicomponent reactions,^{15–18} azide–nitrile cycloaddition,¹⁹ regioselective ring opening of aziridines,²⁰ iodination of imidazoheterocycles,²¹ tetrahydropyranylation of alcohols,²² the synthesis of dipyrromethanes and bis(indolyl)-methanes,²³ and the synthesis of 4-hydroxy-3-thiomethylcoumarin derivatives.²⁴ Both the cation and the anion in inner salts cooperatively affect the reactions mentioned above, and their

application in the catalysis field should be expanded due to their high efficiency and greenness.

Herein, in continuation of our work on green catalytic production of HMF,^{25–29} we have explored imidazolium- and pyridinium-based zwitterionic-type molten salts, *viz.*, inner salts, as a new class of neutral organocatalysts in the dehydration of fructose-based carbohydrates into HMF. These requisite zwitterionic-type inner salts have been designed and prepared to elucidate the cooperation of the cation and anion. The compatibility of inner salts with solvent has been investigated through evaluating the effect of the solvent type on the HMF yield. Moreover, the influence of process parameters on HMF formation and the substrate tolerance with the stability of the catalyst have also been studied in depth as well as a plausible catalytic mechanism.

2. MATERIALS AND METHODS

2.1. Materials. D-Fructose (99%), D-glucose (98%), sucrose (99%), maltose (99%), inulin (97%), HMF (99%), 1-methylimidazole (99%), 1-ethylimidazole (99%), 1-butylimidazole (99%), 1,2-dimethylimidazole (99%), ethyl chloroacetate (99%), pyridine (99%), 1,4-butanedisulfone (99%), 1,3-propanedisulfone (99%), sodium methanesulfonate (CH₃SO₃Na, 99%), methanol (CH₃OH, high-performance liquid chromatography (HPLC)), D₂O (99.8%, TMS as the internal standard), and CDCl₃ (99.8%, TMS as the internal standard) were supplied by the J&K Chemical Company (Beijing, China). The common solvents, such as MeOH (>99%), ethanol (EtOH, >99%), *n*-propanol (*n*-PrOH, >99%), *i*-propanol (*i*-PrOH, >99%), *n*-butanol (*n*-BuOH, >99%), *i*-butanol (*i*-BuOH, >99%), 2-butoxy ethanol (>99%), glycol (>99%), glycerol (>99%), tetrahydrofuran (THF, >99%), acetone (>99%), dimethyl sulfoxide (DMSO, >99%), acetonitrile (CH₃CN, >99%), and ethyl acetate (EtOAc, >99%), were purchased from the Guangzhou Chemical Reagent Factory. The ILs 1-butyl-3-methylimidazolium chloride ([Bmim]Cl) and 1-butyl-3-methylimidazolium methanesulfonate ([Bmim][CH₃SO₃]) were purchased from Qingdao Olike New Material Technology Co., Ltd. (Qingdao, China). All the reagents were used as received without further purification.

2.2. Typical Procedures for the Synthesis of Inner Salts. The inner salts (Scheme S1), such as 4-(3-methylimidazolium)butane sulfonate (MimBS), 4-(1,2-dimethylimidazolium)butane sulfonate (DmimBS), 4-(3-ethylimidazolium)butane sulfonate (EimBS), 4-(1-butylimidazolium)butane sulfonate (BimBS), 4-(pyridinium)butane sulfonate (PyBS), 3-(pyridinium)propane sulfonate (PyPS), and 2-(1-methylimidazolium)-acetate (MimAC), were synthesized according to the reported procedures^{30,31} and characterized by nuclear magnetic resonance (NMR) on a Bruker DRX 400 spectrometer using D₂O as the solvent. The detailed synthesis method of inner salts is given in the Supporting Information. The geometrical structures of the inner salts were sketched using a ChemBioDraw Ultra 14 software.^{32,33} All drawn structures are set for the lower energy job to get the most stable geometry, which are plotted as Figures S1–S7 in the Supporting Information. For these guesses, it was assumed that the interaction between the cation and the anion is optimal where the most negative sites of the anion are close to the most positive sites of the cation.^{34,35}

2.3. Typical Procedures for the Catalytic Dehydration of Fructose. All experiments were carried out in batch mode using a 25 mL hydrothermal autoclave reactor equipped with a

Table 1. Catalytic Conversion of Fructose into HMF by Different Inner Salts^a

Entry	Catalyst		Conversion (mol%)	HMF	
	Abbreviation	Structure		Yield (mol%)	Selectivity (mol%)
1	—	—	13.2	ND	—
2	MimBS		93.2	68.8	73.8
3	DmimBS		89.8	18.4	20.5
4	EimBS		85.6	26.9	31.4
5	BimBS		72.4	15.4	21.3
6	PyBS		97.9	88.2	90.1
7	PyPS		96.0	84.2	87.7
8	MimMC		41.5	9.9	23.9
9	[Bmim]Cl		14.1	ND	—
10	CH ₃ SO ₃ Na		76.6	12.3	16.1
11	[Bmim][CH ₃ SO ₃]		16.8	trace	—

^aReaction conditions: 10 mmol of fructose, 15 mol% of inner salt, 10 mL of *i*-PrOH, 120 °C for 1.5 h; ND: not detected.

