Synthesis of cheaper resolving agent, \(N\)-alkyl glucamines: Some aspects of process development

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Reductive amination of \(D\)-glucose was studied from the viewpoint of process research and development to synthesize \(N\)-alkyl glucamines which are recently used as the resolving agent for racemic modifications of products containing carboxylic acids. Different amines like methyl amine, ethyl amine and butyl amines were taken as the aminating agent and Raney nickel was used as the catalyst. At a temperature of 85\(^\circ\)C and a hydrogen pressure of 95 atm, 97% selectivity was achieved at a glucose conversion level of 92%.

Among the various routes for the production of amines from carbonyl compounds, reductive amination is a process of considerable industrial significance (Table 1) and various fine-chemicals and pharmaceuticals are prepared by this method. This involves the reaction of the carbonyl compound with ammonia or amine and subsequent hydrogenation of the imine formed. Several investigators claimed the use of Raney nickel catalyst on the reductive amination of various aliphatic and aromatic ketones and aldehydes\(^6\text{-}16\).

Usually, costly resolving agents like cinchonidine are used to separate racemic modifications of products containing carboxylic acid groups. The use of cheaper resolving agents like \(N\)-alkyl glucamine is worth considering. \(N\)-alkyl glucamines generally prepared by reductive amination\(^17\text{-}18\) of glucose, is used as a resolving agent\(^19\text{-}21\) for racemic modifications of products containing carboxylic acids. But the information regarding catalyst loading and life of catalyst for the synthesis of glucamine from \(D\)-glucose is inadequate and needs substantiation. In the present study, attempts have been made to find out the suitable process parameters from the viewpoint of process research and development for the reductive amination of glucose (Scheme 1) and to draw a simple kinetic interpretation.

Experimental Procedure

Material

\(D\)-Glucose, technical grade; methylamine, L.R; ethylamine, L.R; butylamine, L.R; Raney nickel "F" type, technical grade were used in this study.

Experimental set-up

The experiments were carried out in a 100 mL capacity hastelloy B2-Parr autoclave equipped with four bladed magnetically driven impeller. The autoclave was heated externally by a heating element. The temperature of the reaction was maintained within ±1\(^\circ\)C of the desired value.

Procedure

Predetermined quantity of \(D\)-glucose, \(N\)-alkylamine and Raney Nickel catalyst were charged in the autoclave. Before hydrogen was passed, the reaction mixture was allowed to keep under stirring for 1 h with a view to complete the formation of imine by the reaction of ammonia and aldehyde. Subsequently, the heating was started to get the desired temperature. Once the desired temperature was attained, the autoclave was pressurized with hydrogen to the
Effect of speed of agitation on conversion of glucose.

Table 1: Industrial relevance of reductive amination

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylacetone</td>
<td>Amphetamine</td>
<td>Stimulators for central-nervous system</td>
</tr>
<tr>
<td>+ ammonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novoloketone</td>
<td>Novoldiamine</td>
<td>Intermediate for anti-malarial drug</td>
</tr>
<tr>
<td>+ ammonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>Cyclohexylamine</td>
<td>Manufacture of pesticide, organic intermediate</td>
</tr>
<tr>
<td>+ ammonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetophenone</td>
<td>α-phenylethylamine</td>
<td>Organic</td>
</tr>
<tr>
<td>+ ammonia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Material balance

<table>
<thead>
<tr>
<th>Materials</th>
<th>Glmol</th>
<th>%Glucose accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Glucose (taken)</td>
<td>0.0555</td>
<td>100</td>
</tr>
<tr>
<td>N-Glucamine</td>
<td>0.04953</td>
<td>89.24</td>
</tr>
<tr>
<td>Secondary amine</td>
<td>0.0008325</td>
<td>1.5</td>
</tr>
<tr>
<td>Glucose unreacted</td>
<td>0.0039</td>
<td>7</td>
</tr>
<tr>
<td>Unaccounted</td>
<td>0.001256</td>
<td>2.263</td>
</tr>
<tr>
<td>Total</td>
<td>0.0555</td>
<td>100</td>
</tr>
</tbody>
</table>

Reaction conditions: Glucose concentration, 20% w/v; temperature, 85°C; mole ratio of glucose : amine, 1 : 5; reaction time, 3 h; hydrogen pressure, 90 atm, catalyst loading, 1% w/v; reaction volume, 50 mL.

