New Method for the Generation of Chiral Stationary Phases on Nonporous Zirconia for Fast Chiral Separations

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Abstract

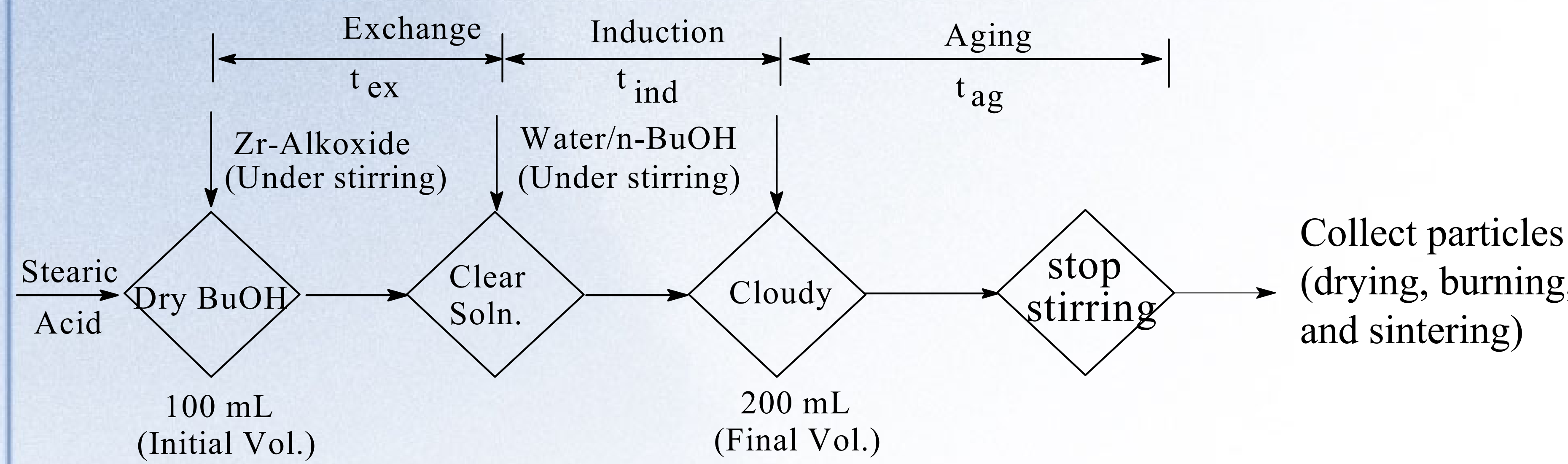
The synthesis and use of a new class of nonporous zirconia chiral stationary phase (CSP) for ultrafast chiral analytical HPLC is described. The particle size of these nonporous zirconia spheres is easily controlled within the average diameter range of 1-3 microns. A method for the modification of nonporous zirconia with different chiral selectors is described that uses the Lewis acid-base properties of the zirconia surface for attachment of brush-type (i.e. Pirkle-type) chiral stationary phases. The general method develop here for modifying nonporous zirconia with different chiral selector involves two main steps: 1) attach an appropriate anchor group to the zirconia surface through a Lewis acid-base reaction and 2) covalently attach the desired CSP to the anchor group using standard EEDQ (N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) amide bond formation chemistry. In this work we use aminopropylphosphonic acid (APPA) as a Lewis base anchor group and 3,5-dinitrobenzoyl-Leucine (DNB-LEU) as a chiral selector. The stability of the zirconia-based CSP was studied and found to be very stable under very aggressive (49.5/49.5/1 Hexane/IPA/TFA) conditions, which quickly degraded an analogous silica-based CSP. The nonporous nature of the particles allows for very good mass transfer properties compared to porous substrate particles. A number of fast chiral separations are shown.

Outline

- **Development of a Method for the Synthesis of Nonporous Zirconia**
- **Verification of the Nonporous Nature of Particles**
- **Nonporous Zirconia Surface Chemistry**
- **New Synthetic Method to Make Nonporous Zircona-based CSPs**
- **Stability Comparison Between Porous Zirconia-based and Silica-based CSPs**
- **Chromatographic Comparison Between Porous and Nonporous Zirconia-based Chiral Stationary Phases**
- **Conclusions-The Zirconia-based CSPs Developed Here Offer a Chemically Flexibile Way to Produce a Variety of Stable Pirkle-Brush Type CSPs.**