Teflon liner. In a typical reaction, 1.8 g (10 mmol) of fructose was charged into the reactor along with 15 mol % catalyst and 10 mL of *i*-PrOH. The charged reactor was previously flushed with N₂ three times to displace the air and then heated to the determined temperature and time (e.g., 120 °C for 1.5 h) with 500 rpm stirring. As soon as the reaction time was complete, the reactor was cooled down rapidly to room temperature in 10 min by placing it in an ice bath to stop the reaction.

2.4. Typical Analysis Procedures. After the reaction, an aliquot of the product mixture was diluted 10 times with distilled water and was filtered through a 0.2 μm PTFE filter before analysis on an Agilent 1200 HPLC system equipped with an HPX-87H column (300 × 7.8 mm, 5 μm, 5 mM H₂SO₄ solution as the mobile phase at 0.6 mL/min and 65 °C) and an RID detector for unreacted substrates and a C18 reversed phase column [250 × 4.6 mm, 5 μm, 1:4 (v/v) CH₃OH/H₂O as the mobile phase at 0.6 mL/min and 30 °C] and a UV detector (284 nm) for HMF. To estimate the concentration of residual substrates, formed HMF, and intermediates, the commercially available standard substrates were used to obtain the corresponding standard calibration curves. Conversion of fructose (Conv., mol %), yield of HMF (Y_{HMF} , mol %), and selectivity of HMF (S_{HMF} , mol %) were calculated according to eqs 2–3. All analysis experiments were conducted in triplicate to minimize error, and the data given in the following are the mean values.

$$\text{Conv. (mol\%)} = \left(1 - \frac{M_{\text{RF}}}{M_{\text{F}}}\right) \times 100\% \quad (1)$$

$$Y_{\text{HMF}} \text{ (mol\%)} = \frac{M_{\text{HMF}}}{M_{\text{F}}} \times 100\% \quad (2)$$

$$S_{\text{HMF}} \text{ (mol\%)} = \frac{Y_{\text{HMF}}}{\text{Conv.}} \times 100\% \quad (3)$$

where M_{F} , M_{RF} , and M_{HMF} are the amounts (mol) of the original fructose, residual fructose, and formed HMF, respectively.

2.5. Typical Procedures for Product Separation and Recycling of Inner Salts. After cooling the reaction mixture, the solvent was recovered first through a rotary evaporator, and then the formed HMF in the resulting product mixture was extracted with 3 × 10 mL of EtOAc (Scheme S2). The collected EtOAc phase containing HMF was pooled and evaporated to obtain the crude HMF product as a brown oil. The structure of HMF was confirmed by NMR (CD₃Cl as the solvent), and the purity of HMF was 95% according to the HPLC quantitative analysis.

The residual mixture after extraction with EtOAc containing the inner salt, possible unreacted substrate, and intermediates can be reused into the next run after dryness under vacuum at 60 °C.

3. RESULTS AND DISCUSSION

3.1. Catalytic Conversion of Fructose with Various Inner Salts. Various imidazolium- and pyridinium-based sulfonate inner salts were synthesized and tested first for the catalytic conversion of fructose, a model substrate, into HMF (Table 1).

To verify the catalytic specificity of these sulfonate inner salts for fructose dehydration, a control experiment without addition of the catalyst was examined, and no yield of HMF with very low conversion of fructose (13.2%) was present, indicating that autocatalysis could be disregarded under the investigated conditions (Table 1, entry 1). Impressively, when a catalytic amount (15 mol %) of the inner salt MimBS was

added into the reaction system, the conversion efficiency of fructose improved extensively, achieving 93.2% fructose conversion with 68.8% HMF yield (Table 1, entry 2). It was reported that the C-2 hydrogen of the imidazole ring plays a major role for conversion of fructose into HMF due to its acidity.³⁶ However, this reason was not suitable for imidazolium sulfonate inner salt because of a certain catalytic activity of DmimBS without a C-2 hydrogen (Table 1, entry 3). The above results confirm that the inner salt with the $-\text{SO}_3^-$ group does catalyze the dehydration of fructose into HMF.³⁷ On the other hand, the alkyl group at the imidazolium ring also has a remarkable impact on the reaction outcome. The catalytic activity decreased as the alkyl length of substituents increased. Further control experiments showed that the substantial differences in the HMF yields catalyzed by MimBS, DmimBS, EmimBS, and BimBS are thought to be due to the steric effect of the alkyl groups on the imidazolium ring, which may hinder the ion–dipole-type interaction between the imidazolium ring and the fructose molecule (Table 1, entries 2–5).³⁸ In fact, imidazolium-based inner salts display a higher degree of 3-D structural organization in view of the presence of a virtually rigid and planar ring.³⁹ Due to the weak hydrogen bond (C–H \cdots O) between C–H of the alkyl group (ethyl and butyl) and O of the $-\text{SO}_3^-$ group, the alkyl group and $-\text{SO}_3^-$ group located the same side of the rigid and planar imidazolium ring (Figures S1–S4),^{35,40} further prohibiting the synergistic effect of the positively charged imidazolium head group (cation) and the negatively charged $-\text{SO}_3^-$ group (anion) to interact with a substrate. Hence, as the lengths of the alkyl groups are longer in EimBS and BimBS, their catalytic activities are correspondingly lower.

