Chiral Separations of Pharmaceuticals and Other Compounds on Lewis Acid-Base Anchored Zirconia Chiral Stationary Phases

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Chiral Probe Solutes Used in This Study

Synthesis of Lewis Acid-Base Modified Zirconia CSPs

General method for attaching CSPs to zirconia by Lewis acid-base anchors.

• Three different anchor groups:
  - APPA (aminopropylphosphonic acid)
  - DHNP (Dihydroxynorphedrine)
  - ASPA (Aspartic acid).

• These anchor groups were used to bond:
  - DNP-PG (3,5-dinitrobenzoyl-phenylglycine)
  - DNB-L-Leu (3,5-dinitrobenzoyl-Leucine)
  - DNB-PR (3,5-dinitrobenzoyl-proline).

• NAP-VAL (Naphthyl-valine)
• 1 or 2- NAP-LEU (Naphthyl-leucine)
• NAP (naproxen).

For this probe solute the new silica-based CSPs were better able to separate the enantiomers, whereas in other cases the zirconia-based CSPs were more selective.

List of Zirconia and Silica CSPs Studied

<table>
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<tr>
<th>Column</th>
<th>CSP</th>
<th>Anchor</th>
<th>Column Length (mm)</th>
<th>Normalized X (mm)</th>
<th>N/meter</th>
<th>Stability Rank</th>
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<td>1.14</td>
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</table>

Effect of Anchor on Separations by Zirconia-based CSPs

• The anchor type has relatively little effect on the ability of a given chiral selector to achieve a separation.

K' = K' initial

Effect of Selector on Separations by Zirconia-based CSPs

• There was very little effect between DNB-L-Leu and DNB-L-PG.
• Data shown is for DNB-L-Leu based Zirconia phases

Selective Component

Naphthyl-Leucine

Retention Factor

Retention Factor

Normalised Retention Factor

For this probe solute the new silica-based CSPs were better able to separate the enantiomers, whereas in other cases the zirconia-based CSPs were more selective.

List of Chiral Compounds Studied

- Trifluoranthryl ethanol
- APPA (aminopropylphosphonic acid)
- DHNP (Dihydroxynorphedrine)
- ASPA (Aspartic acid).
- DNP-PG (3,5-dinitrobenzoyl-phenylglycine)
- DNB-L-Leu (3,5-dinitrobenzoyl-Leucine)
- DNB-PR (3,5-dinitrobenzoyl-proline).
- NAP-VAL (Naphthyl-valine)
- NAP (naproxen).
- APPA anchored zirconia based CSPs have better chemical stability compared to the analogous silica based CSPs.
- Zirconia based CSPs have comparable chromatographic performance compared to the commercial silica based CSPs for a wide range of chiral compounds.
- Column to column and batch to batch reproducibility of the zirconia CSPs is very good.

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Zirconia-based CSP Column Stability

Zirconia-based CSP Column Challenge Conditions

Flushing eluent: 80/20 CH2Cl2/40mM NH4OAc in IPA (3000 column volumes) and 100% MeOH (2000 column volumes).

Flushing eluent: 100% IPA (1000 column volumes), 100%MeOH (3200 column volumes), 49.25/49.25/0.5 column volumes.

Effect of Parent Compound on Separations by Zirconia-based CSPs

Sample Separations for DNB-L-Leu/APPA Zirconia CSP

Batch-to-Batch Reproducibility

Conclusions

• APPA is the best anchor in terms of column stability.
• APPA anchored zirconia based CSPs have better chemical stability compared to the analogous silica based CSPs.
• Zirconia based CSPs have comparable chromatographic performance compared to the commercial silica based CSPs for a wide range of chiral compounds.
• Column to column and batch to batch reproducibility for the zirconia CSPs are very good.