Particle Synthesis and Characterization

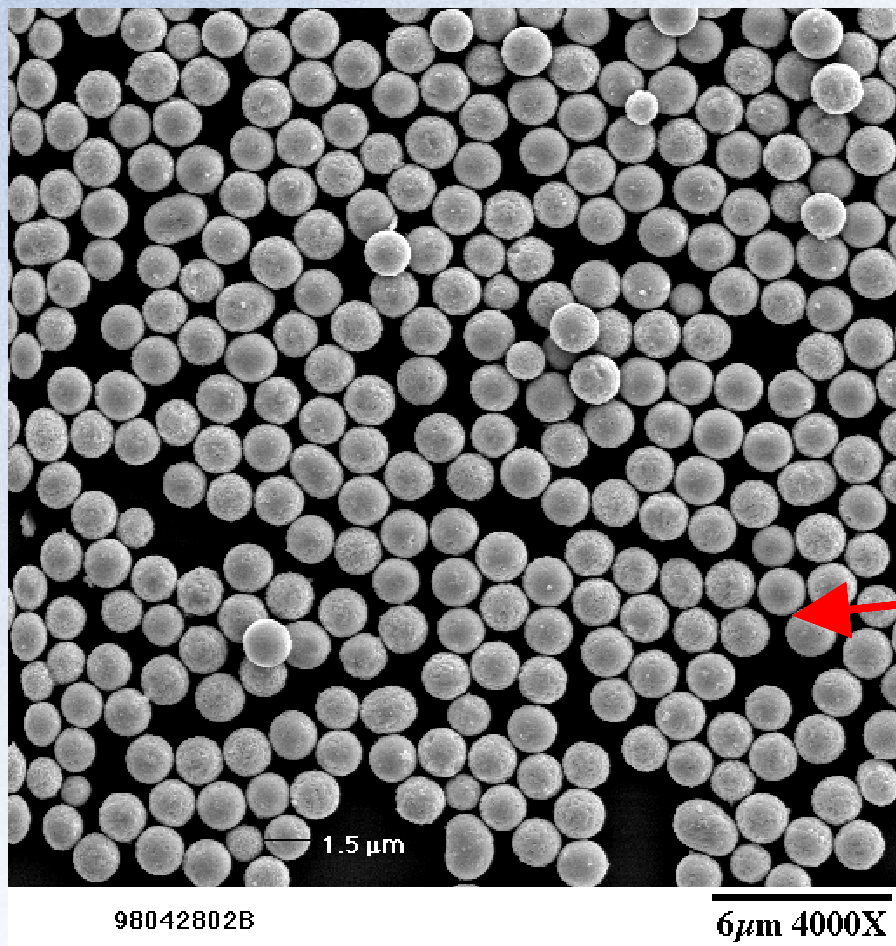
1.) Preparation of mono-dispersed nonporous zirconia particles.



2.) Determination of surface area using fluoride adsorption.

3.) Electron scanning microscopy.

SEM of Nonporous Zirconia Particles



The resulting particles are monodisperse, spherical and nonaggregated.

Surface Area of Nonporous Zirconia Based on Fluoride Adsorption

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Batch No.	Weight of ZrO_2(g)	Surface area[a] (m^2/g)
1	0.11351	1.78
2	0.10284	1.87
3	0.12012	1.82
4	0.10967	1.87
5	0.11064	1.76
Average	---	1.82
Standard Deviation	---	0.051

