ABSTRACT: In the present study, natural polyamine spermine is demonstrated as a potential basic catalyst for glucose-to-fructose isomerization. For instance, spermine achieves a decent fructose yield (30% wt) and selectivity (74%) during the single-step aqueous phase isomerization under the modest operating conditions (100 °C for 15 min). In addition to the expected reaction byproduct monosugar mannose, spermine also assists in the synthesis of rare and important monosugar, that is, psicose up to 4% wt. Psicose is a zero calorie rare sugar, exhibits a low caloric value, and possesses anti-adipogenic property. A comparative study involving other polyamines concluded that the presence of 2° amines tends to exhibit the most significant impact in improving the target product yield by releasing a higher number of OH− ions, which are responsible for isomerization through the formation of an enediol anion. An attempt was made to further improve the fructose yield through the addition of neutral salts, but it promoted a meager achievement. In an alternate study, a selective extraction strategy was followed for the isolation of fructose from the reaction mixture. The employed aryl monoboronic acid remarkably improved the net fructose concentration, that is, fructose productivity up to 75% wt (cumulative) and 70% selectivity within three consecutive extractions and isomerization cycles, which is comparatively three times shorter than that reported in the literature. Notably, spermine itself provided the essential and necessary basic environment for selective fructose extraction and glucose isomerization, ruling out the use of any external reagents and thus establishing itself as a versatile material suitable for a typical isomerization reaction in an upscaled reactor.

INTRODUCTION

The isomerization of glucose to fructose is prioritized as an essential reaction in the food and beverage industries for the production of high fructose syrup, which is frequently used in the preparation of a variety of food products.1,2 Among all the naturally occurring sugars, fructose has the highest relative sweetness and at the same time has the lowest glycemic index. In recent years, the significance of this reaction is widely recognized in the field of lignocellulose-derived sugar (glucose) conversion to liquid biofuel precursor synthesis, including 5-hydroxymethylfurfural (HMF), 2,5-furandicarboxylic acid, levulinic acid, and 2,5-dimethylfuran, wherein fructose serves as the essential intermediate compound as it has more reactivity than the initial glucose (reactant) for the subsequent dehydration reactions and is easier to convert into versatile platform chemicals.2−4 However, reversible reaction feature, thermodynamic product degradation, equilibrium between glucose and fructose sugars, and unwanted and/or uncontrolled side reactions are the typical constraints of the reaction.5 Till date, the fructose yield close to the thermodynamic equilibrium (up to 42% wt and 80% selectivity) has been achieved only by enzyme-assisted catalysis (glucose isomerase) and is widely employed for the commercial level production of fructose. However, this method suffers from serious drawbacks, including expensive enzymes, prolonged reaction, irreversible deactivation, the addition of buffers as a reaction supplement, and so forth.5,6 Alternatively, intensive investigations have been undertaken by the researchers to develop an efficient chemo-catalyst system for the isomerization reaction. In view of establishing a low-cost technique and faster and safer post-synthetic reaction, most studies recommended the Lewis acids or base catalysis for the glucose isomerization in the aqueous phase. However, the performance of those chemo-catalysts is slightly lower than the classical enzymatic conversion in terms of the product yield (averagely 30−40% wt).2,6 Also, the Lewis acid and Bronsted base-catalyzed isomerization accommodates the uncontrolled side reaction, forming unwanted products, including humins

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and other organic acids which negatively impacts the target product synthesis. For example, recent studies have introduced organic amines like basic amino acids, polyethylenimine (PEI), and trimethylamine as a potential basic catalyst for glucose conversion that resulted in a better product concentration (30–35% wt and 60–75% selectivity), which is comparatively higher than the traditional Bronsted base isomerization, that is, typically 10–36% wt and 40–73% selectivity. Furthermore, the kinetic and mechanistic investigations of the organic amine-catalyzed glucose isomerization reactions disclosed that those followed the typical Lobry de Bruyn–Alberda van Ekenstein (LdB–AvE) rearrangement mechanism, where the C-2 proton on the acyclic glucose is abstracted by the base, resulting in the formation of a 1,2-enediol intermediate, followed by a proton shift from O-2 to O-1 and protonation of C-1 for the formation of fructose. Hydroxide (OH\(^-\)) ions generated after the protonation of lone pair of nitrogen atoms in the amines proved to be the most influencing species rather than amine groups for favorable glucose transformation reactions. Of course, the basicity of amines is not only dependent upon the electron releasing (+I) effect of the substituted alkyl or aryl group but also on other critical factors like steric and hydration effects. Based on these conclusive factors, secondary (2\(^\circ\)) amines can be considered more basic than primary (1\(^\circ\)) and tertiary (3\(^\circ\)) amines and can influence higher glucose conversion. The above fact is evidenced in the literature, wherein 33–36% fructose yield with 66–77% selectivity was achieved in the presence of PEI consisting a higher number of 2\(^\circ\) amines than 1\(^\circ\) and 3\(^\circ\) in the mere aqueous medium. Not surprisingly, the organic amine-based catalysis is accompanied by undesired byproducts, such as N-substituted glycosylamine via reaction with sugars, so called Maillard reaction.

In the present study, we investigated the potential use of amine-type organic base catalysts such as spermine, spermidine, cadaverine, and diethylenetriamine, a class of biologically active polyamines, in the glucose-to-fructose aqueous phase isomerization reaction. Chemical structure, nature of the amine groups (primary, secondary, and tertiary amines), and \(pK_a\) are the major factors that affect amine catalyst activity. Among these chemical catalysts, spermine is of particular interest, it is one of the three major polyamines present in plant species and is an essential constituent of eukaryotic and prokaryotic cells and has been extensively employed as a low-cost and eco-friendly catalyst in the production of value-added chemicals, pharmaceuticals, polymers, and pesticides. Structurally, it is a linear aliphatic polyamine in a zig-zag fashion consisting of 2\(^\circ\) amines in the center and two pendant 1\(^\circ\) amine groups on the edge. The role of the amines is to generate a hydroxide ion necessary to catalyze the isomerization reaction. Based on the comprehensive studies using different polyamines, the structural architecture and \(pK_a\) values could significantly influence the basicity of the reaction medium.

