The clarification of the partition property of substrates in a water / organic biphasic system is useful in the development of a reaction / separation process for value-added materials, especially under high temperature and pressure conditions. In this study, the water / methyl isobutyl ketone (MIBK) biphasic system was investigated under various temperatures (25 – 190 °C) at 10 MPa. The partitioning behavior of substrates such as furfural derivatives, amino acids, and saccharides, depended on the temperature and the flow rate ratio of MIBK to the water phase. The scale of hydrophobicity ($HF$) of the water / MIBK biphasic system to determine the partitioning behavior of substrates was estimated based on the partitioning behavior of amino acids. The $HF$ value for the water / MIBK phase flow system was greater than that for the batch system and comparable to that for conventional aqueous two-phase systems such as polyethylene glycol / dextran and liposome membrane systems. It was probably because an increase of the surface-to-volume ratio and the vortex field in the slug flow contributed to the mass transfer of substrates and their distribution.

1. Introduction

Recently, treatments of biomass have been studied for the development of green processes to recover value-added materials such as 5-hydroxymethylfurfural (HMF) [1-5], 2,5-furandicarbocyclic acid (FDCA) [6], lactic acid [7,8], and others. For examples, a variety of recovery methods using the acid-induced production of HMF [1,3], the microwave-assisted hydrothermal degradation [9], or the heterogeneous catalyst such as ytterbium triflate [10], zeolite [11], and zirconium [12], have been reported. The production process of HMF affords many by-products in the reaction pathway such as the conversion of fructose to HMF [13]. The recovery of HMF without its decomposition is also required because it is decomposed in water [1,9,13]. The water / organic biphasic system has recently been investigated to recover HMF because it is well-known that no decomposition of HMF takes place in the organic phase [1].

It has been pointed out, however, that the batch reaction using a biphasic system requires refreshing of the organic phase by combining an evaporator with the extractor [1]. In recent studies, the continuous production of HMF in a biphasic system and its extraction from the aqueous phase has been investigated by
using catalysts at temperatures greater than 450 K [11]. The continuous extraction of HMF has been reported by using a slug flow under high temperature and pressure conditions [14]. Liquid-liquid slug flow is a promising two-phase system because the surface-to-volume ratio of the liquid-liquid biphasic system can be increased by the generation of slug flow in the capillary through a Y- or T-junction [15,16]. In fact, those systems exhibit excellent mass transfer characteristics and provide a well-defined interfacial area [17,18]. However, the two-phase slug flow system under the high temperature and pressure conditions has not been characterized in detail. The investigation with respect to the partitioning behavior of substrates would give a better understanding of the slug flow from the aspects of thermodynamics and fluid mechanics.

In this study, the water / MIBK phase under high temperature and pressure conditions were characterized by using some substrates including HMF. The influence of the velocity of liquid-liquid slug flow and the temperature on the partition coefficient was investigated. Finally, the advantages of slug flow for the partitioning field to the batch system were discussed.

2. Experimental

2.1 Materials

Methyl isobuthyl ketone (4-methyl-2-pentanone; MIBK) was purchased from Wako Pure Chemical Industry, Ltd. (Osaka, Japan). Thirteen substrates shown in Table 1 were purchased from Sigma Aldrich (Tokyo, Japan). Other chemical reagents were of analytical grade. Poly(tetrafluoroethylene) (PTFE) tubes and SUS316 tubes were obtained from GL Science, Co. Ltd. (Tokyo, Japan).

2.2 Set up of the partitioning system

The flow system used in this study is shown in Figure 1(a). In short, 1.5 g/L of HMF solution was injected to mix with the organic MIBK solvent. The mixture was incubated in a heating bath (25 - 190 °C) and thereafter cooled to 20 °C. The pressure was elevated to 10 MPa by controlling the back pressure valve. The time for the partition of HMF was defined as the residence time, which was determined by the flow rate. The same operation was performed for other substrates. In the batch system (Figure 1(b)), 6.0 mL of solution containing substrates (0.1 g/L) was added to the reaction cell. Thereafter, the reaction cell was placed in the oil bath to increase the temperature to 180 °C. The distribution was monitored for 400 sec to quantify the amount of HMF in the MIBK phase. No significant influence of both the cooling bath and the final separation to the partition behavior of substrates was confirmed in advance.

