ENANTIOSELECTIVE EXTRACTION OF KETOPROFEN ENANTIOMERS USING ESTER ALCOHOL R, R-DI-TARTARATES OR S, S-DI-TARTARATES AS CHIRAL SELECTOR

K. HUANG, F. JIAO, S. LIU, X. LI and D. HUANG

School of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China
jiaofg@163.com

Abstract—Distribution behavior of ketoprofen enantiomers was examined in a two-phase system containing R, R-di-tartarates or S, S-di-tartarates. The influences of different alkyl chain of R, R-di-tartarates or S, S-di-tartarates, concentrations of R, R-di-tartarate, organic solvent and content of methanol on partition coefficient and separation factor were investigated, respectively. The experimental results show that R, R-di-tartarates studied all form more stable diastereomeric complexes with ketoprofen S-enantiomer than with R-enantiomer. The partition coefficients and enantioselectivity generally increase with the addition of length of alkyl chain of alcohol. The concentration of chiral selector and methanol also have bigger influences on enantioselectivity.

Keywords—Enantioselective extraction, ketoprofen enantiomers, partition coefficient, separation factor, chiral selector.

I. INTRODUCTION

Ketoprofen, 2-(3-benzoylphenyl) propionic acid is a nonsteroidal anti-inflammatory drug (NSAID) which has potent inhibitory effects on prostaglandin synthesis. It is commonly used in the treatment of rheumatoid arthritis and osteoarthritis. Therapeutic doses of ketoprofen have proven to be as effective as those of the other commonly used NSAIDs. Ketoprofen is marketed as the racemate although, like the other members of the 2-arylpropanoic acid class, it exhibits enantioselectivity in its action and disposition. Specifically, in vitro experiments proved that the S (+) enantiomer exhibited pharmacological effects, but the R (-) enantiomer was inactive. Furthermore, an in vivo experiment showed that the chiral inversion takes place from R (-) to S (+) with the degree of inversion varying from one animal species to another (Blanco et al., 1998). Various approaches such as diastereomcr crystallization (Yoneyoshi et al., 1996; Lukas et al., 1991), kinetic resolution (Antona et al., 2002; Park et al., 1999; Jaeger and Reetz, 1998; Crescenzo et al., 2000; Kato et al., 2000; Jin et al., 2003; Kumar and Jolly, 2001; Madhav and Ching, 2001; Kim et al., 2000; Lui et al., 2000; Shen et al., 2002; Kim et al., 2002a; Choi et al., 2003; Kim et al., 2002b; Xi and Xu, 2005; Liu et al., 2004), asymmetric synthesis (Babin and Whiteker, 1996; Laue et al., 1994; Ram-}

minger et al., 2000; Rossi et al., 1993; Shimizu et al., 1991; Fadel, 1992), chromatography separation (Blanco et al., 1998, Davies, 1997; Boisvert et al., 1997) and preferential crystallization (Eikeren et al., 1997; Manimaran and Potter, 1992) were reported for the production of S-enantiomer of ketoprofen. However, the major limitation of S-ketoprofen production is that the maximum yield is limited to 50 % of the desired enantiomer based on the racemic starting substrate, which consists of equimolar of R-enantiomer and S-enantiomer. The use of enantiomeric technology is only in the separation of the 50 % of the desired S-enantiomer, while the other 50 % of R-enantiomer remained as byproduct. The effort of recovering the 50 % of the byproduct is important in order to achieve the maximum yield of more than 50 %.

To avoid the problems above, extraction with an optically active extractant is a very attractive option (Vladimir et al., 1989, Jérôme et al., 2000). Though the selectivity of a single extraction is small, extractions with many stages can be well established. The capacity of extraction is often much greater than that of chromatography etc, extraction can easily be operated continuously.

Diester derivatives of tartaric acid are well known as effective chiral selectors. Because these derivatives are symmetric in C2 axis and two kinds of functional groups, hydroxyl and carbonyl, attached to asymmetric carbons in these derivatives are stereochemically equivalent to those groups attached to other carbons; these structural features are favorable for them to be chiral selectors (Heldin et al., 1991). Ketoprofen has a carboxylic acid group at the chiral center that could participate in additional interactions with the hydroxyl and carbonyl groups of the enantiopure di-tartarates.