Moreover, when the planar imidazolium moiety (cation part) was replaced by the planar *pyridinium* structure, its catalytic performance for fructose dehydration could be improved notably, affording more than 95% fructose conversion with more than 85% HMF selectivity (Table 1, entries 6 and 7). The planar geometry of the *pyridinium* moiety without alkyl groups that depress the steric effect for inhibition of the interaction of inner salts with fructose through the alkyl- SO_3^- side chain reorients itself and forms a closed structure with the $-\text{SO}_3^-$ binding to the *pyridinium* groups, as shown in Figure S5.³⁵ These results indicated that the structure of the cation played a key role for fructose conversion. Furthermore, the length of the alkyl group linked to the cation and anion showed little negative effect for HMF yield after comparing the catalytic activity of PyBS with PyPS (Table 1, entries 6 and 7; Figures S5 and S6).^{41,42} In addition, the anion also has a significant effect for fructose conversion, and the inner salt MimMC with carboxylate ($-\text{COO}^-$) as the anion showed the lower conversion of fructose with a lower yield of HMF (Table 1, entry 8). This result might be caused by the weak alkaline nature of carboxylate, which lacked catalytic ability for fructose dehydration like an acid.⁴³

To understand these catalytic roles of the cation and anion, the controlled experiments with [Bmim]Cl, $\text{CH}_3\text{SO}_3\text{Na}$, and [Bmim][CH_3SO_3] as the catalysts were done carefully (Table 1, entries 9–11). It was interesting to see that both [Bmim]Cl and [Bmim][CH_3SO_3] showed no obvious catalytic ability for fructose conversion after comparison with the catalyst-free system (Table 1, entry 1). In addition, the free anion CH_3SO_3^- did not show a cooperative effect with the free imidazolium cation (Table 1, entry 11). Therefore, on the grounds of these findings, we hypothesize that, in general, the cooperation of the

cation and anion of inner salts presented the main contribution on the conversion of fructose into HMF.

Therefore, the above results demonstrated that the inner salt PyBS could be selected as a promising neutral organocatalyst with high activity for the dehydration of fructose into HMF.

3.2. Catalytic Conversion of Fructose in Various Solvents. The common solvents including both protic solvents (water and alcohols) and aprotic organic solvents (THF, acetone, DMSO, and CH_3CN) were used to conjugate with the inner salt for fructose dehydration, and the obtained results are listed in Table 2.

Table 2. Catalytic Conversion of Fructose into HMF in Different Solvents^a

entry	solvent	conversion (mol %)	HMF	
			yield (mol %)	selectivity (mol %)
1	H ₂ O	90.9	7.8	8.6
2	MeOH	99.2	4.0	4.0
3	EtOH	99.6	41.7	41.9
4	<i>n</i> -PrOH	99.4	56.6	56.9
5	<i>n</i> -BuOH	98.5	72.5	73.6
6	<i>i</i> -PrOH	97.9	88.2	90.1
7	<i>i</i> -BuOH	98.7	76.2	77.2
8	2-butoxy ethanol	100	71.6	71.6
9	glycol	100	ND	
10	glycerol	100	ND	
11	THF	96.3	77.8	80.8
12	acetone	94.6	74.2	78.4
13	DMSO	99.5	95.1	95.6
14	CH_3CN	62.3	4.1	6.6

^aReaction conditions: 10 mmol of fructose, 15 mol % PyBS, 10 mL of solvent, 120 °C for 1.5 h; ND, not detected.

Due to the dehydration reaction of fructose to produce HMF, the water is not a suitable solvent in this inner salt-catalyzed system, and only 7.8% HMF was formed with more than 90% fructose conversion (Table 2, entry 1). In the subsequent experiments, a series of alcohols including aliphatic monoalcohols (MeOH, EtOH, *n*-PrOH, etc.) and polyols (glycol and glycerol) were used as the nonaqueous solvents for fructose dehydration. It is found that only the bulky monoalcohols, such as *n*-PrOH, *i*-PrOH, *n*-BuOH, *i*-BuOH, and 2-butoxy ethanol, facilitated the formation of HMF from fructose dehydration processes. These results are in line with the previous reports,^{29,44,45} demonstrating that the polarity of an alcohol and its stereostructure were major factors for fructose dehydration into HMF in the presence of inner salts.⁴⁶ When the inner salt-catalyzed fructose dehydration occurred in the glycol or glycerol solvent, no HMF could be detected after the reaction, except the dark-brown reaction mixture, implying that the side reactions contributed to the full conversion of fructose, and the humins were the main side products in the polyol systems.⁴⁷

In addition, when the inner salt-catalyzed dehydration was performed in the nonaqueous aprotic organic solvents, a satisfactory HMF yield could still be obtained, except for the CH_3CN (Table 2, entries 11–14), a weak basic solvent, which could accelerate the occurrence of the side reactions of the formed HMF to form humins.⁴⁸ Especially in the DMSO solvent, more than 95% HMF was formed with almost full

