Synthesis of A New Class of Pirkle-Type Chiral Stationary Phases on Zirconia

BINGWEN YAN¹, CLAYTON V. MCNEFF¹, PETER W. CARR², THOMAS R. HOYE². ¹ZirChrom Separations, Inc. 617 Pierce St., Anoka, MN 55303, ²University of Minnesota, 207 Pleasant Street SE, Minneapolis, MN 55455.

Specialists in High Efficiency, Ultra-Stable Phases for HPLC.
Goal-To Make Zirconia Based Chiral Stationary Phases (CSPs)

- Why Zirconia?
- General Synthetic Method
- Comparison of Zirconia-based CSPs with Commercial Silica-based CSPs
- Chromatographic Comparison of Different Anchors
- Stability Study of Zirconia-based CSPs
- Examples of Enantiomer Separations on Zirconia Based CSPs
- Conclusions – Zirconia Based CSPs Have Comparable Chromatographic Performance Compared to Silica Based CSPs. Fast Chiral Separations Can Be Achieved on Nonporous Zirconia Based CSPs.
Surface Chemistry of Zirconia

Brönsted Acid: \[ \text{ZrOH} + \cdot\text{OH} \rightleftharpoons \text{ZrO}^- + \text{H}_2\text{O} \]

Brönsted Base: \[ \text{Zr}_4^- + \text{H}^+ \rightleftharpoons \text{Zr}_4^+ \cdot \text{H}^+ \]

RPO$_3^{2-}$ or Catechol

Lewis Acid: \[ \text{Zr}^{4+}: \text{H}_2\text{O} + \text{R-COO}^- \rightleftharpoons \text{Zr}^{4+}: \cdot\text{OOC-R} + \text{H}_2\text{O} \]
New Way to Attach Chiral Selectors to Zirconia Surface

\[ ZrO_2 \]

\[ \text{Lewis Base (Anchor)} \]

\[ \text{Chiral Selector} \]
Three Anchors in This Study

- **APPA** (Aminopropylphosphonic acid)
- **ASPA** (Aspartic acid)
- **DHNP** (3,4-Dihydroxynorephedrine)

Anchors should have two function groups: (1) A group anchoring to zirconia surface, and (2) A group bonding to Chiral selector.
Chiral Selectors in This Study

- **DNB-LEU** (3,5-dinitro-benzoylLeucine)
- **DNB-PG** (3,5-dinitro-benzoylphenylglycine)
- **DNB-PRO** (3,5-dinitro-benzoylproline)
- **NAP-VAL** (Naphthoyl-valine)
- **2-NAP-LEU** (2-Naphthoyl-leucine)
- **NAP** (naproxen)
Example of Lewis Acid-Base Modified Zirconia CSPs

Steric Site

H-donor

EEDQ coupling reaction

π-acceptor

Lewis acid-base reaction

(APPAA)
List of Zirconia and Silica CSPs Studied

<table>
<thead>
<tr>
<th>Column</th>
<th>CSP</th>
<th>Anchor</th>
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<tbody>
<tr>
<td>Z1</td>
<td>DNB-Leu</td>
<td>APPA</td>
</tr>
<tr>
<td>Z2</td>
<td>DNB-Leu</td>
<td>Aspartic acid</td>
</tr>
<tr>
<td>Z3</td>
<td>DNB-Leu</td>
<td>DHNP</td>
</tr>
<tr>
<td>Z4</td>
<td>DNB-PG</td>
<td>APPA</td>
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<td>DNB-Pro</td>
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<tr>
<td>R1</td>
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</tr>
<tr>
<td>R2</td>
<td>DNB-Leu</td>
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</table>

Z1-Z10 zirconia based CSPs, R1, R2-commercialized silica based CSPs
Chromatographic Comparison of Zirconia- and Silica-CSPs

Probe solute: Trifluoroanthryl ethanol
Conclusion: Zirconia based CSPs performed quite well.
Much better separations for napropamide and 1-naphthyl leucine ester are obtained on zirconia-based CSPs.
Stability of Zirconia-based DNB-L-LEU

Retention Factor Stability for S-Napthyleucine ester

Flush Solvent: 49.5/49.5/1 Hexane/IPA/TFA

Zirconia-based CSP is a very stable CSP.
Chromatographic Comparison of Differently Anchored Zirconia-based DNB-L-LEU

Different anchors show different selectivity.
Stability Comparison of Differently Anchored Zirconia-Based DNB-L-LEU

Flush Solvent: 100% MeOH

Flush Solvent: 99/1/0.1 Hexane/IPA/TFA

Test solute: trifluorantrhyl ethanol. Note that the retention factor ratio is for the less retained isomer.
Enantiomer Separations on DNB-L-LEU Modified Zirconia Phase Anchored via APPA

Selected Chromatograms of Chiral Compounds on Zirconia Based DNB-L-LEU Anchored with APPA.
Fast Chiral Separation on Nonporous Zirconia-based DNB-L-Leu

Chiral compounds on nonporous and porous zirconia-based DNB-L-Leu anchored with APPA. Chromatographic conditions: mobile phase 99/1 Hexane/IPA, probe solute: (±)1-naphthyl leucine ester.
Conclusions

• Flexible attachment chemistry.
• APPA is the best anchor in terms of column stability.
• Zirconia based CSPs have comparable chromatographic performance compared to the commercial silica based CSPs for a wide range of chiral compounds.
• Fast Separation can be achieved on nonporous zirconia based CSPs.
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