In this paper, the distribution behavior of ketoprofen enantiomers was examined in the aqueous and organic solvent of a two-phase systems containing R, R-di-tartarates or S, S-di-tartarates. The effects of different alkyl chain of R, R-di-tartarates, concentration of chiral selector, organic solvent and content of methanol on enantioselectivity (α) and partition coefficient (k) were investigated to find favourable experimental conditions for resolution. As far as we know, there is no report on the enantioselective extraction of ketoprofen enantiomers using R, R-di-tartarates or S, S-di-tartarates as chiral selector.
II. MATERIAL AND METHODS

A. Chemicals
Racemic ketoprofen was purchased from Xunda Group Corporation Pharmaceutical Factory in China (> 98 %). Vancomysin was obtained from Huabei Group Corporation Pharmaceutical in China. For the determination of enantioselivities different R, R-di-tartarates or S, S-di-tartarates were used, which were prepared in our laboratory from R, R-tartaric acid or S, S-tartaric acid and alcohol, respectively, and were > 98 % (Heldin et al., 1991). Other reagents utilized were all of analytical grade and were purchased from different suppliers. Water was deionized and bidistilled.

B. Analytical Method
Chromatographic studies were performed using a LC-10 AD pump (Shimadzu, Japan), an SIL-10 A injection loop, an SPD-10 A UV/VIS spectrophotometer detector (Shimadzu, Japan) at 300 nm. An AT-130 temperature controller (Autoscience, Tianjin, PR, China) was used to control column temperature. A Lichrospher C8 column (200 mm×4.6 mm i.d., 5 μm) was used to control column temperature. A di-tartarates were used, which were prepared in our laboratory from R, R-tartaric acid or S, S-tartaric acid and alcohol, respectively, and were > 98 % (Heldin et al., 1991). Other reagents utilized were all of analytical grade and were purchased from different suppliers. Water was deionized and bidistilled.

C. Enantioselective Experiments
The aqueous phase was prepared by dissolving a certain concentration of ketoprofen in aqueous phase is especially important, which was proved to be no influencing on experimental results. The organic phase was prepared by dissolving a certain concentration of ketoprofen in organic solvents. In a 10 mL separatory funnel, 5 mL of the aqueous phase was intensely shaken for some minutes with 5 mL of the organic phase at ambient temperature 20 °C. The flow-rate was set at 0.6 ml/L.

D. The effect of different alkyl chains of R, R-di-tartarates
Extraction of racemic mixtures is dependent on the difference in stability of the two diastereomeric complexes which are formed by chiral selector with the two enantiomer. So chiral extraction performance is related to the structure of chiral selector. It is very necessary to study the influence of different alkyl chains of R, R-di-tartarates or S, S-di-tartarates on k and α of both ketoprofen enantiomer, with the chiral selector concentration of 0.2 mol/L, 0.5 g/L ketoprofen, 50 % methanol and 1, 2-chloroethane as organic solvent. It is seen from Table 1 that kS is always bigger than kR, that is to say, the complexes of R, R-di-tartarates with ketoprofen S are more stable than that of R, R-di-tartarates with ketoprofen R, while the S, S-di-tartarates possess reversed characteristics. The partition coefficients and enantioselectivity increase with the addition of length of alkyl chain of R, R-di-tartarates or S, S-di-tartarates. Relating to the other chiral selectors, R, R-di-benzyltartarate or S, S-di-benzyltartarate has better performances of chiral extraction. Because the aromatic rings of R, R-di-benzyltartarate or S, S-di-benzyltartarate might allow for a more stereospecific and stronger interaction with aromatic ring of ketoprofen, which increases the stabilization of complexes of chiral selector with ketoprofen molecules. But then, in the following study, we used R, R-di-butyltartarate (DBT) as chiral selector in view of R, R-di-benzyltartarate’s high cost.

E. The effect of organic solvent
Chiral extraction performance is not only related to the structure of chiral selector, but also to the properties of organic solvents. So it is very important to investigate the influence of different organic solvent on k and α of ketoprofen enantiomers, with the R, R-DBT concentration of 0.2 mol/L, ketoprofen of 0.5 g/L and 50 % methanol. From Table 2, we can see that the extraction performance for the three kinds of organic solvents is

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**Table 1.** The influence of different alkyl chains of chiral selector on chiral extraction