Figure 1. Experimental systems for HMF production using (a) the flow and (b) the batch system.
2.3 Determination of the concentration of substrates

The concentration of substrates in the water and MIBK phases was analyzed by the high performance liquid chromatography. The column used was a COSMOSIL 5C18-AR-II Packed Column (4.6×250 mm, Nacalai Tesque Co. Ltd., Japan). The sample (5 μL) was loaded onto the column (equilibrated at 40 °C) at a flow rate of 1.0 mL/min. The mobile phase was MeOH / H₂O = 20 / 80 (wt / wt). The HMF in the sample was detected by a peak at 254 nm of wave length, by using the photo diode array detector (SPD-M20A, Shimazu Co. Ltd.). The peaks derived from the water and the MIBK phases were eluted at 10 and 45 min. Some substrates were detected by the reflex index (RI) detector.

2.4 Numerical calculation of slug flow

A mathematical method was adopted to simulate the liquid-liquid slug flow with a free surface and in order to study and predict slug generation, shape and hydrodynamics. The hydrodynamics were calculated by the finite-volume method [15] and implemented in the open source software OpenFoam. The fluids were described using the incompressible Navier-Stokes equations. The governing equations of the volume-of-fluid method formulations for liquid-liquid systems are comprised of the equation of continuity, the equation of motion, and the volume fraction equation.

3. Results and Discussion

3.1 Partition behavior of HMF in slug flow under various temperatures

In the first series of experiments, the formation of slug flow in the PTFE tubes was visually observed by staining the water phase with a commercial blue-colored ink, so that the biphasic water / MIBK phase could be definitely distinguished. The flow rate of MIBK and the water phase was defined as V_{MIBK} and V_{water}, respectively. the formation of the slug flows was confirmed (Figure 2(a)). With increasing the V_{MIBK} / V_{water} value, the amount of MIBK phase (defined as b in Figure 2(a))) increased relative to the water phase (defined as a). Therefore, the amount of the slug flow could be roughly determined by the V_{MIBK} / V_{water} value.

The apparent partition coefficient (K_{ex}) of HMF as a model substrate was examined. The K_{ex} value increased depending on the contact time of both phases after 60 sec from the beginning. Meanwhile, the K_{ex} value was constant after 60 sec. Therefore, the K_{ex} value at 60 sec was adopted in this study. Figure 2. (a) Visualization of slug flows under various flow rate ratios. (b) Relationship between the apparent partition coefficients of HMF in the slug flows and the flow rate ratios. All the experiments were, at 10 MPa, performed at least three times.
Second, the influence of the dimension of the slug flow on the $K_{ex}$ value was examined. Overall, the $K_{ex}$ value decreased with an increase in the $V_{MIBK} / V_{water}$ value (Figure 2(b)). At 25 °C, the $K_{ex}$ value was obviously reduced by 0.3. In contrast, no significant decrease in the $K_{ex}$ value was observed at the higher temperature range (especially, 170 ~ 190 °C).

### 3.2 Partition behavior of the variety of substrates

The influence of the chemical properties of the substrates on the partition behavior in the slug flow was examined. Table 1 shows the partition coefficient of various substrates under the batch and flow system. In the case of the batch system, the $K_{ex}$ value ranged from 0.005 (row no. 4) to 1.14 (row no. 1) at 25 °C. Elevating the temperature to 180 °C showed overall enhanced $K_{ex}$ values. For the flow system, the $K_{ex}$ values were greater than those for the batch system. Furfural and its derivatives (row no. 1-4) had the higher $K_{ex}$ value, by comparison with other substrates such as amino acids (row no. 5-9) and saccharides (row no. 10-13), in both batch and flow systems.

