From Concept to Application: An Industrial Look at the CISS Effect for Chiral Separation

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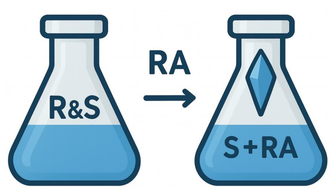
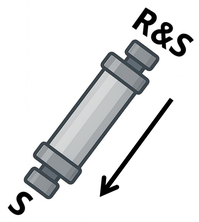
Chirality is a critical factor in the pharmaceutical industry. Although significant progress has been made in developing routes to enantiopure compounds, existing methods often suffer from inefficiencies. This drives ongoing search for alternative strategies that can overcome these limitations. Could the Chirality-Induced Spin Selectivity (CISS) effect, present a new strategy for enantioselective control?

The Industrial State of Chiral Separation

Classical resolution
- \+ Scalable
- \+ Cost-effective
- − Identifying good chiral resolving agent
- − Require acid or basic functional group



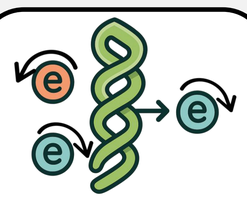
Chromatographic resolution
- \+ Highly selective & precise
- \+ Broad range of substrate types
- − Scale up limited
- − Expensive



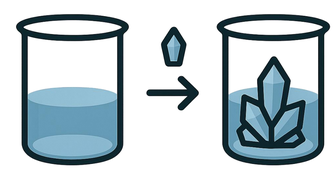
Enantiopure

?

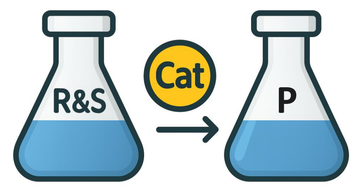
CISS Effect



Preferential crystallization
- Scalable +
- No need for a resolving agent +
- Conglomerate −
- Low predictability −

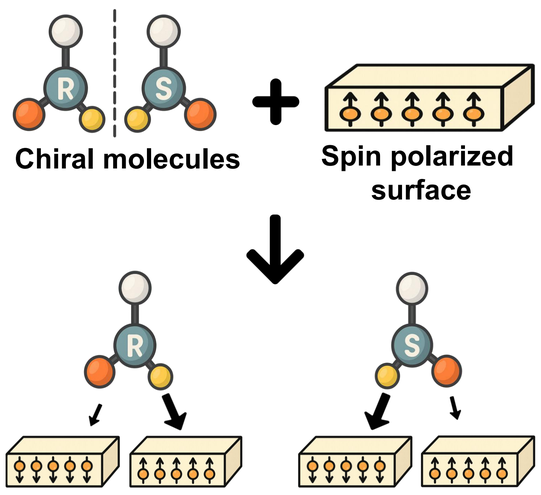


Kinetic resolution
- Highly selective +
- Broad range +
- Require high selectivity −
- Enzyme/catalyst specificity −



The CISS effect as a Chiral Separation Technique?

Proposed Mechanism

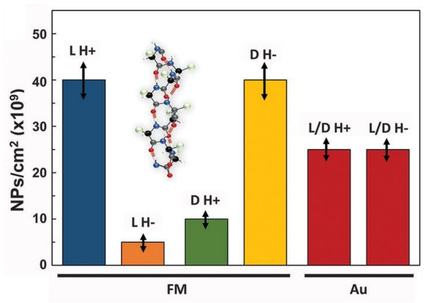


Chiral molecules exhibit a **spin selective interaction** with the substrate:

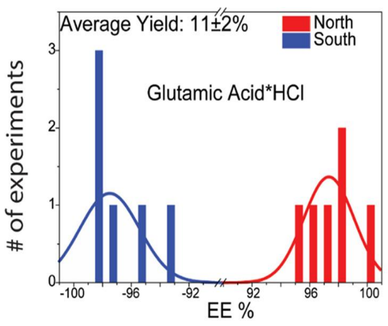
Each enantiomer **favors one spin** polarization over the other, leading to **preferred adsorption**.

Key Experimental Insights

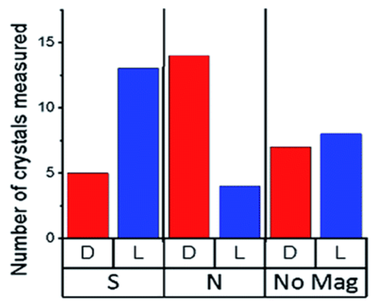
Banerjee-Ghosh et al. (2018)[1]
- Peptides, dsDNA & Cys on ferromagnetic substrate.
- Enantiospecific adsorption depending on the magnetization direction
- Adsorption rate of one enantiomer was faster.



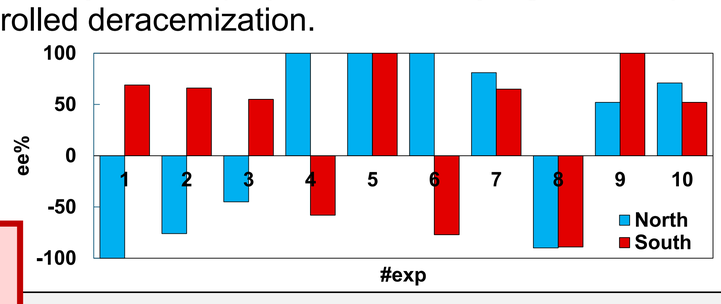
Bhowmick et al. (2021)[3]
- Asn, Glu ·HCl, Thr & imeglimin·HCl on ferromagnetic substrate.
- Enantiospecific crystallization on opposite magnetic direction simultaneous.
- Up to 97% enantiomeric excess



Tassinari et al. (2019)[2]
- Asn, Glu ·HCl & Thr on ferromagnetic substrates
- Enantiospecific crystallization depending on magnetization direction
- Enantiomeric excesses up to 60% observed.



Current Study (2025)
- Sodium chlorate crystallized on ferromagnetic substrate under controlled environment
- Preliminary data display no statistically significant spin-controlled deracemization.



A compelling Principle – But a Practical Tool?

Scalability, no demonstrated route to industrial scale

Reproducibility, reported results vary depending on setup and systems

Sensitive systems, highly dependent on controlled setup

Low yields, high enantiomeric excesses often come with cost of low yields

Limited scope, only shown for a few systems, limited to conglomerates

Can spin-based approaches even compete with traditional enantioselective methods?

Not yet. However, if CISS-based separation is to move beyond conceptional curiosity, it likely needs to be re-engineered into **continuous flow systems**, like column chromatography. This aligns with the non-equilibrium, short-ranged interaction and selective adsorption potential of the CISS effect.

[1] Banerjee-Ghosh et al., *Science*, (2018), 360, 1331–1334
[2] Tassinari et al., *Chem. Sci., (*2019), 10, 5246–5250
[3] Bhowmich et al., *Cryst. Growth Des*. (2021), 21, 2925−2931

"Funded by the European Union, in the framework of the Marie Skłodowska-Curie Actions - CISSE Doctoral Network, under Grant Agreement n° 101071886. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Executive Agency (REA). Neither the European Union nor the granting authority can be held responsible for them."