Good Batch-to-batch reproducibility

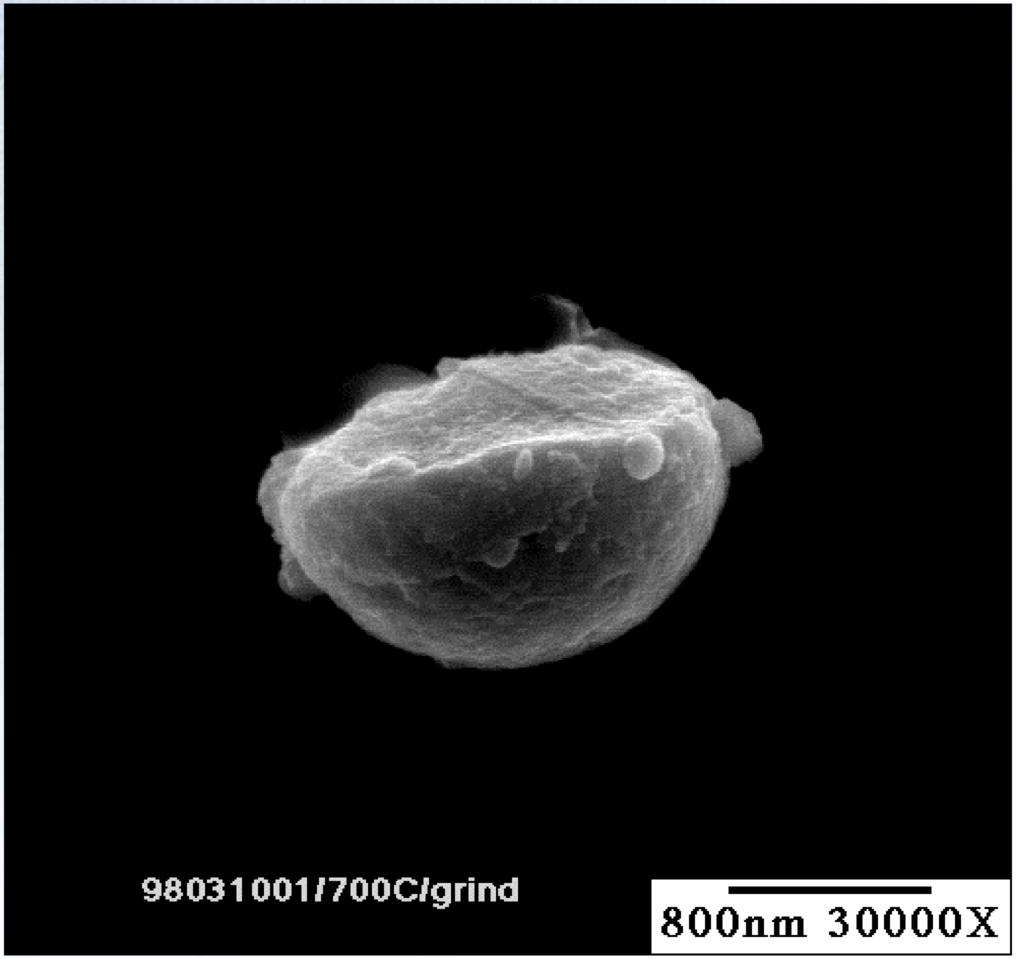
Only 2.9 times theoretical area of 1.65 micron spheres--easily accountable by surface texture

[a] Based on using porous zirconia of known surface area (by BET) as standard

[b] The particle size is 1.65 micron, the density of zirconia is 5.8 g/ml, theoretical surface area is 0.63 m^2/g.

SEM of the Interior of a Nonporous Zirconia Particle

The nonporous nature of the particles was verified by grinding a sample and looking at the interior of a broken particle.



Surface Chemistry of Nonporous Zirconia

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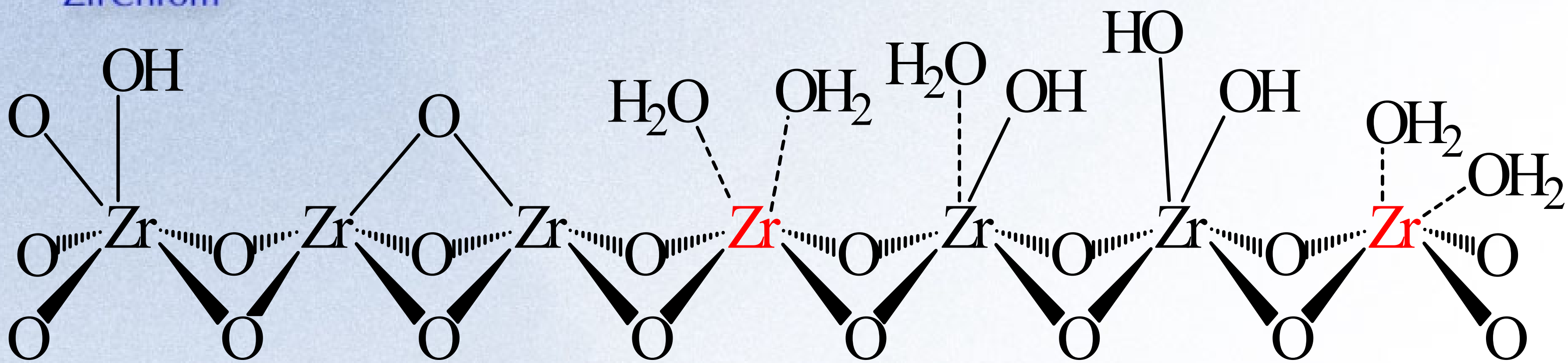
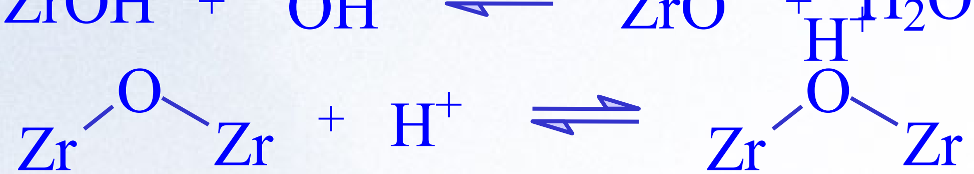


Brönsted Acid: $ZrOH + {}^{-}OH \rightleftharpoons ZrO^{-} + H_2O$

Brönsted Base:

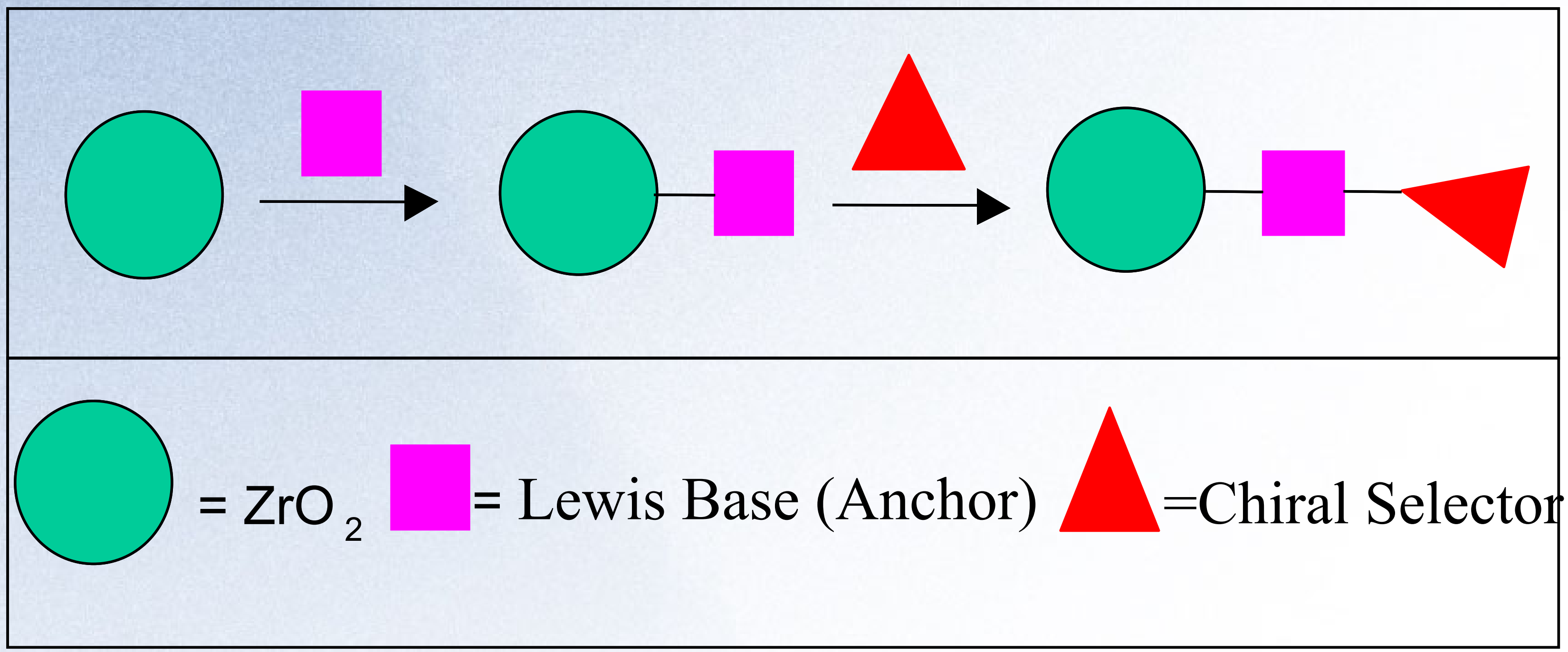


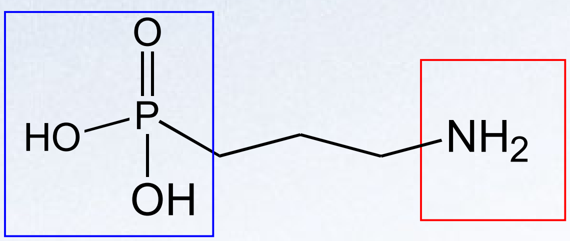
RPO_3^{2-} or Catechol

Lewis Acid: $Zr^{4+}: H_2O + R\text{-}COO^{-} \rightleftharpoons Zr^{4+}:{}^{-}OOC\text{-}R + H_2O$

Lewis acid sites allow for the attachment of chiral stationary phases that have a Lewis base functionality.