In recent years, efforts are being made to overcome the unfavorable aldose-to-ketose conversion equilibrium for achieving higher productivity, for example, sequential selective extraction of fructose and isomerization strategy, wherein fructose forms complexes with active binding agents like lipophilic aryl boronic acids. Till date, numerous studies have used boron acids and its derivatives, including phenylboronic acid (PBA), naphthalene-2-boronic acid (NBA), ortho-hydroxymethyl phenylboronic acid, and ortho-dimethyl-aminomethyl phenylboronic acid, because it has the tendency to form more stable complexes preferably with ketoses over aldoses, thereby providing the opportunity for aldose–ketose separation during the isomerization reaction. One such example is that up to 72% of fructose extraction with 76% selectivity could be achieved using PBA as an extraction agent under optimized conditions from a glucose-fructose mixture. Similarly, ~89% fructose was extracted using NBA with 90% purity through the back-extraction technique during the preparation of 5-HMF from glucose. Over the past decade, this technique has been popularly used for sensing of monosaccharides in biological systems because boronic acids are ideal molecular receptors, predominantly for cis-1,2- or 1,3-diols (e.g., glucose, fructose, and xylose). Moreover, it rapidly and reversibly interacts with carbohydrates present in the aqueous medium under only basic conditions, preferably at pH ≥ 8. On the basis of the tendency of spermine to create basicity while reacting with water, we speculate that polyamine can offer versatile performances like maintaining basic condition favorable for glucose isomerization and fructose extraction in the presence of boronic acids through the compensation of OH\(^-\) ions and thus may provide a breakthrough in the glucose–fructose isomerization reaction.

## RESULTS AND DISCUSSION

**Spermine-Catalyzed Glucose-To-Fructose Isomerization.** Several comprehensive studies have substantiated the mechanism of glucose transformation to fructose under basic solutions that it first involves the formation of a 1,2-enediol intermediate which prompts the aldose protonation at the C-2 position and the ketose protonation at the C-1 position. Relative studies often advice that it is not easy to find clear correlations between the structural properties and catalytic performance of organic amines. Therefore, the study was limited to optimize the process parameters, such as catalyst dose, temperature, reaction time, and addition of neutral salts to achieve maximum fructose productivity. The various physicochemical properties of spermine including miscibility in water and alcohol solvents, melting point 30 °C (solid form at room temperature), and boiling point 150 °C are required for a typical reaction. Naturally, it consists of both 1\(^\circ\) (two at the sides) and 2\(^\circ\) amines (two in the middle), as displayed in Figure S1, and the respective \(pK_a\) values of its conjugated acids are estimated to be 10.1–10.9 (1\(^\circ\)) and 7.9–8.4 (2\(^\circ\)), respectively. Consequently, the effect of the catalyst dose (spermine) to the isomerization reaction was studied within 2 to 18% mol rate at four equal intervals. The pH of the reaction mixture prior to the addition of the catalyst was observed to be 7.5. The results obtained with the corresponding incremented dosage levels of spermine inferred that it had a detrimental effect on fructose productivity. For instance, an increasing fashion of response was achieved up to the optimum, that is, 6% mol dose, yielding a 29% wt fructose yield, and 76% selectivity and further incremented dosages resulted in a relatively 13% lower yield and 26% selectivity (Figure S2). The possible reason for the decrease in the fructose yield with an increased dose of spermine could be due to the higher basicity generated through the release of more OH\(^-\) ions which in turn could thermally degrade the fructose in the glucose transformation reaction at 90 °C for 15 min. Moreover, the consistently increasing result of glucose conversion, that is, averagely 41% at each intermittently increased loadings of the catalyst suggested that the isomerization reaction was accompanied by an uncontrolled as well as
irreversible sugar degradation under harsh conditions and led to the formation of unwanted side products (e.g., formic, acetic, glycolic, and lactic acid) and condensation products (like humins). These side products can be excluded from the scope of the work because of the determination complications.

Additionally, the change in color of the reaction medium from pale yellow to deep brown during the course of the reaction indicated that the typical Maillard reaction was proceeded due to the interface between amines and reducing sugar and produced the N-substituted glycosylamine under basic conditions, as displayed in Figure S3. The results obtained were in good agreement with the literature reports.7,8,16 It is interesting to notice that spermine also assisted in the synthesis of pseudofructose (psicose) to the extent of up to 4% wt along with the usual byproduct mannose (up to 5% wt) (Table 1).

Figure 1. $^{13}$C NMR spectrum of (a) standard fructose, (b) glucose, and (c) isomerization mixture of sugars from 2-D-glucose. Reaction conditions: 10% wt glucose, 6% mol spermine relative to glucose, 1 mL of D$_2$O/H$_2$O at 100 °C for 15 min.

The hypothesis about the mechanism and production of fructose as a target product and mannose and psicose as byproducts in the isomerization reaction catalyzed by spermine was further supported by the acquired $^1$H, $^{13}$C, and HSQC NMR characterization results. It might be useful to recall that characteristic glucose can co-exist in both forms as ring and open chain forms in aqueous medium. Based on the analysis, it can be summarized that deprotonation of O-1 and cleavage of C1−O5 ether linkage bond led to the formation of an open ring structure of glucose, and hence, glucose isomerization started from an open ring structure with organic polyamine as a catalyst. While amines reacting with H$_2$O molecules generated OH$^-$ anions which abstracted the proton from C-2 of glucose resulting in the formation of a 1,2-enediol.