<table>
<thead>
<tr>
<th>Ester alcohol moiety</th>
<th>kR</th>
<th>kS</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Butanol</td>
<td>18.8094</td>
<td>24.8592</td>
<td>1.3216</td>
</tr>
<tr>
<td>iso-Butyl alcohol</td>
<td>117.7982</td>
<td>93.2296</td>
<td>0.7914</td>
</tr>
<tr>
<td>n-pentanol</td>
<td>43.3764</td>
<td>48.7472</td>
<td>1.1238</td>
</tr>
<tr>
<td>n-hexanol</td>
<td>28.2099</td>
<td>27.3159</td>
<td>0.9683</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>275.6534</td>
<td>360.6730</td>
<td>1.3084</td>
</tr>
<tr>
<td></td>
<td>442.8615</td>
<td>315.4639</td>
<td>0.7124</td>
</tr>
<tr>
<td></td>
<td>250.1903</td>
<td>330.9621</td>
<td>1.3228</td>
</tr>
<tr>
<td></td>
<td>242.3207</td>
<td>220.4247</td>
<td>0.9096</td>
</tr>
<tr>
<td></td>
<td>287.5100</td>
<td>456.8039</td>
<td>1.5888</td>
</tr>
<tr>
<td></td>
<td>382.2201</td>
<td>495.7660</td>
<td>1.2971</td>
</tr>
</tbody>
</table>
Table 2 The influence of organic solvent on chiral extraction

<table>
<thead>
<tr>
<th>Organic solvent</th>
<th>$k_R$</th>
<th>$k_S$</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2-Chloroethane</td>
<td>21.7675</td>
<td>28.4742</td>
<td>1.3081</td>
</tr>
<tr>
<td>$n$-Heptane</td>
<td>0.1209</td>
<td>0.1384</td>
<td>1.1447</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>0.4997</td>
<td>0.4659</td>
<td>1.0725</td>
</tr>
<tr>
<td>$n$-Heptanol</td>
<td>28.3517</td>
<td>28.8717</td>
<td>1.0183</td>
</tr>
<tr>
<td>$n$-Octanol</td>
<td>479.9455</td>
<td>392.9293</td>
<td>1.2215</td>
</tr>
<tr>
<td>$n$-Octanol</td>
<td>81.7104</td>
<td>97.1071</td>
<td>1.1884</td>
</tr>
</tbody>
</table>

Fig. 1 Influence of the concentration of $R, R$-DBT on chiral extraction

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Different, for example, 1, 2-dichloroethane > heptane > cyclohexane, which might be related with the polarity and interacts of different organic solvent with solute. The partition coefficients and enantioselectivity generally increase with the addition of length of alkyl chain of alcohol, $n$-octanol owns perfect extraction performances.

**F. The effect of concentration of chiral selector**

The effect of the concentration $R, R$-DBT on $k$ and $\alpha$ were investigated under the following conditions: 0.5 g/L ketoprofen, 50% methanol and 1, 2-chloroethane as organic solvent. It is found from Fig. 1 that the performances of chiral extraction increase with the increase of concentration of $R, R$-DBT. Because $R, R$-DBT forms complexes with the ketoprofen enantiomers, the increase of concentration of DBT facilitates the production of complexes. However, the performances of chiral extraction only increase slightly when the $R, R$-DBT concentration is above 0.2 mol/L. So the concentration of $R, R$-DBT was better about 0.2 mol/L.

**G. The effect of content of methanol**

The effect of the content of methanol on $k$ and $\alpha$ were investigated under the following conditions: 0.5 g/L ketoprofen, 0.2 mol/L $R, R$-DBT and 1, 2-chloroethane as organic solvent. We can see from Fig. 2, the performances of chiral extraction decrease with the increase of methanol content. The changes in enantioselectivity may be due to two different phenomena. First of
all, the lower concentration of methanol influences the solubility of ketoprofen in aqueous phase. On the other hand, the higher concentration of methanol (above 95%) might cause part organic solvent infiltrate into the aqueous phase which affects the performances of chiral extraction. Methanol and chiral selector might compete in actions with ketoprofen enantiomers by hydrogen bonding, which results in debasing the enantioselectivity. So the content of ethanol was better about 50%.

III. CONCLUSIONS

R, R-di-tartarates or S, S-di-tartarates are suitable for separation of ketoprofen enantiomers by enantioselective extraction at room temperature. The experimental results show that R, R-di-tartarates studied all form more stable diastereomeric complexes with ketoprofen S-enantiomer than with R-enantiomer.

IV. ACKNOWLEDGE

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REFERENCES