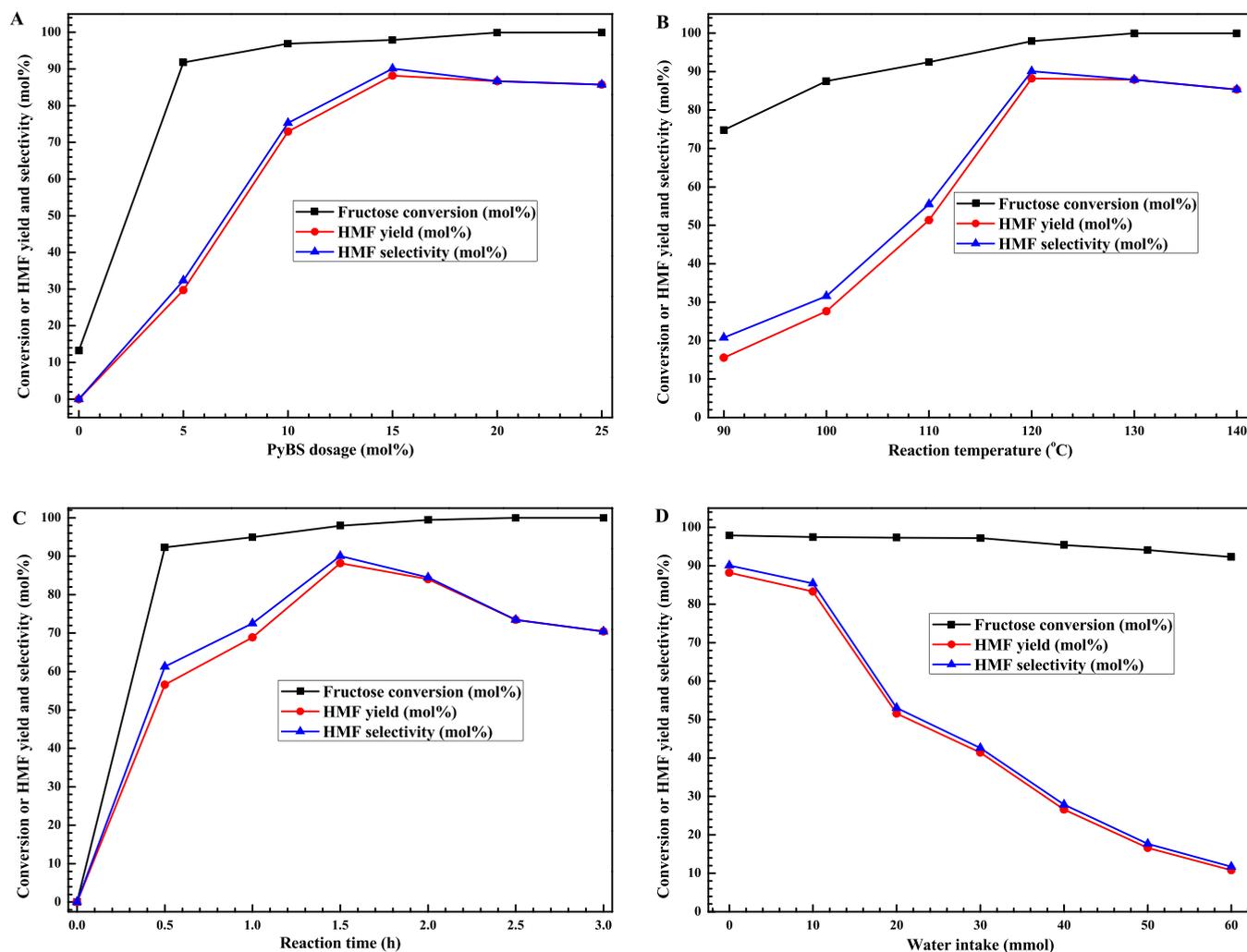


Figure 1. Influence of catalyst dosage (A), reaction temperature (B), reaction time (C), and water content (D) on fructose dehydration ((A) 10 mmol of fructose, 10 mL of *i*-PrOH, 120 °C for 1.5 h; (B) 10 mmol of fructose, 15 mol % PyBS, 10 mL of *i*-PrOH, 1.5 h; (C) 10 mmol of fructose, 15 mol % PyBS, 10 mL of *i*-PrOH, 120 °C; (D) 10 mmol of fructose, 15 mol % PyBS, 10 mL of *i*-PrOH, 120 °C for 1.5 h).

conversion of fructose (Table 2, entry 13). It was concluded that aprotic, polar, and neutral solvents are more suitable for this dehydration system, which can be attributed to their ability to stabilize the product.^{46,49,50} DMSO is known as one of the most favorable solvents for the dehydration reaction of fructose to HMF due to its ability to prevent the formation of byproducts such as LA and humins,^{8,51} but its high boiling point (189 °C, 1 atm) is detrimental in using it on a larger scale and in the separation of the product from it.⁵²

Therefore, based on the satisfied catalytic performance of inner salts in the bulky monoalcohols (*n*-PrOH, *i*-PrOH, *n*-BuOH, *i*-BuOH, and 2-butoxy ethanol) and aprotic organic solvents (THF, acetone, and DMSO), we can conclude that the inner salt with $-\text{SO}_3^-$ groups presented the excellent compatibility with many solvents and expanded the catalyst–solvent combination for HMF production from sugars. Furthermore, regarding the low boiling point (82.45 °C, 1 atm) and toxicity of *i*-PrOH as well as the good HMF yield, *i*-PrOH is selected as a solvent for the subsequent experiments.