### Table 1. Results of Effect of Temperature on Spermine-Catalyzed Glucose Isomerization in the Aqueous Phase

| temp (°C) | $Y_{Fru}$ (% wt) | $Y_{Man}$ (% wt) | $Y_{Psi}$ (% wt) | conv$_{Glu}$ (%) | carbon balance (%) | TOF$_G$ $\times 10^{-3}$ | TOF$_F$ $\times 10^{-3}$ | $k$ $\times 10^{-3}$ (s$^{-1}$) |
|-----------|-----------------|-----------------|-----------------|-----------------|------------------|------------------|------------------|------------------|
| 40        | 3.9             | 0.5             | 0.0             | 14.3            | 74.23            | 0.67             | 4.8              | 0.05             |
| 60        | 7.9             | 0.6             | 0.0             | 17.7            | 44.64            | 1.37             | 5.4              | 0.30             |
| 80        | 24.6            | 3.0             | 2.0             | 67.7            | 36.28            | 4.24             | 6.5              | 0.50             |
| 100       | 29.7            | 5.0             | 4.1             | 73.8            | 40.27            | 95.48            | 5.13             | 7.1              | 0.70             |
| 120       | 28.6            | 4.8             | 3.8             | 63.0            | 42.90            | 91.24            | 6.17             | 7.6              | 1.60             |

*Reaction conditions: 6% catalyst dose for 15 min. TOF$_G$/TOF$_F$—Turn over frequency is calculated as mole of converted glucose and fructose formed per mole of nitrogen atom contained in spermine per unit second. Carbon balance is derived based on the difference between moles of carbon in products (fructose and mannose) and unreacted glucose and to the mole of carbon in the initial glucose. $Y_x$ and $S_x$ are the yield and selectivity data of the respective compounds.
intermediate and the formation of mannose took place through the rotation around the C2–C3 bond. For instance, $^{13}$C NMR revealed the characteristic peak of mannose at $\delta = 97.7$ ppm, thereby confirming the production of mannose as a reaction byproduct (Figure 1c). Further, the little rearrangement in the 1,2-enediol intermediate led to the synthesis of the target product fructose because the formation of ketose predominated and isomerization took place. Further, OH$^-$ anions abstracted proton from C-3 of fructose leading to the formation of a 2,3-enediol intermediate and ultimately, yielded psicose, which was once again confirmed through the $^{13}$C NMR displaying the characteristic peak at $\delta = 74.15$ ppm (Figure 1c). In addition to the characteristic peaks of obtained sugars, the $^1$H NMR of the isomerized reaction mixture disclosed few minor peaks in the region from $\delta = 2$ to 2.5 ppm and was attributed to the presence of residual spermine (Figure 2b). Thus, the fate of all the products obtained during isomerization of glucose was dependent upon the formation of the 1,2-enediol intermediate. Through NMR results, the formation of this important intermediate was confirmed by comparing the $^{13}$C NMR of the isomerized mixture obtained from glucose and glucose-2-D in water and water-$^2$D ($D_2O$), respectively. Because deuterium was present at the C-2 position of glucose-2-D, its NMR spectrum was found to be a bit different than the unlabeled glucose (Figure 1). The three peaks around $\delta = 3.15$ ppm of glucose were missing in the spectrum of glucose-2-D, as compared to unlabeled glucose (Figure 2a). Moreover, the NMR spectrum of fructose obtained from labeled glucose-2-D in $D_2O$ did not have multiple peaks around $\delta = 3.5$ ppm because of the presence of a deuterium atom at the C-1 position (Figure 2b).$^{11}$ HSQC NMR characterization analysis of the isomerized mixture confirmed the fructose production, and the results are comparable to the standard solution of sugars (Figure S4). Also, the isomerized mixture of sugars obtained from unlabeled glucose in water displayed all characteristics peak of glucose and fructose, indicating that fructose obtained from glucose did not have deuterium at C-2 (Figure S4a). The decrease in the resonance signal at $\delta = 63.8$ and 62.6 ppm in the NMR spectra of fructose obtained from glucose-2-D confirmed the presence of deuterium at the C-1 position gained from $D_2O$ (Figure S4b). Thus, these results verified that the mechanism of isomerization of glucose catalyzed by the spermine advanced via the 1,2-enediol intermediate mechanism, including the removal of a proton at the C-2 position, followed by regaining a proton from solution. The formation of the 1,2-enediol intermediate was also confirmed by UV spectroscopy. Separation and purification of reaction media are often challenging, especially when homogeneous catalysts are employed.$^9$ However, homogeneous catalysts have advantages over heterogeneous catalysts, such as the possibility of carrying out the reaction at milder conditions, higher activity and selectivity, ease of spectroscopic monitoring, and controlled and tunable reaction sites, but have limited industrial applications due to the difficult and costly catalyst separation and recovery. The unwanted colored byproducts in the isomerized mixture were separated by simple purification with activated carbon.$^7$ The reactant mixture turned colorless after the purification as colored byproducts got adsorbed over the activated carbon. The comparative UV spectra of the isomerized solution before and after the purification are given in Figure S5. A sharp peak at 286 nm and a broad peak at 330 nm in the UV spectrum of the colored solution indicated the presence of the 1,2-enediol intermediate and colored by-products which disappeared after the purification with activated carbon due to the drop in the pH value from 9 to 6.$^{22}$ A weak peak at 260 nm in the UV spectrum of the colorless solution might be due to the neutral acyclic aldehyde form of glucose.$^{23}$ To further confirm the presence of psicose as a byproduct in the isomerization reaction, the traditional fermentation method was employed to the resulting reaction mixture using Baker’s yeast. As a result, all the fermentable sugars, such as glucose, fructose, and mannose, got entirely degraded after 24 h fermentation except psicose and those led to the formation of ethanol with a least amount of methanol,$^{24}$ based on the high-performance liquid chromatography (HPLC) analysis (Figure S6). The non-deconvoluted chromatograms of the other sugar compounds and reaction mixture are shown in Figure S7. It is established that psicose is known as a rare sugar moiety of an antibiotic psicofuranine, not found in nature in situ, and moreover, a non-fermentable sugar.$^{25}$ Psicose was further isolated from the above reaction mixture after fermentation except psicose and those led to the formation of ethanol with a least amount of methanol, based on the high-performance liquid chromatography (HPLC) analysis (Figure S6). The non-deconvoluted chromatograms of the other sugar compounds and reaction mixture are shown in Figure S7. 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temperatures up to 80 °C, nominal fructose concentration was attained, that is, 25% wt yield with 68% selectivity only after prolonged isomerization (24 h) (Figure 4a–c). The highest fructose productivity was achieved at 100 °C (30% yield with 74% selectivity), and a further rise in temperatures showed an inverse effect, resulting in a ~26% relatively lower fructose yield (Figure 4d). The plots of glucose concentration versus time at different temperatures while other parameters maintained constant (6% mol catalyst dose) are displayed in Figure S9. Concerning reaction byproducts, nearly similar to the fructose synthesis response trend was attained to mannose with the corresponding rising temperatures. However, no or less formation of psicose was noticed up to 80 °C, and the formation up to 4% wt was observed at 100 °C, suggesting that 2,3-enolization is temperature-dependent. The results obtained were compared and found to be consistent with the literature. Hence, the 6% catalyst (spermine) loading to glucose at 100 °C for 15 min was selected as an optimum condition for further evaluation studies. Although a consistently increased glucose conversion was achieved, the unwanted side reaction impeded the target product formation under harsh conditions. Additionally, the turnover frequency (TOF), calculated as a mole of converted glucose and produced fructose per mole of nitrogen atom contained in spermine per unit time (Table 1) proposed that activation of polyamine was highly dependent on temperature ($R^2 = 0.95$ while correlating with the reaction temperature as shown in Figure S10). The specific rate constant data of the reactant well supported the above statement that it increased as when the temperature increased (Table 1), but the maximum fructose yield was achieved at 100 °C, suggesting that a higher thermal degradation of products led to unwanted side product formation under raised temperatures. Overall, results displayed that spermine genuinely promoted the degradation of a carbohydrate skeleton to achieve a wider spectrum of products (predominantly fructose) through two different enolization reactions in an aqueous medium. The relative differences in the product (including byproducts such as mannose and psicose monosugars) concentrations were probably attributed to the stability of the intermediate molecules under a basic environment.

