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# Enantioseparation of Racemic Naproxen Esters on Cellulose Tris (4-methylbenzoate) Chiral Stationary Phase

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**Abstract:** Several kinds of racemic naproxen ester were successfully separated on CTMB chiral stationary phase with hexane-ethanol (98:2, vol./vol.) as the mobile phase. The influence of mobile phase composition and structure of racemic naproxen ester on chiral separation was studied and the chiral recognition mechanism of CTMB was discussed.

**Keywords:** Cellulose tris (4-methylbenzoate), naproxen, chiral stationary phase, enantioseparation.

Naproxen is a kind of widely used profen-type nonsteroidal anti-inflammatory agents. The enantiomers of racemic naproxen or its derivatives were often separated on non-cellulose based chiral stationary phase (CSP)[1]. We reported the chiral separation of racemic naproxen ethyl ester on cellulose tribenzoate (CTB)[2]. But no applications of cellulose tris(4-methyltribenzoate) (CTMB) chiral stationary phase for separating racemic naproxen or its derivatives were reported. In this paper, we successfully separated several kinds of racemic naproxen ester using self-prepared CTMB chiral column and the chiral recognition mechanism of CTMB was discussed.

The CTMB chiral column (25 cm × 0.4 cm i.d.) was prepared as previously reported[3]. (S)-Naproxen ((+)-6-methoxy-α-methyl-2-naphthylene acetic acid) and racemic naproxen were kindly donated by Xianju Pharmacy Factory and their ester derivatives (methyl, ethyl, *n*-propyl, *n*-butyl, 2-propyl, *sec*-butyl, *tert*-butyl and benzyl) were prepared with corresponding alcohols. Enantioseparations were performed using Waters 2690 Separations Module equipped with a Waters 996 Photodiode Array Detector and Waters Millennium$^{32}$ System.

The influence of the molar concentration of ethanol in hexane on the chiral separation was studied. Plots of the retention factors ($k'$) and separation factor ($\alpha$) of 2-propyl ester of racemic naproxen *vs* ethanol concentration are presented in panels (a) and (b) of **Figure 1**, respectively. As seen in **Figure 1a**, the retention of each enantiomer decreases with increasing mobile phase polarity. This suggests that the polar interaction between racemic naproxen ester and stationary phase (CTMB) is very strong. With increase in mobile phase polarity, the solubility of the esters in the mobile phase increases, then the decrease in $k'$ of each enantiomer is observed. But the enantioselectivity (**Figure 1b**) is essentially unchanged over the entire range of alcohol concentration. This indicates that this polar interaction is one type of achiral interaction and contributes little to the chiral recognition.

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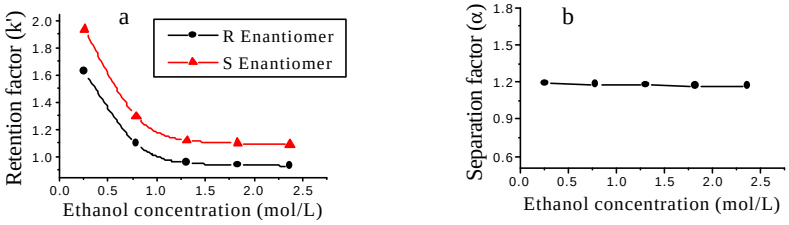
**Figure 1** Influence of the ethanol concentration in hexane on (a) *k*' and (b) α



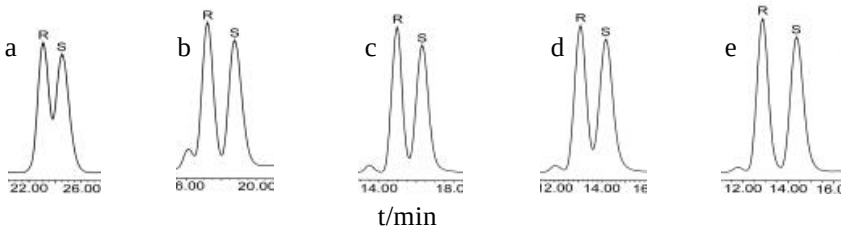

The influence of the structure of racemic naproxen ester on the chiral separation is listed in **Table 1**. As seen in **Table 1**, as the size of the end group of ester increases and as the end group becomes more sterically hindered, the retention factor ($k_1'$) decreases. This indicates that the smaller the size or the less the steric hindrance of the end group the stronger the inclusion of the solute into the chiral cavities. But stronger inclusion does not mean better resolution. The inclusion of 2-propyl ester is weaker than that of *n*-propyl ester, but its resolution (α and $R_P$) is the best among all eight kinds of racemic naproxen ester. This indicates that the fitness of the size and the steric structure of the solute are the decisive factor for the chiral recognition of CTMB. **Figure 2** shows the chromatograms of five kinds of ester of racemic naproxen under optimized conditions.

**Table 1** Influence of the structure of racemic naproxen ester on the chiral separation

| Esters | Methyl | Ethyl | *n*-Propyl | *n*-Butyl | 2-Propyl | *sec*-Butyl | *tert*-Butyl | Benzyl |
|---|---|---|---|---|---|---|---|---|
| $k_1'$ | 2.66 | 1.82 | 1.48 | 1.21 | 1.20 | 1.00 | 0.76 | 0.49 |
| α | 1.08 | 1.11 | 1.11 | 1.11 | 1.16 | 1.15 | 1.11 | 1.00 |
| $R_P$ | 0.45 | 0.68 | 0.73 | 0.59 | 0.90 | 0.59 | 0.22 | — |

$k_1'$: the retention factor of the first eluted enantiomer; $R_P$: Kaiser's peak separation index, $R_P = ((h_1 + h_2)/2\text{-}h_V)/((h_1 + h_2)/2)$, where $h_1$ and $h_2$ are the peak heights of the two enantiomers respectively and $h_V$ is the valley height between two enantiomer peaks.

**Figure 2** Chromatograms of five kinds of racemic naproxen ester




(a) methyl ester; (b) ethyl ester; (c) *n*-propyl ester; (d) *n*-butyl ester; (e) 2-propyl ester. Mobile phase, hexane-ethanol (98:2, vol/vol); detector wavelength, 273 nm; t, 25°C; flow rate, 0.5 mL/min. The configuration was identified with corresponding s-naproxen ester.

## References

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