A General Scheme to Attach Chiral Selectors to Nonporous Zirconia





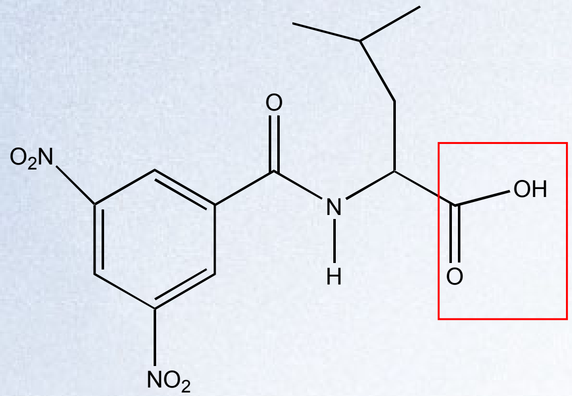
APPA

(aminopropylphosphonic acid)

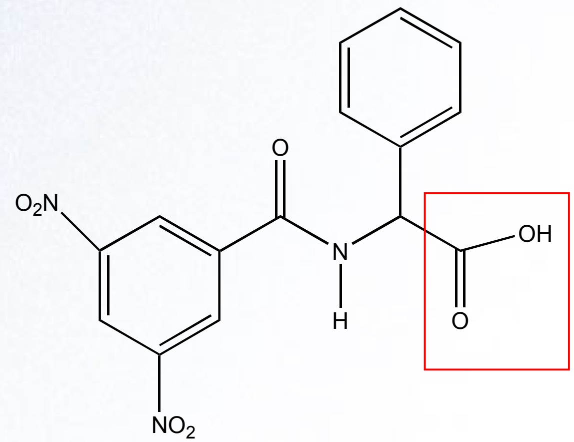
Anchors should have two function groups: (1) A Lewis base group chemisorptions to the zirconia surface, and (2) A group capable of bonding to Chiral selector.

Chiral Selectors and Probe Solutes in This Study

Selectors

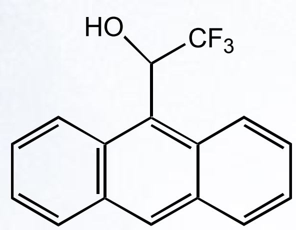


DNB-LEU (3,5-dinitro-benzoylLeucine)

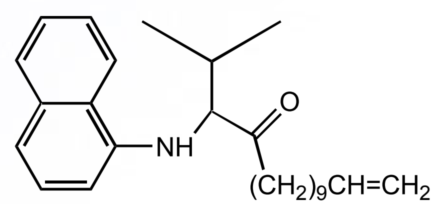


DNB-PG (3,5-dinitro-benzoylphenylglycine)