**Evaluation of Polyamines for Glucose-To-Fructose Transformation.** Subsequently, several other natural and synthetic polyamines, such as cadaverine, diethylenetriamine, and spermidine, which are having an identical linear alkyl chain conformation but differs in the number of 1<sup>ε</sup> and 2<sup>ε</sup> amines (as displayed in Figure S1) have been evaluated for the comparative studies in glucose isomerization in the aqueous phase. The estimated pKₐ values of the corresponding polyamines lie in the range between 10 and 11. The kinetic results obtained under the optimum conditions (6% mol catalyst dose at 100 °C for 15 min) showed that all of the polyamines proceeded in the same pattern for the formation of fructose (Figure 5), that is, a gradual increase in the fructose yield and selectivity up to the optimum condition and beyond that a decreasing trend of responses were recorded which could be attributed to the participation of unwanted side reactions under higher severity conditions. Among tested polyamines, cadaverine (has two 1<sup>ε</sup> amines) showed the least isomerization performance, that is, 22% wt fructose yield and 47% selectivity (Figure 5a). However, others (diethylenetriamine and spermidine) have an additional 2<sup>ε</sup> amines in the centre of the linear structure responded rather 23% wt yield and 25% selectivity over cadaverine. Overall, in anticipation, the results obtained with other polyamines were comparatively lower than spermine (has two 2<sup>ε</sup> amines located at equal distances in the linear chain with two 1<sup>ε</sup> amines at both ends) which achieves an exceptionally higher result, that is, up to 12–42% fructose yield and 23–54% selectivity as compared to other tested polyamines (Figure 5d). The findings honestly suggested that structural characteristics of polyamines, particularly the presence of 2<sup>ε</sup> amines affected the glucose transformation. Thus, the combinatorial effect of 1<sup>ε</sup>, 2<sup>ε</sup> amines, and other critical factors, such as solvation effects and steric hindrance tend to influence the glucose-to-fructose isomerization positively. While referring the fructose selectivity, a 39% relative increment was observed with the tested polyamines in the order of spermidine > diethylenetriamine > cadaverine possibly attributed to the increased basicity...
strength, though all had nearly the same $pK_a$ values. Naturally, in addition to the protonation ability of the nitrogen atom in the amine group, it can form inter- and intra-molecular hydrogen bonds through their lone pair of electrons. Hydrogen bonding between amines and glucose is said to be beneficial for the adsorption of glucose molecules, but the inter- and intra-molecular hydrogen bonding with water hampered the glucose adsorption for the reaction. At the same time, the hydrogen bonding with water and fructose molecules significantly influenced the accessibility of glucose to amine, thereby obstructing the isomerization reaction. Therefore, the low catalytic performance of the cadaverine was most likely due to the result of the strong inter- and intra-molecular hydrogen bonds. However, other polyamines showed an improved effect depending on the number of $2^0$ amines present, which provided less chance to form inter- and intra-molecular hydrogen bonding due to steric hindrance. Moreover, the alkyl groups could enhance the basicity through raising the energy of the lone pair of electrons. However, the steric hindrance offered by the substituent groups could diminish the basicity of amine. In a nutshell, all of the tested amines showed identical responses toward the synthesis of mannose and psicose monosugars; however, the concentrations were varied depending upon the selected polyamines. Except for cadaverine, other polyamines exhibited nearly the same concentrations averagely 4.9 and 3.9%, respectively (mannose and psicose), corresponding to the increased basicity in correlation with the $2^0$ amines. While discussing glucose conversion and carbon balance, it was observed that only diethylenetriamine promoted higher glucose conversion (43% beyond the average), but it also failed to control sugar degradation through side reactions by offering higher basicity to the medium due to the proximity placement of $1^0$ and $2^0$ amines in the linear alkyl chain, suggesting that additional effects due to the solvation of the amines or interactions between the amines and the carbohydrates may play a role that remained to be elucidated. Otherwise, all the amines showed a fair result with the corresponding increased basicity.