Table 3: Effect of speed of agitation on conversion of glucose

<table>
<thead>
<tr>
<th>Speed of agitation, rpm</th>
<th>% Conversion of glucose</th>
<th>% Selectivity to product</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>500</td>
<td>62</td>
<td>96</td>
</tr>
<tr>
<td>800</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>1100</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>1200</td>
<td>93</td>
<td>97</td>
</tr>
</tbody>
</table>

Reaction conditions: Glucose concentration, 20% w/v; temperature, 85°C; mole ratio of glucose : amine, 1 : 5; reaction time, 3 h; hydrogen pressure, 90 atm; catalyst loading, 1% w/v; reaction volume, 50 mL.

Table 4: Effect of initial concentration of glucose and period of reaction on overall conversion

<table>
<thead>
<tr>
<th>Time, min</th>
<th>% Conversion for 5% reactant concentration</th>
<th>% Conversion for 15% reactant concentration</th>
<th>% Conversion for 20% reactant concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>32</td>
<td>36</td>
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<td>60</td>
<td>55</td>
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<td>120</td>
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<td>81</td>
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</tr>
<tr>
<td>180</td>
<td>89</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>210</td>
<td>92</td>
<td>93</td>
<td>93</td>
</tr>
</tbody>
</table>

Reaction conditions: Temperature, 85°C; mole ratio of glucose : amine, 1 : 5; reaction time, 3 h; hydrogen pressure, 90 atm; catalyst loading, 1% w/v; reaction volume, 50 mL.

Desired pressure level. A constant pressure was maintained throughout the reaction period.

Analysis

The unreacted glucose was estimated by the usual oximation reaction using hydroxylamine hydrochloride at 45°C. The liberated hydrochloric acid was estimated by titrating potentiometrically against standard sodium hydroxide solution.

To ensure any by-product formation in the reaction mixture, samples were taken for H.P.L.C. The conditions are: column used, C-18 (Octadecyl column); solvent system, acetonitrile-water (65:35); flow rate, 1 mL/min; wave length, 254 nm.

Results and Discussion

Material balance

The material balance of D-glucose was estimated for a typical run (Table 2). It would be possible to account 97.7% D-glucose. Unaccounted material balance may be due to loss in handling or error in analytical methods.

Effect of speed of agitation

Speed of agitation was varied from 500 to 1200 rpm (Table 3). There was a significant change in the overall conversion when the agitator speed was varied from 500 to 1100 rpm indicating the presence of the mass transfer limitation for the diffusion of hydrogen from the gas liquid interface to the bulk liquid. When the speed of agitation was further increased to 1200 rpm, there was no significant change in the overall conversion indicating that mass transfer effects are mostly eliminated above 1100 rpm. So all the subsequent reactions were carried out at 1200 rpm.

Effect of partial pressure of hydrogen

The partial pressure of hydrogen was varied from 50 to 95 atm (Fig 1). When the pressure was increased from 90 to 95 atm, it was observed, that the overall conversion remained almost same in the above range. Thus, the reaction is independent of partial pressure of hydrogen in the range of 90-95 atm.

Effect of concentration of D-glucose and period of reaction

There was a slight change in the overall conversion of D-glucose when the concentration of D-glucose was varied from 5-20% w/v (Table 4).

With an increase in the reaction period from 50 min to 200 min, the overall conversion of D-glucose increased from 35 to 92% for a 20% initial reactant concentration (Table 4).
Fig. 1 — Effect of hydrogen pressure on overall conversion

Fig. 2 — $\ln(1-X_A)$ vs $t$ at different catalyst loading

Fig. 3 — $\ln(1-X_A)$ vs $t$ at different temperature

Effect of catalyst loading
The catalyst loading expressed as weight percent of catalyst based on the total reaction volume was varied from 0.3% to 1.2% w/v (Table 5). The overall conversion increased significantly with an increase in catalyst loading.