3.3. Influence of Process Parameters on the Inner Salt-Catalyzed Fructose Dehydration. Regarding the catalytic specificity and excellent solvent compatibility of the inner salt for fructose dehydration, the influence of reaction

conditions, such as catalyst loading, reaction temperature, reaction time, and water content, on its catalytic performance should be understood inevitably, and the results are pictured in Figure 1.

Due to the excellent catalytic performance of the inner salt PyBS, its loading amount on fructose conversion was first investigated ranging from 0 to 25 mol % (Figure 1A). As the inner salt loading increased from 0 to 5 mol %, the conversion degree of fructose increased dramatically from 13.2 to 91.8%, demonstrating that a small amount of inner salts can improve the conversion of fructose efficiently. However, only 29.7% HMF was yielded, implying that 5 mol % PyBS was insufficient for catalytic elimination of three waters from fructose consecutively.⁵⁰ Unknown products (62.1%) may be the intermediates from the partial dehydration of fructose, which can be confirmed by the fact that when 10 mol % inner salt was loaded into the reaction system, the efficiency of the catalytic dehydration of fructose into HMF elevated remarkably. Up to 73% HMF yield with 96.9% fructose conversion indicated that the inner salt dosage played a key role for HMF formation from fructose dehydration. The maximum yield of HMF was 88.2% at 15 mol % catalyst dosage, which was slightly declined into 85.7% with the increase of inner salt loading to 25 mol %.

It was found that the color of the reaction system darkened gradually with an increase in the dosage of the catalyst, indicating that the humins with dark brown from the possible condensations of the substrate, intermediates, and HMF were the main side products under the higher catalyst dosage.^{53,54} In fact, we cannot detect the LA and FA through HPLC and GC–MS methods after the reaction, confirming that the rehydration of HMF was negligible in this inner salt-catalyzed reaction system.

Furthermore, the stability of HMF in this inner salt-catalyzed reaction system was also examined through the controlled experiments with HMF as the substrate at 25 mol % inner salt dosage. The recovery of HMF was more than 95% with no LA and FA detected, demonstrating the excellent stability of HMF in the presence of PyBS and also implying that the humins may be formed through the HMF–HMF condensations (Figure S8). The obtained results above showed that the inner salt with $-\text{SO}_3^-$ groups was the preferred neutral catalyst for fructose dehydration into HMF as expected. Therefore, when the PyBS was used as the catalyst, 15 mol % catalyst loading was more popular absolutely.

It is well known that the fructose dehydration is sensitive to the reaction temperature; herein, the effect of the reaction temperature on the inner salt-catalyzed fructose dehydration into HMF was inspected. As shown in Figure 1B, the dehydration of fructose could be achieved under the mild conditions ($<120\text{ }^\circ\text{C}$), but only 15.5% HMF was yielded, accompanying with 74.8% fructose conversion at $90\text{ }^\circ\text{C}$. As the reaction temperature was elevated to $120\text{ }^\circ\text{C}$, the HMF yield increased to 88.2% with almost full conversion of fructose. These results showed that the low reaction temperature ($<120\text{ }^\circ\text{C}$) facilitated the partial dehydration of fructose into intermediates, but only the high enough reaction temperature ($\geq 120\text{ }^\circ\text{C}$) could further dehydrate the formed intermediates into the target product HMF efficiently.⁵⁰ In addition, when the reaction temperature was elevated to $140\text{ }^\circ\text{C}$ gradually, the yield of HMF presented a slight decrease, but still 85.3% HMF could be obtained, further confirming the stability of HMF under the higher reaction temperature. Therefore, the suitable reaction temperature of PyBS-catalyzed fructose dehydration into HMF in the *i*-PrOH solvent is $120\text{ }^\circ\text{C}$.

The effect of reaction time on inner salt-catalyzed fructose dehydration was further examined in the range of 0–3.0 h (Figure 1C). HMF can be formed rapidly in the first 0.5 h, and the yield of HMF gradually increases to a peak value of 88.2% in the 1.5 h (Figure S10). After that value, the HMF yield decreases to 70.4% at 3.0 h. The reduction in HMF yield and specificity over time is because of the formation of condensation side products (humins), which increases in content dramatically with longer reaction times ($>1.5\text{ h}$). The trendline of HMF recovery versus time presented that treatment of HMF at harsh conditions with long time was detrimental to the stability of HMF (Figures S8 and S9). Moreover, the formed humins will accelerate the side reactions of HMF through the self-polymerization and even some HMF–humin cross-polymerization to generate more humins with large molecular weights, resulting in a dramatic decrease in HMF recovery (Figures S8 and S9).^{53,55} Hence, from the results of Figure 1C and HMF recovery experiments (Figures S8 and S9), we can conclude that the obvious decline in HMF yield at the reaction time longer than 1.5 h can attribute to the extensive formation of humins through the possible condensation of HMF with intermediates to form the primary

humins with low molecular weight, which could be further condensed with the formed HMF at longer reaction times.⁵³ Therefore, 1.5 h is regarded as the optimal reaction time for the catalytic dehydration of fructose into HMF.