**Augmentation of Fructose Productivity with a Modified Medium.** The above results indicated that higher electron releasing capability of the alkyl groups of spermine facilitated the glucose transformation and therefore, an attempt

![Figure 4](https://dx.doi.org/10.1021/acsomega.9b03918)
was made to improve the target product yield by modifying the reaction medium through external addition of neutral salts.

In theory, the polyamine could form hydrogen bonding with H₂O molecules by gaining a proton from H₂O (reversible reaction) and resulted in the release of OH⁻ anions, responsible for the glucose isomerization. This routine performance made the polyamine with a positively charged polyatomic ion (quaternary ammonium ion), which could specifically bind with the anion of neutral salt (e.g., K⁺ Cl⁻) through the electrostatic attractive interactions. As a result, the specific binding could shift the acid–base reaction equilibrium between amine and water, which could favorably generate more OH⁻ ions in the medium. The evaluation test was performed by the addition of individual common neutral salts, such as KCl, NaCl, NaBr, KI, and LiCl, in aqueous medium in the presence of spermine under optimum conditions at pH 8.5. The comparative result displayed that KCl exhibited superior characteristics, attaining 33% fructose yield and 73% selectivity along with 6% wt mannose and 5% wt psicose (Figure 6). Perhaps KCl has the lowest covalent character among all the neutral salts and highest ionic property. Only <2% variation of results was achieved with the salts (probability, p is >0.05 and 1.28 standard deviation) and might be attributed to the slight differences in the ionization potential between 7.5 (for KI) and 10.01 eV (for LiCl). Unfortunately, even with the synergistic effect of addition of neutral salts and polyamine (spermine) in the reaction medium, there was only 3% increase in yield and selectivity compared to the reaction with absence of salts, indicating that the addition of salts could have increased the favorable pH of the reaction (≥9.0) which might have given rise to the unwanted side reactions.

Likewise, organic solvents also help in shifting the equilibrium between glucose and fructose molecules toward the latter, that is, in favor of fructose; as a result, improved productivity is achieved well above the theoretical yield. Polar aprotic solvents, such as dimethyl sulfoxide and N-methyl-2-pyrrolidone, have been commonly used in the conventional studies owing to its higher monomeric sugars dissolution capacity, but those offer significant complications because of its high boiling point (189–204 °C) property and other toxic side effects. In an alternative, recent studies have extensively explored the use of lower alcohols in the carbohydrate conversion processes and achieved impressive yield results. For instance, highest fructose yield (56% wt) and product selectivity (80%) was achieved over hydrotalcite heterogeneous catalyst in ethanol medium, wherein the layered hydroxide structure exhibited the basic sites for effective glucose isomerization. It was postulated that the addition of ethanol into water shifted the isomerization equilibrium
between glucose and fructose toward the latter molecule.\textsuperscript{27} The solvation effect could reasonably explain this shift in equilibrium that fructose more readily underwent the solvation by ethanol as compared to the glucose. Therefore, we tested the glucose isomerization reaction using the diluted lower alcohols (ethanol/methanol) at 50:50 v/v ratio.\textsuperscript{32,33} Unfortunately, the reaction with ethanol resulted in 15% fructose yield and 74% selectivity, was comparatively 2-times lower yield than the aqueous phase reaction achieved after prolonged isomerization (up to 4 h) (Figure S11). Whereas, diluted methanol responded comparatively worse say 10% wt yield and 57% selectivity than the other. The possible reason behind this poor rate of product formation was the insufficient protonation of polyamine to release the OH\textsuperscript{−} ions necessary to maintain the basic ambient for isomerization, based on the proton exchange mechanism. This statement was verified with the results obtained when the reaction was conducted using plain alcohol medium and 4−5% fructose yield with 57−64% selectivity was observed (Figure S11). Nevertheless, the systems (both diluted and plain forms) skipped the epimerization reaction, allowing no or less formation of mannose (an epimer of glucose) and psicose (an epimer of fructose) and that greatly helped in achieving a higher selectivity (up to 74%) even at low productivity (15% wt) (Figure S8). Thus, the above results projected that OH\textsuperscript{−} ions were contributing more for the glucose transformation that could be achieved through complete protonation of amines while reacting with water.