Effect of temperature
The temperature was varied in the range of 65 to 105 °C (Table 6). The conversion of D-glucose increased from 38 to 98%. The selectivity with respect to glucamine was maximum at 85 °C. At 105 °C, the selectivity was as low as 69% due to residue formation.

Effect of mole ratio
The mole ratio of aldehyde to ammonia was varied from 1:1 to 1:10 using 1% w/v of catalyst at 85 °C (Table 7). As expected, with increase in the mole ratio, the selectivity with respect to the glucamine increased. From a pragmatic point of view, one may use a mole ratio of 1:5, since the selectivity obtained was as high as 97%.

Effect of different type of catalyst and reusability of the catalyst
Different type of nickel catalysts obtained from different sources were examined (Table 8) for this reaction and it was found that Raney nickel "F-Type" was the most effective. Attempts were made to see whether the catalyst can be used repeatedly. However, results obtained indicating that with fresh catalyst 92% conversion was achieved in 3 h, in the very first reuse the conversion of D-glucose was 81% and in the
Reaction volume, mole ratio of glucose: amine, amine, ethyl amine and butyl amine were used. It was observed (Table 10) that almost same conversion level was obtained with these amines for a specified reaction time.

Effect of different type of amines

Different type of N-alkyl amines like methyl amine, ethyl amine and butyl amine were used. It was observed that the conversion leveled off with that of fresh catalyst and it was observed that the conversion leveled off with that of fresh catalyst. Therefore, catalyst could be reused repeatedly if 15% fresh catalyst was mixed with the spent one.

Kinetic interpretation

The reactions are carried out at a high speed of agitation to eliminate the mass transfer effects. There was absolutely no increase in the conversion level when hydrogen pressure is increased from 90 atm to 95 atm. It indicates that at or above 90 atm pressure the reaction is zeroth order with respect to hydrogen.

It is seen from Table 11, that for a given initial concentration of the reactant the reaction is first order with respect to the glucose, catalyst loading of 1% w/v.

From the slopes of Fig 2, the rate constants are found out and given in Table 12. It is observed that the initial rate increases linearly with the increase in catalyst loading. Since for the size of the catalyst used and conditions employed, the role of diffusion of hydrogen from the bulk liquid to the solid is estimated to be unimportant, the data appears to represent the true kinetics of the process at a catalyst loading of 1.0% w/v.
temperatures are found to be $1.3 \times 10^{-6}$ and $9.8 \times 10^{-6}$ s$^{-1}$ atm$^{-1}$ g-cat$^{-1}$ at $65, 75, 85$ and $105 \, ^\circ C$ under the reaction conditions. Energy of activation is found to be $12.3 \text{ kcal/mol}$ from the slope of the Arrhenius plot (Fig 4).

**Conclusion**

The reductive amination of $D$-glucose to $N$-methyl glucamine gave as high as $97\%$ selectivity towards $N$-methyl glucamine using Raney nickel as catalyst.

The reusability problem of Raney nickel catalyst was solved and it will definitely cut short the process cost.

A high speed of agitation of $1200 \text{ rpm}$ was used to eliminate the mass transfer effects to study the true kinetics of the reaction.

The reductive amination of $D$-glucose was found to be zeroth order with respect to hydrogen concentration above a hydrogen partial pressure of $90 \text{ atm}$.

It would be necessary to allow the mixture of aldehyde and ammonia to react for $1 \text{ h}$ before hydrogenation because the reduction to alcohol could be a competing side reaction.

Under the best suitable conditions ($D$-glucose $20\%w/v$; mole ratio of glucose : methyl amine, $1:5$; temperature, $85 \, ^\circ C$; solvent, water; hydrogen pressure $95 \text{ atm}$; catalyst loading $1\% \text{ w/v}$; reaction period, $3\text{ h}$; speed of agitation, $1200 \text{ rpm}$), $D$-glucamine could be obtained with $97\%$ selectivity when the overall conversion of $D$-glucose was $92\%$.

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**References**