The water content was also an unavoidable factor for HMF production from the inner salt-catalyzed system because of the dehydration mechanism of HMF formation from fructose and the reactions between the formed water and HMF or other reaction intermediates, leading to LA or complex products (Figure 1D). The initial water concentration in the solution may be a sensitive issue. To address this concern, we ran the reactions in the presence of various amounts of water.^{56,57} When the 10 mmol water was added to the reaction system additionally, the yield of HMF could still be acceptable, and more than 80% HMF yield demonstrated a certain water tolerance of this inner salt-catalyzed system, also implying that the excessive pre-drying of the reaction system (catalyst, solvent, substrate, etc.) is not to be considered needily. However, as the water content increased from 10 to 60 mmol, the efficiency of inner salt-catalyzed conversion of fructose into HMF decreased significantly, and only 10.8% HMF was formed at 60 mmol of water intake, implying the detriment of water for inner salt-catalyzed HMF formation through the dehydration processes. Impressively, the conversion degree of fructose still maintained a high level ($>90\%$), demonstrating that the possible autocatalytic partial dehydration of fructose into intermediates occurred under high content of water,^{26,58} and the PyBS was the weak catalyst for the deep dehydration of intermediates into HMF under these water-rich conditions.^{50,59}

It should be noted that, under the reaction conditions with additional water intake, we cannot detect the product from rehydration of HMF into LA and FA, meaning that the neutral inner salt presented no catalytic activity for HMF rehydration as well as the negligible autocatalysis of HMF rehydration by hot water at the present conditions.^{26,58} These results clearly suggest that excess water reduced the deep dehydration reaction of intermediates but had little effect on the fructose conversion degree. Overall, the water intake still had a prominent effect on the dehydration of fructose into HMF. To obtain the high HMF yield, the water content of the reaction system should be less than 10 mmol.

Hence, based on the results above, the key factors such as catalyst loading, reaction temperature, reaction time, and water content had a noticeable effect on the dehydration of fructose into HMF, especially for the deep dehydration of the formed intermediates from the partial dehydration of fructose into HMF. To obtain the high enough HMF yield in this inner salt-catalyzed dehydration of fructose, a number of factors should be optimized through multifactorial experiment design seriously.

3.4. Inner Salt-Catalyzed Dehydration of Various Carbohydrates. Due to the fascinating neutrality and excellent activity of the inner salt for the catalytic dehydration of fructose into HMF, its application in various catalytic feedstocks should be generalized unavoidably. The substrates with fructose moieties (sucrose and inulin) and glucose structure (glucose, sucrose, and maltose) were subjected to the inner salt-catalyzed dehydration reactions (Table 3). It was observed that when the reactions were performed using glucose and maltose as the feedstocks, no HMF can be detected with the low conversion degree (Table 3, entries 2 and 4), indicating the lack of ability of the inner salts for

Table 3. Catalytic Conversion of Various Carbohydrates into HMF^e

entry	substrates ^a	conversion (mol %)	HMF	
			yield (mol %)	selectivity (mol %)
1	fructose	97.9	88.2	90.1
2	glucose	6.3	ND	
3	sucrose	90.7	82.0 ^b	90.4 ^b
4	maltose	30.6	ND	
5	inulin		40.6	
6 ^c	inulin		76.4	
7 ^d	fructose	97.1	87.7	90.3

^aThe sugar unit is 10 mmol. ^bCompare to the fructose unit in sucrose.

^cThe reaction temperature is 140 °C. ^d100 mmol of fructose, 15 mol % PyBS, 100 mL of *i*-PrOH, 120 °C for 1.5 h. ^eConditions: substrate, 15 mol % PyBS, 10 mL of *i*-PrOH, 120 °C for 1.5 h; ND, not detected.

catalytic isomerization of aldohexose (glucose) into ketohexose (fructose), resulting in the invalidation for catalytic glucose-based carbohydrates into HMF.

Fortunately, when the substrates bear the fructose unit in a molecular structure, its fructose moieties can be converted into HMF selectively (Table 3, entries 1, 3, and 5). For example, sucrose containing one fructose unit and one glucose unit in its molecule can be converted into HMF with 82.0% HMF yield and 90.4% HMF selectivity according to the baseline of the fructose unit content in feed sucrose. Moreover, inulin, a famous fructose-based biopolymer, can also be converted into HMF through successive hydrolysis and dehydration processes to give a 40.6% HMF yield (Table 3, entry 5). When the reaction was carried out under the higher temperature (140 °C), more HMF (76.4%) can be obtained through the inner salt-catalyzed hydrolysis and dehydration processes. Hence, these results show that our neutral inner salts have specific applicability for the catalytic conversion of fructose-based carbohydrates into HMF with acceptable yield.

Furthermore, when the inner salt-catalyzed system was scaled up 10 times, the 87.7% HMF yield could still be afforded (Table 3, entry 7), reflecting the potential practicability of this inner salt-catalyzed system for the scalable production of HMF in industrial processes. Therefore, the results demonstrated the capability of inner salts to convert various fructose-based carbohydrates in good yields of HMF.

3.5. Reusability of the Inner Salt. The reusability of the catalyst is an important benefit, especially for commercial applications. Thus, the recovery and reusability of the catalyst were investigated according to the procedures given in Scheme S2, and then the recovered catalyst was reused in a new experiment under the same reaction conditions as the previous one (Figure 2).