### Selective Extraction and Isomerization for Higher Fructose Production

Recent studies have demonstrated the selective fructose extraction strategy to isolate it from the post-isomerization mixture consisting of equal or more amounts of glucose and other reaction byproducts (typically mannose and psicose) for achieving an improved product concentration further beyond the thermodynamic equilibrium conversion, for example, 75% yield and 70% selectivity. In a typical practice, monoboronic acids and its derivatives have been popularly employed in medical applications for biosensing of monosaccharide sugars. To better understand the monosaccharide complexation mechanism, assuming the mixture predominantly consisted of aldose and ketose, the boronic acid derivatives existed mostly in their conjugate-base form (BA\textsuperscript{−}) at the organic−aqueous interface developed through the addition of an organic extraction solvent (1-octanol). The resulting conjugate base could bind and form stable complexes preferably with ketoses (K) than aldoses to form a boronate ester analogous to the carboxylic acid ester (BAK\textsuperscript{−}), which typically accumulates at the interface. The introduction of a quaternary ammonium salt (Q\textsuperscript{+} Cl\textsuperscript{−}), such as Aliquat 336, to the organic phase enhanced the dissolution of the negatively charged conjugate-base in the organic phase. The ion-pair formation between the ammonium cation (Q\textsuperscript{+}) and ester conjugate (BAK\textsuperscript{−}) yielded a neutral complex (Q\textsuperscript{+}Cl\textsuperscript{−}) which was soluble in the organic phase, thereby allowing the movement of sugar in priority to ketose from aqueous to the organic phase. The whole phenomenon was conditionally effective when the reaction medium was maintained at basic condition pH ≥ 8. The strength of boronic acid binding to monosaccharides was determined by the orientation and relative position of the hydroxyl groups in the system. It could be noted that spermine favored the synthesis of other various monosaccharides to an extent which was rather beyond our interest like the formation ofmannose and psicose during the glucose-to-fructose isomerization. Therefore, initially, screening of monoboric acids, such as NBA and PBA, which were selected from literature reports as carbohydrate complexing agents, was performed to verify their suitability for spermine-assisted isomerization for selective fructose extraction. In a typical practice, it is critical to maintain the boronic acid concentration to the Aliquat 336 ratio under ideal conditions. The test was performed using the 1-octanol organic medium consisting of known concentration of PBA and Aliquat 336 (at

### Table 2. Result of Sequential Extraction and Isomerization Using Naphthalene-2-boronic Acid as the Complexing Agent

| run | [Glu]₀ | [Fru]₀ | [Man]₀ | [Psi]₀ | [Glu] | [Fru] | [Man] | [Psi] | Run I | Fructose (%) | Glucose (%) | Mannose (%) | Psicose (%) | Overall-Isomerization (%) |
|-----|-------|-------|--------|--------|--------|-------|-------|-------|------|-----------|-------------|-------------|-------------|-------------|-------------------------|
| I   | 88    | 12    | 0      | 54     | 32     | 4.93  | 4.12  |       |      | 60.82     | 14.23       | 30          |             | 75.20       | 23.33       |
| II  | 85    | 15    | 0      | 52     | 34     | 4.93  | 4.3   |       |      | 58.79     | 18.84       | 53          |             | 75.20       | 23.33       |

\textsuperscript{a}Isomerization conditions: 6% spermine dose at 100 °C for 15 min. \textsuperscript{b}Extraction conditions: 2 mL of solution containing 3% mol of spermine, fructose and glucose (aqueous phase), and 2 mL of solution containing 0.1 M NBA, 0.4 M Aliquat 336, 1-octanol (organic phase) were shaken together for 1 h at room temperature. \( R_x \) (calculated as the difference in the concentration of monosugar before and after extraction) and \( Y \) is the yield of sugars, where \( x \) can be glucose, fructose, mannose, and psicose.

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equal ratio) to the aqueous phase isomerization catalyzed by spermine and a biphasic system was generated. However, a strong interaction between PBA and monosugars was noticed, resulting in 43% glucose extraction, which was not expected. Therefore, the combination was optimized to 4:1 (PBA/Aliquat 336) as it depicts the highest fructose selectivity (70%) and lowest glucose extraction (31%) (Table S3). The recovery of fructose and other sugars was estimated through the typical back extraction protocol where the organic medium was treated with dilute H2SO4 to lower the pH. The organic extraction process could be repeated to the same aqueous medium for the complete recovery of fructose. The protocol took six consecutive extractions within a single extraction procedure to achieve the maximum result, that is, 44% fructose recovery and 63% selectivity (Table S3). NBA exhibited better results under the same operating conditions, that is, up to 70% fructose recovery and 70% selectivity but within four consecutive extractions (Table 2), suggesting the structural characteristics of aryl monoboronic acid could greatly influence the binding affinity to carbohydrates (Figure 7). Subsequently, the aqueous mediums which were rich in residual glucose concentration from all of the extraction steps were collectively isomerized with the additional supplementation of spermine to maintain the desired pH and to compensate the loss of OH− anions due to the transfer to the organic phase (based on the initial and final pH values of the medium). The considerably improved fructose yield results with the sequential extraction and isomerization procedures, that is, relatively 70% encouraged to repeat the cycle to achieve the highest 75% fructose yield and 70% selectivity up to 3 and beyond that, no significant improvement was achieved (≤1% wt fructose yield).