Probe Solutes

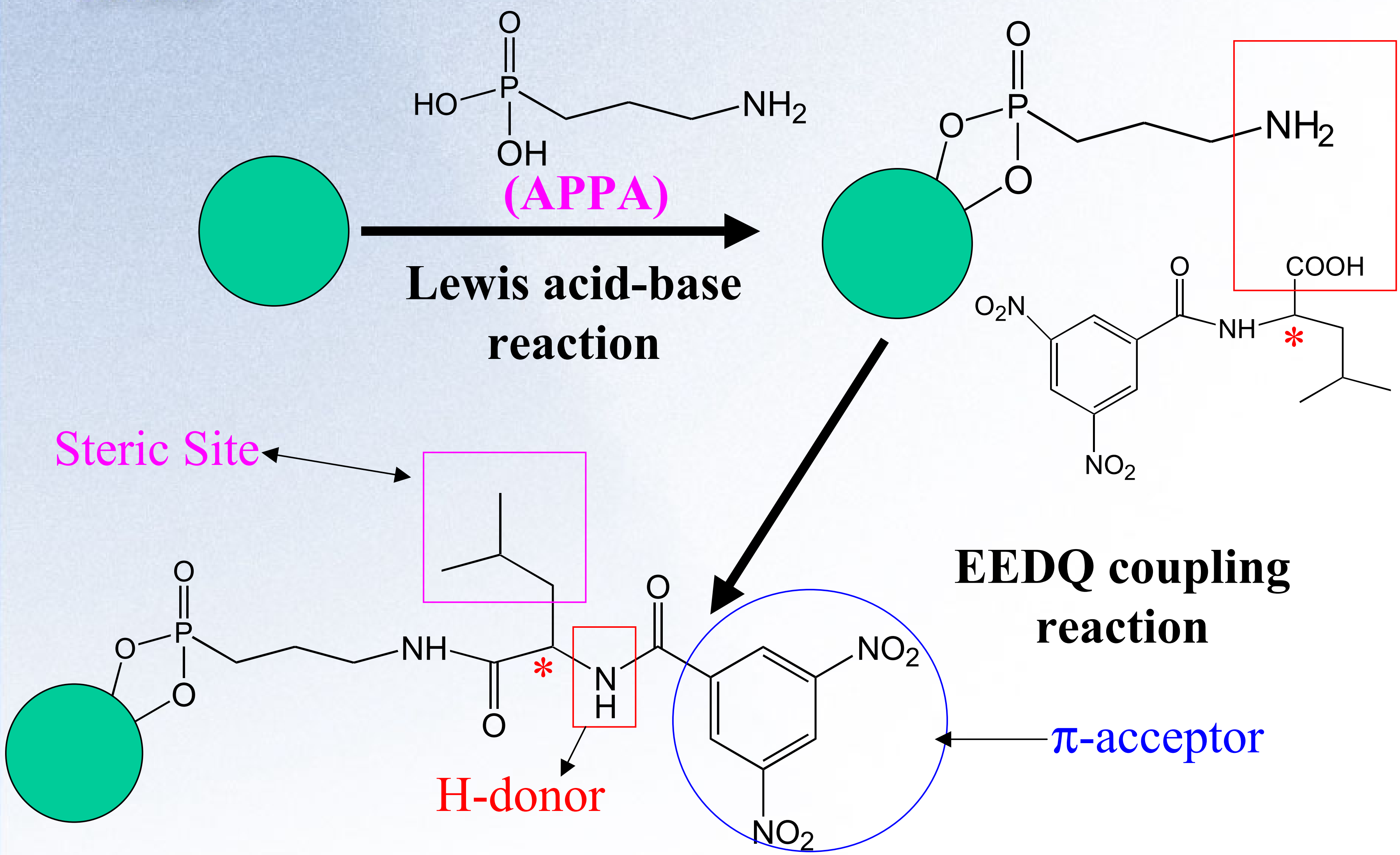


Napropamide



1-naphthyl leucine ester

Example Synthesis of a Lewis Base Modified Nonporous Zirconia CSP



Stability Comparison of Porous Silica and Zirconia-based DNB-L-LEU

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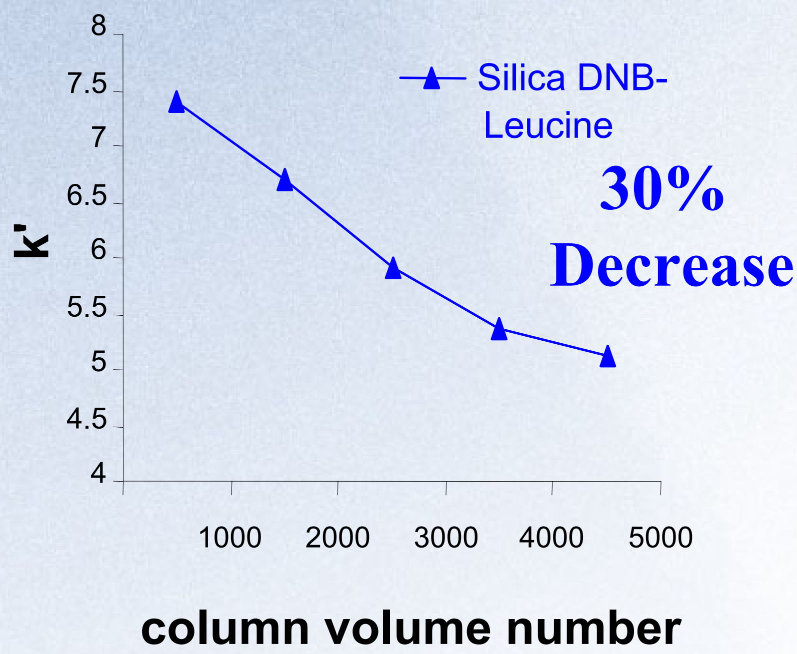
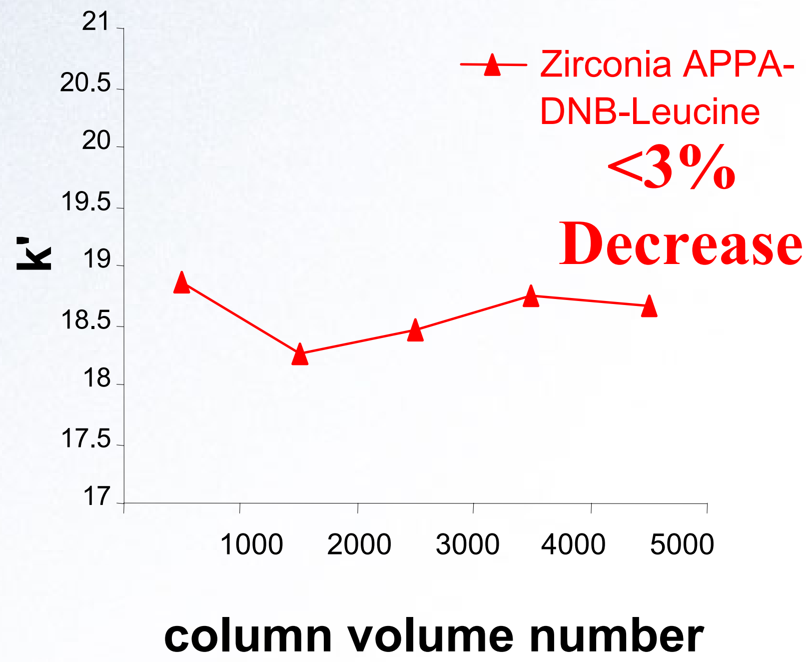
Retention Factor Stability for S-Napthylleucine ester