Catalyst recycle studies indicate that the PyBS catalyst can be reused without substantial deactivation over four cycles with a reduction in the HMF yield of about 4 wt % observed from the first to the fourth trial in this sequence. Moreover, the yield of HMF is still kept 74% even after being recycled six times, which is probably due to the inevitable loss of the partial catalyst during experimental operations. It should be noted that the yield of HMF in the second and third cycles was even higher than the first one, which can be attributed to the retention of HMF or residual formed intermediates from the previous cycle,^{28,60,61} and has been confirmed by the NMR spectra of the recovered catalyst after the sixth run (Figure S11). It was found that the NMR spectra (Figure S11) of reused PyBS after six runs were nearly the same as a fresh sample, except for peaks attributed to the residual HMF and *i*-PrOH. In fact, the recovered catalyst was gelatinous, and the residual HMF and *i*-PrOH existing in the inner of catalyst gel were prohibited to diffuse under vacuum in the recovery process, resulting in a certain amount of HMF and *i*-PrOH existing in the recovered catalyst. This finding demonstrated the excellent stability and recyclability of the inner salt (PyBS) in the catalytic dehydration of fructose into HMF.

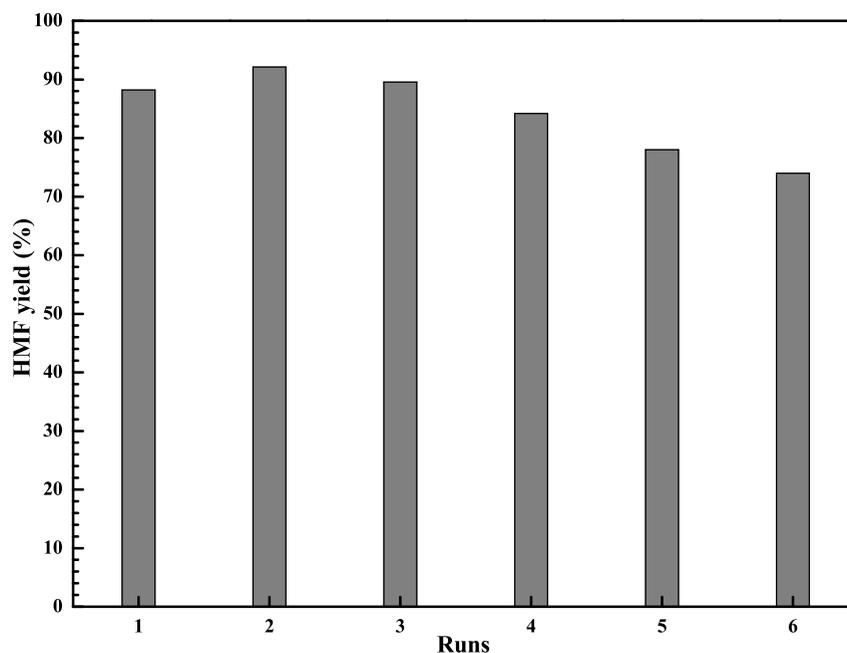
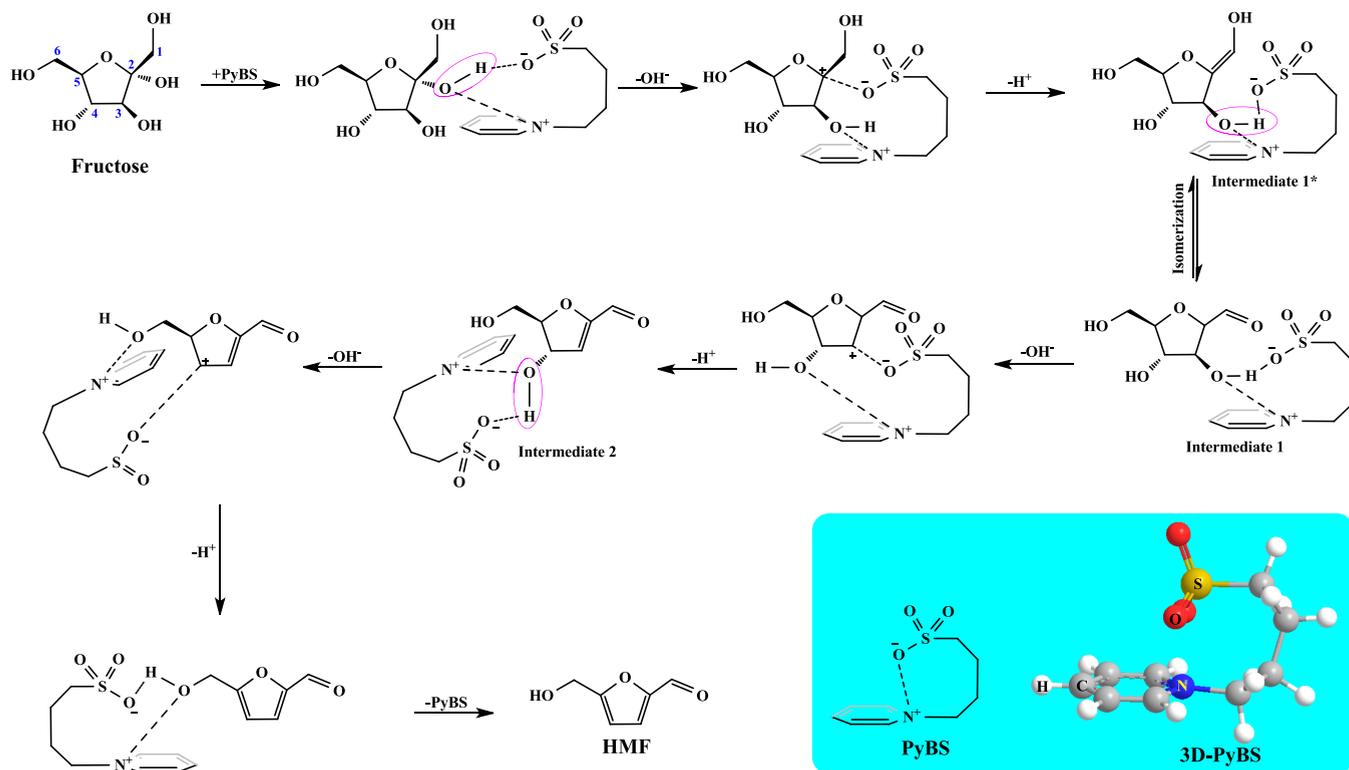