It was concluded that each of the extraction procedure required at least 4 repeat extractions and all of them attained nearly the same proportion of fructose recovery say averagely 22, 16, 12, and 9% (Table 2 and Figure 8). In addition, all of the extraction protocols carried traces of other monosugars, including glucose, mannose, and psicose up to 5% wt and it was significant beyond 4 extractions, particularly to glucose. This attitude of NBA is due to its binding affinity to OH groups of other monosaccharides to a certain extent. The binding affinity of aryl boronic acids to sugars is generally arranged in the order of fructose > galactose > mannose >...
glucose.\textsuperscript{34} The formation of the diol–borate complex due to the covalent binding between sugars and NBA was also confirmed by fluorescence spectroscopy. Fluorescent boronic acids have been extensively used as fluorescent probes for the detection of biologically important monosaccharides. Figure S12 displays the fluorescence spectrum of NBA dispersed in 1-octanol and Aliquat 336 at an excitation wavelength of 370 nm and a sharp emission peak at $\lambda = 408$ nm was observed,\textsuperscript{35} whereas the spectrum of the assay containing isomerized mixture of sugars bonded covalently with NBA in organic phase exhibited significant decrease in fluorescence intensity along with red shift due to the photoinduced electron transfer mechanism, indicating the formation of the diol–borate complex which is non-fluorescent in nature.\textsuperscript{36} The different binding characteristics of these sugars can be attributed to the different dihedral angles of diols of these sugars.\textsuperscript{37} Based upon the order of affinity of boronic acids toward sugars, their corresponding selective binding positions and mechanisms have been proposed. It has been reported that the relative affinity of boronates for diols in most carbohydrates is of the order: cis-1,2-diol > 1,3-diol $\gg$ trans-1,2-diol.\textsuperscript{38} Thus, certain monosaccharides have an intrinsically higher affinity for boronic acids. Taking all the important considerations into account, we attempted to identify the binding position between sugars and boronic acids, for example, NBA tended to bind at C-1 and C-2 positions of $\alpha$-D-glucopyranose, and $\alpha$-D-glucopyranose cis-C-1,2 diol borate complex is formed. Similarly, $\alpha$-D-mannopyranose cis-C-2,3 diol borate, $\beta$-D-fructofuranose cis-C-2,3 diol borate, and $\alpha$-D-furanopsicose cis-C-3,4 diol borate complexes were expected to form from corresponding sugars depending upon how easily these positions are available to boronic acids. Based on the binding affinity and stability of these complexes, around 80% D-psicose was extracted from the reaction mixture, which is relatively 33% higher than fructose extraction, whereas around 46% D-mannose and 14% D-glucose were extracted from the mixture, and these values are comparatively 40 and 90% lower than fructose extraction (Table 2). Therefore, the above order can be comfortably rearranged as psicose $>\text{fructose} > \text{galactose} > \text{mannose} > \text{glucose}.~\textsuperscript{35}$ Figure 8 vividly portrays the distribution of sugars during each of the isomerization and subsequent extraction procedures. Moreover, the psicose–borate complex when interacted with enzyme systems (like DPEase) shifted the equilibrium between fructose and psicose, thereby enabling the greater formation of psicose from fructose.\textsuperscript{19,25} Further, the borate of the psicose–borate complex could be easily removed using the Amberlite IRA-743 and Dowex 50 resins.\textsuperscript{39} This approach creates a new avenue to produce a relatively attractive sugar molecule through the single-step conversion from bio-derived glucose. Moreover, the use of spermene also ruled out the requirement of buffers to maintain the pH during the extraction protocols (i.e., $\geq$8.0) and thus managed to serve as a catalyst and buffer reagent during the glucose isomerization and selective fructose extraction. Overall, the attractive yield result (30% yield and 74% selectivity) obtained in each isomerization stage by the influence of spermene succeeded over the literature reports involving either inorganic phosphate buffer reagents ($\text{NaH}_{2}\text{PO}_{4} + \text{Na}_{2}\text{HPO}_{4}$) or expensive enzymes (glucose isomerase), which achieved the fructose yield of 15–45% wt and $>52\%$ selectivity.\textsuperscript{1,14}

II CONCLUSIONS

In summary, the current study demonstrates the endogenous polyamine spermene as a potential basic catalyst for glucose-to-fructose isomerization in the aqueous phase. Appreciably, a maximum of 30% fructose yield and 74% selectivity result was attained during the single-step isomerization under the modest reaction conditions with the aid of predominant $2^\theta$ amines of spermene. Further, the polyamine cooperated effectively during the subsequent extraction and isomerization procedures, achieving a reasonable fructose recovery with the help of aryl monoboronic acid, NBA. However, traces of other important reaction byproducts, such as mannose and psicose were also present. It unfastens a new avenue that an appropriate protocol can be applied for further selective extraction of psicose, a rare sugar molecule, to treat with enzyme systems when it is in the psicose–borate complex form to achieve higher product concentration from fructose. Overall, this study shows that the natural endogenous polyamine promoted the synthesis of fructose from glucose through the sequential isomerization and extraction procedures, achieving the highest productivity of 75% wt fructose yield and 70% selectivity within shorter cycles as compared to the literature. This strategy of fructose production could help in improving the furan product concentration during the subsequent dehydration reaction.

II MATERIALS AND METHODS

Chemicals. The reagents used in the present study are listed in Table S1. All the chemicals were of analytical grade and used as received without any modification. Dried Baker’s yeast (crown) was purchased over the counter from the local market in Mohali, India for the fermentation experiment.

Glucose Isomerization. The glucose isomerization reaction was carried out in a 5 mL thick-walled glass reactor. In a typical reaction, glucose [1 mL of 10% (w/v) stock solution prepared using deionized (DI) water] and the catalyst (homogeneous polyamine) were loaded into the glass reactor (maximum 18% mol on glucose) and sealed tightly. The reactor was pre-warmed depending on the reaction temperature and heated up to 120 °C using an oil bath on a hot plate under continuous stirring at 200 rpm. The reaction was allowed to proceed for variable times (1–1440 min) and then stopped immediately by cooling the reactor in an ice bath. Small aliquots of the sample were collected intermittently, diluted using DI water, and stored in the refrigerator at 4 °C until used for sugars and other organic acid analyses. The experiments were performed in duplicate, and error bars were plotted. For conducting the isomerization reaction in a modified medium, the above procedure was repeated with external addition of neutral salts (KCl/NaCl/NaBr/KI/LiCl) at 10% wt or just replacement of water medium into diluted alcohol solution (ethanol/methanol) at a 50:50 ratio (aqueous to alcohol).