<table>
<thead>
<tr>
<th>Row no.</th>
<th>Batch $K_{ex}$ at 25 °C</th>
<th>Batch $K_{ex}$ at 180 °C</th>
<th>Flow $K_{ex}$ at 25 °C</th>
<th>Flow $K_{ex}$ at 180 °C</th>
<th>logP$_{ow}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Furfural</td>
<td>1.14</td>
<td>3.11</td>
<td>5.35</td>
<td>5.83</td>
</tr>
<tr>
<td>2</td>
<td>HMF</td>
<td>0.33</td>
<td>0.85</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>Lactic acid</td>
<td>0.02</td>
<td>0.06</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>4</td>
<td>FDCA</td>
<td>0.005</td>
<td>0.008</td>
<td>0.008</td>
<td>0.010</td>
</tr>
<tr>
<td>5</td>
<td>Tryptophan</td>
<td>0.08</td>
<td>0.29</td>
<td>0.37</td>
<td>0.40</td>
</tr>
<tr>
<td>6</td>
<td>Phenylalanine</td>
<td>0.08</td>
<td>0.26</td>
<td>0.31</td>
<td>0.38</td>
</tr>
<tr>
<td>7</td>
<td>Valine</td>
<td>0.09</td>
<td>0.25</td>
<td>0.28</td>
<td>0.32</td>
</tr>
<tr>
<td>8</td>
<td>Glycine</td>
<td>0.07</td>
<td>0.24</td>
<td>0.24</td>
<td>0.26</td>
</tr>
<tr>
<td>9</td>
<td>Threonine</td>
<td>0.08</td>
<td>0.25</td>
<td>0.25</td>
<td>0.27</td>
</tr>
<tr>
<td>10</td>
<td>Fructose</td>
<td>0.011</td>
<td>0.018</td>
<td>0.018</td>
<td>0.022</td>
</tr>
<tr>
<td>11</td>
<td>Glucose</td>
<td>0.012</td>
<td>0.020</td>
<td>0.021</td>
<td>0.025</td>
</tr>
<tr>
<td>12</td>
<td>Sucrose</td>
<td>0.012</td>
<td>0.015 (0.064)</td>
<td>0.017</td>
<td>0.016 (0.059)</td>
</tr>
<tr>
<td>13</td>
<td>Maltose</td>
<td>0.010</td>
<td>0.013</td>
<td>0.014</td>
<td>0.015</td>
</tr>
</tbody>
</table>

* The value in parenthesis was calculated without further decomposition.

In general, the partition behavior of substrates in the two-phase system is caused by their hydrophobicity [19]. The hydrophobicity of chemical molecules is defined as the partition coefficient of substrate in the water / octanol system (logP$_{ow}$). The hydrophobicities of various materials are in the order: furfural derivatives > amino acids > saccharides. Overall, the $K_{ex}$ value for various substrates in both the batch and flow system correlated with the corresponding logP$_{ow}$ value. This result suggested that the partition behavior of substrates in the slug flow was dominated by the hydrophobicity even under high temperature and pressure conditions.

### 3.3 Comparison of the present method with the conventional two-phase systems

The hydrophobicity of two phase partitioning systems determines the partition behavior of substrates [19]. Therefore, the evaluation of hydrophobicity of water / MIBK in the batch and flow system helps us understanding the overall partitioning behavior of substrates shown in Table 1. The characteristics of the two phase system based on the partition behavior of amino acids was investigated in a previous publications [19]. An amino acid has a relative hydrophobicity scale, defined as relative hydrophobicity (RH) by Nozaki and Tanford [20]. The $K_{ex}$ value for amino acids (row no. 5-9) were plotted against the corresponding RH value (Figure 3(a)). The slope of ln$K_{ex}$ to RH gives the hydrophobic factor (HF) of the two phase system. The HF values for a variety of two-phase systems have been reported [21] and their HF value together with the HF value of the present two phase systems are shown in Figure 3(b). In the batch system, the HF value has no definite temperature dependency. In the case of the flow system, the HF value was larger than that of the batch system and the elevation of temperature enhanced the HF value. This
result suggested that the hydrophobicity of the partitioning field was sensitive to the liquid-liquid slug flow and the temperature.

For a comparison of HF value for slug flow with the conventional two phase system, a ladder of HF values for various partitioning system is shown in Figure 3(c). Interestingly, the hydrophobicity (HF value) of the water / MIBK phase (even in the flow system) was comparable with the conventional aqueous two-phase partitioning systems such as ATPS(1) [21] and liposome membrane systems (LMS) [21,22]. In contrast, the hydrophobicity for slug flow was lower than the two phase system prepared by PEG/salts (ATPS(2)) and the reversed micellar system (RVMS) [21].

3.4 Possible contributions of the liquid-liquid slug flow to the partition behavior

In the last section, the hydrophobicity of the flow system was greater than that of the batch system. The increase in the HF value results in the enhanced distribution of substrates between the MIBK and water phases. Therefore, the enhanced distribution of substrates was discussed with regard to the thermodynamic and fluid dynamic aspects.

3.4.1 Thermodynamic aspect

The van’t Hoff equation is the equation which represents the temperature dependency of the partition coefficient $K_{ex}$. All the experiments (25 and 180 °C at 10 MPa) were performed three times. (b) Hydrophobic factor for various partition conditions. (c) Comparison of the present partition systems with the conventional two-phase ones.