Figure 2. Recyclability of the inner salt (reaction conditions: 10 mmol of fructose, 15 mol % zwitterions, 10 mL of *i*-PrOH, 120 °C for 1.5 h).

Scheme 1. Proposed Plausible Mechanism of HMF Formation from Fructose Catalyzed by PyBS



3.6. Mechanism Hypothesis. Due to the novel specificity of the inner salts with the $-\text{SO}_3^-$ group for catalytic synthesis of HMF from the dehydration reactions of fructose-based carbohydrates, the mechanism is an interesting concern for our constructed neutral catalyst system. Therefore, a mechanistic rationale portraying the probable sequence of events is given in Scheme 1 by using the fructose as the model substrate.

The dehydration reaction is believed to be initiated by the activation of the hydroxy group ($-\text{OH}$) associated to C2 of fructose ($\text{C}_2\text{-OH}$) through the hydrogen-bond interaction between the $-\text{OH}$ group and positively charged *pyridinium* head group and the negatively charged sulfonate group ($-\text{SO}_3^-$), as shown in Scheme 1.^{62–64} Then, with the elimination of the hydroxide ion (OH^-), the positively charged active transitional ion was formed, which can be stabilized by the negatively charged sulfonate group.^{64,65} After removal of the proton (H^+) from the positively charged transitional intermediate, the active intermediate 1* was formed and stabilized/activated by the inner salt through the hydrogen-bond interaction.^{64,66} The intermediate 1* can be isomerized subsequently into the more stable intermediate 1 that can be further catalyzed by dehydration through successive elimination of OH^- and H^+ to form the target HMF. Hence, the electrophilicity of the positively charged *pyridinium*-based cationic moiety and the electronegativity of the $-\text{SO}_3^-$ anionic moiety played the dual roles in the activation of substrates by a relay of cooperative hydrogen-bond and charge–charge interactions. The cooperation of the positively charged *pyridinium* head group and the negatively charged sulfonate group is crucial for the catalytic dehydration of fructose into HMF in excellent yields.

4. CONCLUSIONS

In summary, a series of imidazolium- and *pyridinium*-based zwitterions with sulfonate groups ($-\text{SO}_3^-$) have been synthesized and employed as the highly efficient neutral organocatalysts for dehydration of fructose-based carbohydrates into HMF under mild reaction conditions. It was found that the sulfonate inner salts with smaller steric hindrance afforded the excellent catalytic performance for HMF production, and PyBS presented the highest catalytic activity, achieving 88.2 and 95.1% HMF yields in *i*-PrOH and DMSO, respectively. The inner salt is solvent compatible, substrate tolerant, and recoverable. After recycling four times, the yield of HMF was still kept more than 70%. The excellent catalytic activity of inner salts is attributed to the positive cooperation of the positively charged *pyridinium* moiety and the negatively charged sulfonate group. The investigation of the detailed mechanism of this reaction is underway and will be reported in due course. We believe that the design and utilization of neutral inner salt organocatalysts provide a promising strategy for improving the yield of HMF from fructose-based carbohydrates, thus providing a better and more practical alternative to the existing methodologies and facilitating their potential applications in biochemical production.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c01111>.

Preparation of inner salts; scheme for product separation and recycling of inner salts; geometrical structures of the inner salts; controlled experiments for HMF recovery; and NMR spectra of the reaction mixture and recovered catalyst (PDF)

AUTHOR INFORMATION

Corresponding Authors

Hao Ma – College of Chemistry, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China; orcid.org/0000-0002-3615-869X; Email: thma@gdopt.edu.cn

Junjiang Teng – College of Chemistry, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China; orcid.org/0000-0002-8601-5670; Email: tjteng@gdopt.edu.cn

Authors

Biao Yu – School of Chemistry and Chemical Engineering, Lingnan Normal University, Zhanjiang 524048, P. R. China

Chaochao Yue – College of Chemistry, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China

Yanhui Qiao – College of Chemistry, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China

Ning Li – College of Chemical Engineering, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China

Tao Cai – College of Chemical Engineering, Guangdong University of Petrochemical Technology, Maoming 525000, P. R. China

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsomega.3c01111>

Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The footnote to Table 1 was missing from the original publication of this article. The footnote was added and the article reposted April 28, 2023.