Selective Fructose Extraction. After the isomerization reaction, selective extraction of fructose from the post-reaction liquid medium (aqueous) was performed by external addition of an organic phase which is comprised of PBA/NBA (for complexion of keto molecule) and Aliquat 336 (for dissolution of boronic acid in the organic medium) dissolved in 1-octanol. Briefly, equal volumes of organic phase and aqueous phase (at least 2 mL from the isomerization experiment) were continuously stirred for an hour at room temperature. Afterward, both phases were separated by
centrifugation for 15 min at 8000 rpm. Once the biphasic layer regenerated, the organic phase was separated that consisted of 1-octanol and the aryl borate–fructose complex. After splitting the phases, back extraction was performed by treating the organic phase with 0.4 M H₂SO₄. Meanwhile, the collected aqueous phase was once again treated with fresh organic phase with added spermine (3% mol) to maintain the pH at 8.5 required for isomerization. This organic extraction procedure was consecutively repeated for at least four times to achieve complete recovery of synthesized fructose. After all repeated extraction procedures, the left behind aqueous solution was isomerized with additionally supplemented glucose (depending on the residual concentration) to normalize the reactant concentration and spermine (6% mol) under the same conditions maintained for the first run. Before each isomerization step, a small aliquot was collected, diluted using DI water, and stored in the refrigerator at 4 °C until used for sugars analysis. The whole extraction procedure was carried out in the absence of salts because salts could obstruct the movement of the sugar complex to organic phase in the isomerized mixture.

The results reported from the extraction steps are calculated as

Glucose conversion % = \( \frac{\text{Glu}_{\text{final}}}{\text{Glu}_{\text{initial}}} \times 100 \)

Fructose yield % (wt) = \( \frac{\text{Fru}_{\text{final}} - \text{Fru}_{\text{initial}}}{\text{Glu}_{\text{initial}}} \times 100 \)

Fructose extraction selectivity % = \( \frac{\text{fructose in the aqueous phase}}{\text{fructose and glucose in the aqueous phase}} \times 100 \)

**Characterization and Analysis Method.** All the pH measurements were made using a digital Mettler Toledo pH meter (FiveEasyPlus FP20). Colour measurements of the reaction mixture were done on the Shimadzu UV–vis spectrophotometer (UV-2600). The fluorescence spectrum of the samples was recorded on a Cary Eclipse Fluorescence Spectrophotometer (Agilent Technologies). ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE 400 MHz NMR spectrometer. The residual and product concentrations of glucose, fructose, mannose, and psicose molecules were measured on HPLC (Agilent Technologies 1200 infinity series). The system was equipped with an Agilent Hi-Plex Ca column (300 mm length and 8 mm porosity) and maintained at 85 °C with 0.6 ml/min flow rate using HPLC grade water as a mobile eluent. The concentration of sugars was calculated using the respective calibration charts prepared using commercial grade chemicals. The calibration standards for glucose, fructose, mannose, and psicose were prepared in DI water. Glucose and other product yield and recovery were estimated based on the difference in residual to initial concentration of the respective monosugars. Similarly, the products selectivity was calculated based on the difference in concentration of products to glucose reacted.

**Fermentation of Isomerization Medium.** All the necessary plasticwares used were sterilized under an autoclave condition (121 °C, 15 psi) for 15 min. In a typical fermentation, 6 mL of the reaction mixture (raw isomerized aqueous medium) was taken in a 100 mL autoclavable glass tube along with 8% wt monopotassium phosphate (KH₂PO₄) and 3.5% wt of magnesium sulfate (MgSO₄·7H₂O) as a fermentation supplement. Yeast culture was prepared separately by dissolving 1 gm dried yeast powder in 10 mL of water. The as-prepared yeast culture was introduced to the glass tube containing sugars substrate. The pH of the fermentation broth was adjusted to 7.0 (using diluted NaOH solution). The tube was placed in the shaker incubator maintained at 30 °C and 250 rpm for 24 h. In the end, a small aliquot was collected from each fermentation broth and analyzed on HPLC for the determination of the fermentation product (e.g., ethanol) and residual sugar concentration.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03918.

Detailed information on materials used in this experiment; extraction result of sugars with the corresponding change in Aliquat 336 to PBA ratio; result of sequential extraction and isomerization using phenyl boronic acid as a complexing agent (4:1); chemical structure of polyamines consisting both 1° and 2° amines; response of spermine at different load conditions during glucose isomerization conducted at 90 °C for 15 min; color formation at different dosage levels of spermine during glucose isomerization conducted at 90 °C for 15 min; comparative HSQC NMR analysis report of post-isomerization conducted using (a) 2-D-glucose in D₂O and (b) glucose in water, reaction conditions: 10 % wt glucose, 6% mol spermine relative to glucose, 1 mL of D₂O/H₂O at 100 °C for 15 min; UV absorbance result of post-reaction medium before and after activated carbon treatment; stacked chromatography report of standard versus yeast fermentation broth for determination of ethanol and other residuals concentration; actual chromatograms of glucose, mannose, fructose, psicose, and reaction mixture; ¹H NMR spectra of (A) standard psicose and (B) isolated psicose, ¹³C NMR spectra of (C) standard psicose, and (D) isolated psicose; plot of glucose concentration versus time at different temperatures, such as (a) 40, (b) 60, (c) 80, (d), (e) 110, and (f) 120 °C while other parameters maintained constant (6% mol catalyst dose); correlation chart of turn over frequency versus reaction temperature; results of isomerization conducted in the alcohol medium (methanol/ethanol) at different concentrations (plain and diluted 50:50 aqueous to organic), reaction conditions: 6% mol Spermine loading at 100 °C for 15 min; and comparative fluorescence spectrum of NBA dispersed in 1-octanol and Aliquat 336 solution containing single or mixture of monosugars (PDF)

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Notes
The authors declare no competing financial interest.

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