Figure 3. (a) Relationship between the relative hydrophobicity of amino acids and their partition coefficient $K_{ex}$. The increase in the HF value results in the enhanced distribution of substrates between the MIBK and water phases. Therefore, the enhanced distribution of substrates was discussed with regard to the thermodynamic and fluid dynamic aspects.

\[ \ln K_{ex} = \frac{\Delta S}{R} - \frac{(\Delta H/R)}{T} \]

where $\Delta H$ and $\Delta S$ are the enthalpy and entropy for the partitioning of substrates in the two phase system, respectively. $T$ is the absolute temperature [K] and $R$ is the gas constant.
For various $V_{\text{MIBK}}/V_{\text{water}}$ value, the linear relationship between the $\ln K_{\text{ex}}$ value for HMF and $1/T$ was found as shown in Figure 4(a). The same was true for the batch system. The $\Delta H$ and $T\Delta S$ for HMF estimated are shown in Figure 4(b) as a function of the $V_{\text{MIBK}}/V_{\text{water}}$ value. The $\Delta H$ values were nearly the same as $T\Delta S$ for every condition, suggesting that the partitioning of HMF determined the balance between enthalpic and entropic factors. Furthermore, the $\Delta H$ value was plotted against the corresponding $T\Delta S$ and a linear relationship between both was observed (the enthalpy-entropy compensation) as shown in Figure 4(c). The compensation was observed regardless of the $V_{\text{MIBK}}/V_{\text{water}}$ value and the types of partitioning system, suggesting that the partitioning behavior of substrates was thermodynamically driven by the same mechanism. The $y$-intercept obtained by the extrapolation of $\Delta H$ to 0, $T\Delta S_0$, is the index for the desolvation of the molecule [23]. $T\Delta S_0$ was thereby estimated to be -0.14 kJ/mol. Considering the partition process of HMF from water to the MIBK phase, the estimated $T\Delta S_0$ value implied that the energy for the desorption of water molecules solvating HMF is balanced with the energy for the solvation process of HMF with MIBK molecules. It was considered that the reduction of the desolvation of the substrates contributed to their enhanced partition behavior. Meanwhile, Figure 4(c) indicated that there was no difference in desorption process between the batch and the flow systems. Contributions other than the thermodynamic aspects are discussed in the following system.

Figure 4. (a) van’t Hoff plot of HMF under various conditions. (b) Relationship between the thermodynamic parameters and flow rate ratios. (c) Enthalpy-entropy compensation of HMF in the continuous biphasic system. Condition: 10 MPa.

3.4.2 Aspects of interfacial area

The interfacial area plays a role for the mass transfer of substrates, by the molecular diffusion, in the two phase system. Liquid-liquid slug flow can achieve enhanced mass transfer due to a larger interfacial area (surface-to-volume ratio) [24], as well as fast partition equilibrium [25]. The effect of interfacial area is therefore discussed. The surface-to-volume ratio of the flow system was greater than that of the batch system, as was seen in the experimental setups (Figure 1(a) and (b)). The surface-to-volume ratio was also varied via the $V_{\text{MIBK}}/V_{\text{water}}$ value. It was obvious that a decrease in the $V_{\text{MIBK}}/V_{\text{water}}$ value resulted in an increase in the surface-to-volume ratio (Figure 2(a)). Increasing the $V_{\text{MIBK}}/V_{\text{water}}$ value to 5.0, the decreased $K_{\text{ex}}$ value significantly as shown in Figure 2(b). As was discussed at the last section, the $\Delta H$ and $T\Delta S$ values for $V_{\text{MIBK}}/V_{\text{water}} = 5.0$ were comparable with the batch system (Figure 4(b)). Therefore, the increase in the surface-to-volume ratio should enhance the mass transfer due to the molecular diffusion. Meanwhile, the mechanism of the variation in the $K_{\text{ex}}$ value would require further discussion with respect to factors other...
than mass transfer based on the molecular diffusion from the water to the MIBK phase.

3.4.3 Fluid dynamic aspects

As a supplemental discussion to the effect of interfacial area for the mass transfer of substrates, the contribution of the velocity field in liquid-liquid slug flow system is discussed here. The liquid-liquid slug flows under different \( V_{\text{MIBK}}/V_{\text{water}} \) conditions were numerically calculated by using OpenFoam. The wall film of the MIBK phase was neglected to simplify the numerical calculation. The velocity of the MIBK and water phase was also lowered by \( 1/10 \) times as real conditions, since the \( K_{\text{ex}} \) value at 60 sec was almost the same as that at 600 sec. These simplifications reduced the calculation cost. The calculation result for slug flow generation for the MIBK / water phase is shown in Figure 5.