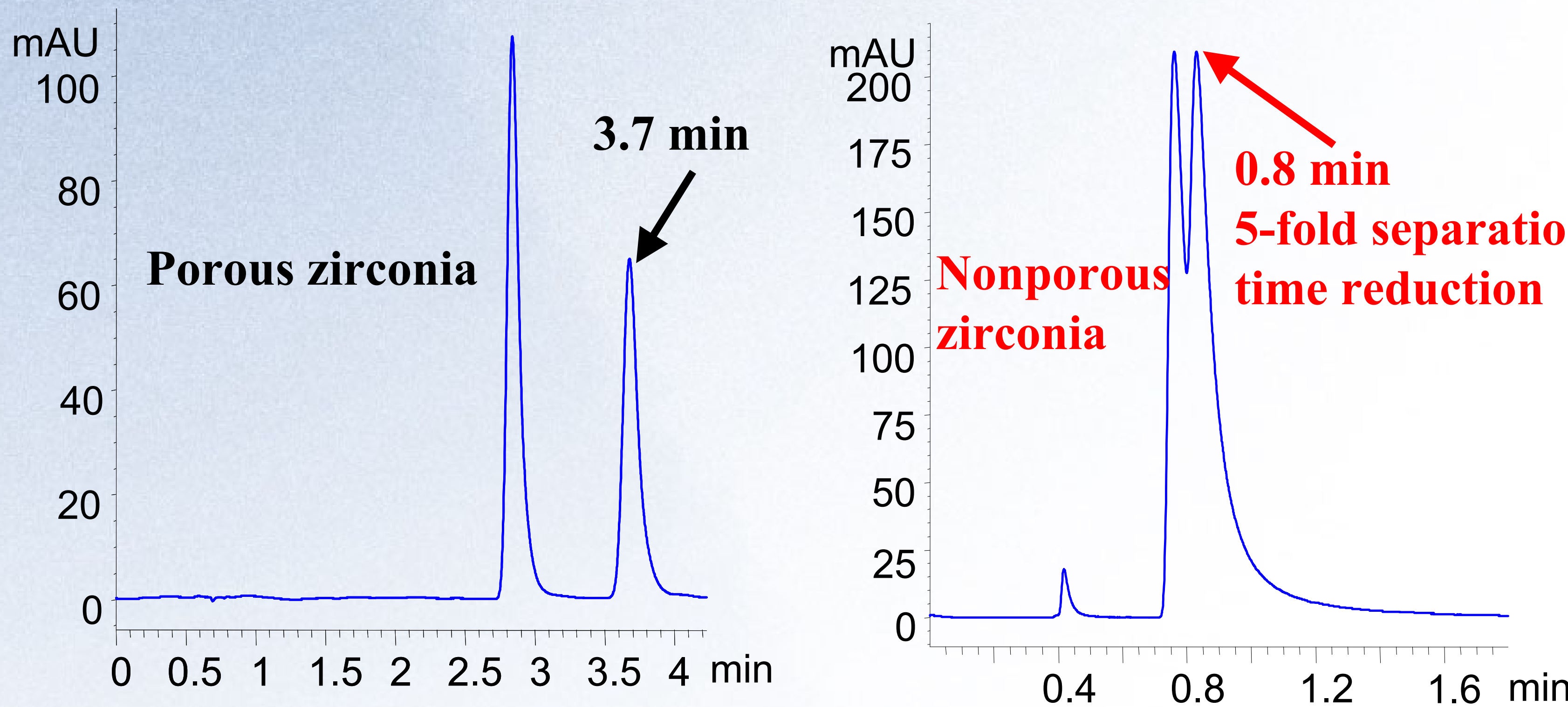




Flush Solvent: 49.5/49.5/1 Hexane/IPA/TFA

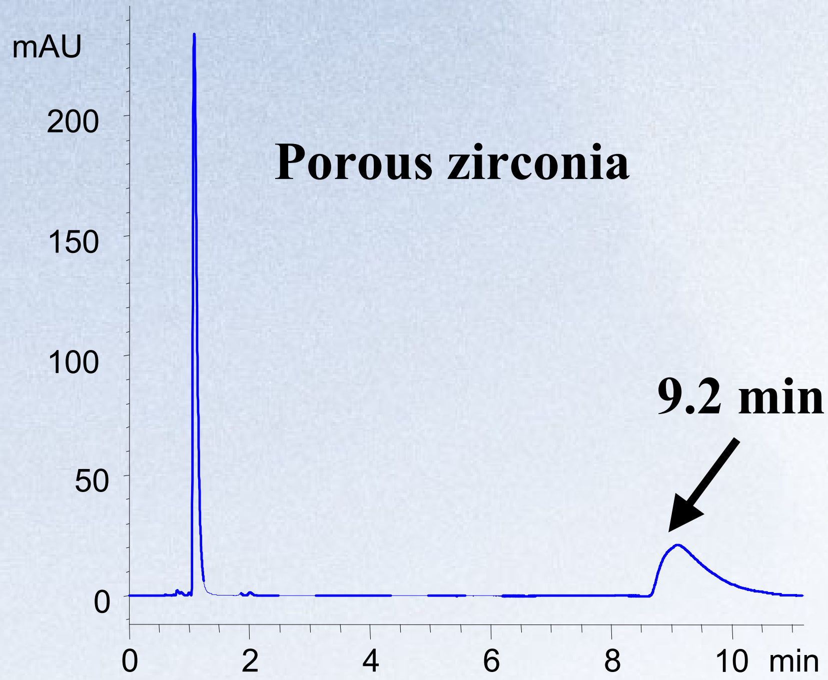
Zirconia-based CSP is much more stable than the silica-based CSP.

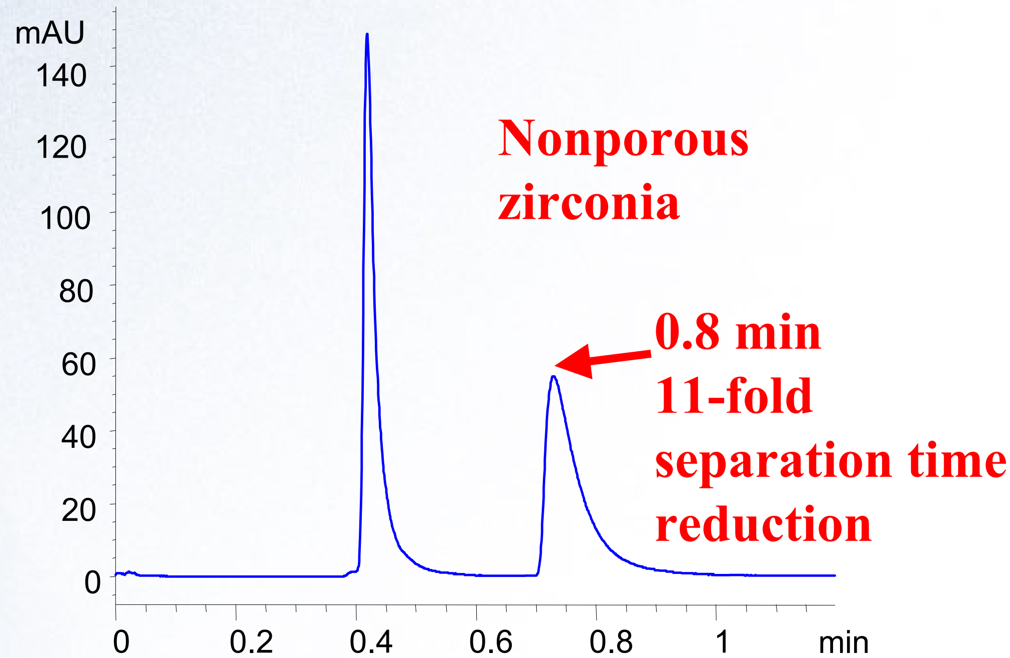
Chromatographic Comparison Between Nonporous and Porous Zirconia-based DNB-L-PG



Chiral compounds on nonporous and porous zirconia-based DNB-L-PG anchored with APPA. Chromatographic conditions: mobile phase 99/1Hexane/IPA, probe solute: (±)trifluoroanthryl ethanol.

Chromatographic Comparison Between Nonporous and Porous Zirconia-based DNB-L-Leu





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

Conclusions

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- A general method was developed for the reproducible production of chiral stationary phases based on nonporous zirconia macrospheres.
- The zirconia particles were shown to be nonporous by SEM of a cross section and fluoride adsorption.
- Flexible attachment chemistry allows for modification of the zirconia surface with different anchors and different chiral selectors.
- APPA anchored chiral stationary phases have better chemical stability than analogous silica based CSPs.
- Fast chiral separations are possible on APPA anchored nonporous zirconia-based chiral stationary phase.

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Acknowledgement

National Science Foundation

(Grant # DMI-990871)