With an increase in the flow rate of the MIBK phase from 3.7 mm/s (\( V_{\text{MIBK}}/V_{\text{water}} = 1 \)) to 5.6 mm/s (\( V_{\text{MIBK}}/V_{\text{water}} = 3.0 \)), the dimension of the slug flow was changed as show in Figure 5(a), which is in agreement with the observed slug flow (Figure 2(a)). The velocity vector in the slug flow was visualized. In both cases, the velocity vector field for the absolute velocity showed a parabolic velocity distribution typical to laminar flow (Figure 5(b) top), which is consistent with the Reynolds number of the operation conditions (\( Re \sim 150 \)). The vector variation was sensitive to the line velocity. Considering the relative velocity (= absolute velocity – mean velocity), the definite top and bottom vortex field was symmetric was observed in slug flow (Figure 5(b) bottom and (c)). The longitudinal and radius direction were defined as the \( x \)- and \( y \)-axis, respectively. By using the velocity field \( U(\text{u}_x, \text{u}_y, \text{u}_z) \), the variation of the term \( \nabla \times U \).

![Figure 5](image-url)

**Figure 5.** (a) Contour of slug flow calculated by OpenFoam. (left) \( V_{\text{MIBK}}/V_{\text{water}} = 1 \), (right) \( V_{\text{MIBK}}/V_{\text{water}} = 3 \). t = 2.0 s after the MIBK phase was injected into the water phase. Calculation conditions were 180 °C and 10 MPa. (b) Absolute and relative velocity field in slug flow. (left) \( V_{\text{MIBK}}/V_{\text{water}} = 1 \), (right) \( V_{\text{MIBK}}/V_{\text{water}} = 3 \). (c) Magnified images of velocity field in slug flow.
\[ \partial y \] can be considered as the intensity of the vortex field in order to simplify the discussion with respect to the vortex field in slug flow. Since the inner diameter of the tube was constant, \( \partial y \) was constant. The \( \partial u/\partial x \) value, that is the difference in velocity between the right and left ends in slug flow, is discussed. The \( \partial u/\partial x \) value at \( V_{\text{MIBK}}/V_{\text{water}} = 1 \) was greater than that at \( V_{\text{MIBK}}/V_{\text{water}} = 3 \). Also, the variation in \( \partial u/\partial y \) is discussed. The \( \partial u/\partial y \) value is the difference in velocity between the right and left ends in slug flow. The \( \partial u/\partial y \) value at \( V_{\text{MIBK}}/V_{\text{water}} = 1 \) was greater than that at \( V_{\text{MIBK}}/V_{\text{water}} = 3 \). Besides, it has been reported that the independent region not contributing to the distribution of substrates was formed back in the slug flow [15], although our calculation could not demonstrate such independent regions because of the reduction of calculation cost. This influence was not negligible as the length of the slug (\( b/a \) in Figure 2(a)) increased. It was, therefore, considered that the convection of substrates by the vortex field in the MIBK phase at \( V_{\text{MIBK}}/V_{\text{water}} = 1 \) would assist their distribution to the MIBK phase more effectively, as compared with that at \( V_{\text{MIBK}}/V_{\text{water}} = 3 \). This argument is consistent with the experimental result of \( K_{\text{ex}} (V_{\text{MIBK}}/V_{\text{water}} = 1) > K_{\text{ex}} (V_{\text{MIBK}}/V_{\text{water}} = 3) \) at 180 °C (Figure 2(b)).

4. Conclusion

The fundamental property of slug flow generated in the water / MIBK phase in the tube was discussed by estimating the apparent partition behavior of various substrates such as furfural derivatives, amino acids, and saccharides. The results of their apparent partition behavior suggested that slug flow could be used as the two-phase system. From the investigation based on the partition behavior of amino acids, the hydrophobic scale (HF) of the slug flow system was comparable with that for the conventional aqueous two-phase system and the liposome membrane system. The hydrophobicity scale of slug flow was greater than that for the batch system. From some aspects, it was considered that this was because of the reduction of the desolvation of substrates during the mass transfer across the interface between both phases, the increase in surface-to-volume ratio for the mass transfer, and the convection effect due to the vortex field.

References