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Deracemization by mechanochemistry: green access to pure enantiomers

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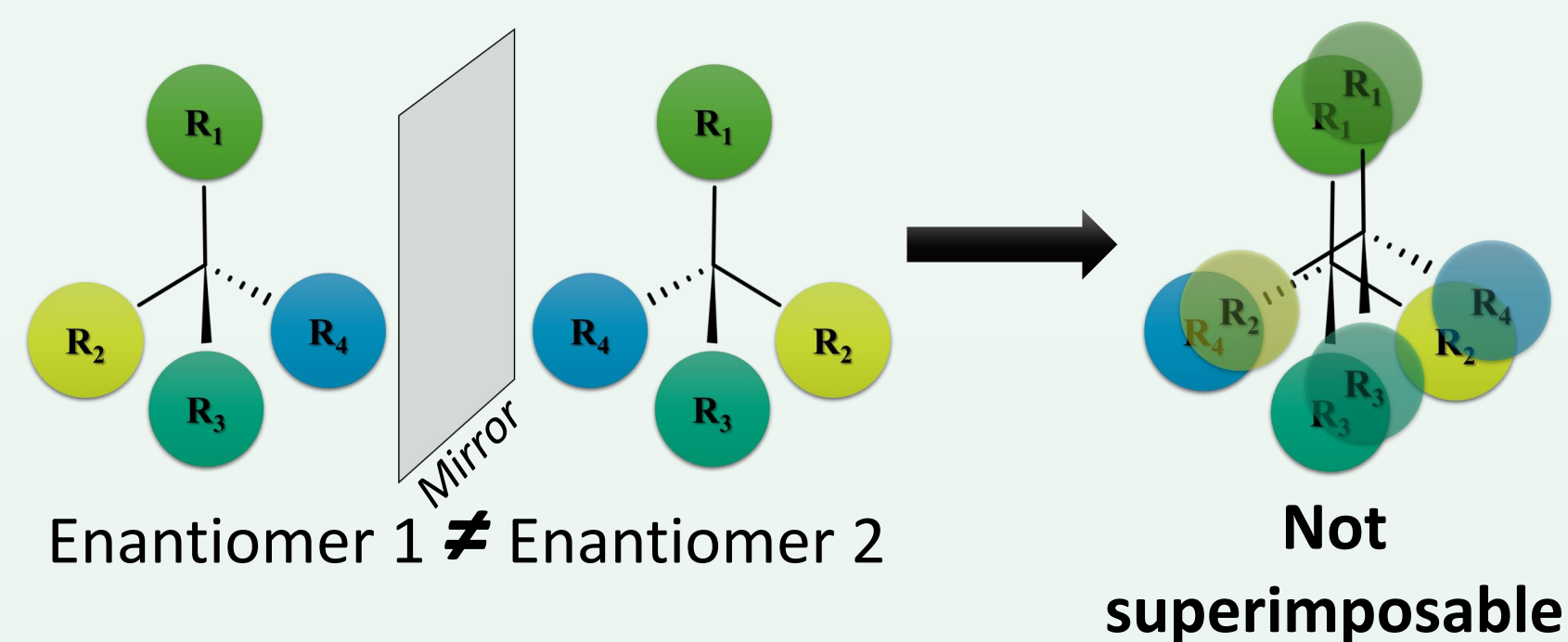
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CONTEXT OF THE STUDY

CHIRALITY AND ITS ISSUE



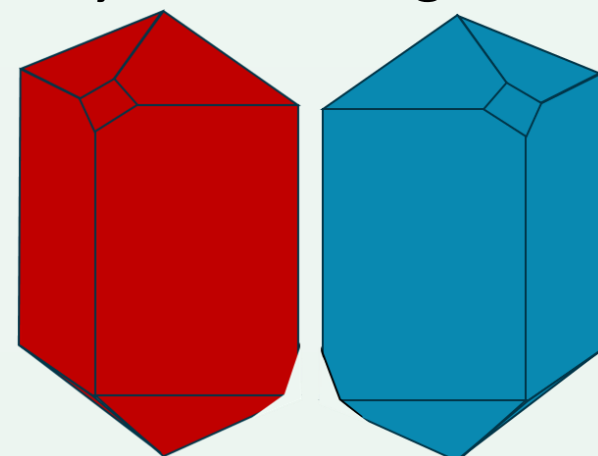
Two enantiomers can have **different biological effects**.

50% of the marketed drugs are **chiral** and the undesired enantiomer can induce **side effects**.^[1]

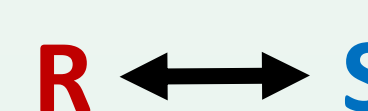
NECESSITY TO SEPARATE ENANTIOMERS

Three requirements^[2]:

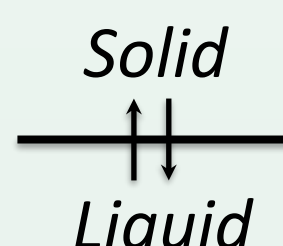
✓ **Conglomerate forming system**
Both enantiomers don't crystallize together



✓ **Racemization**

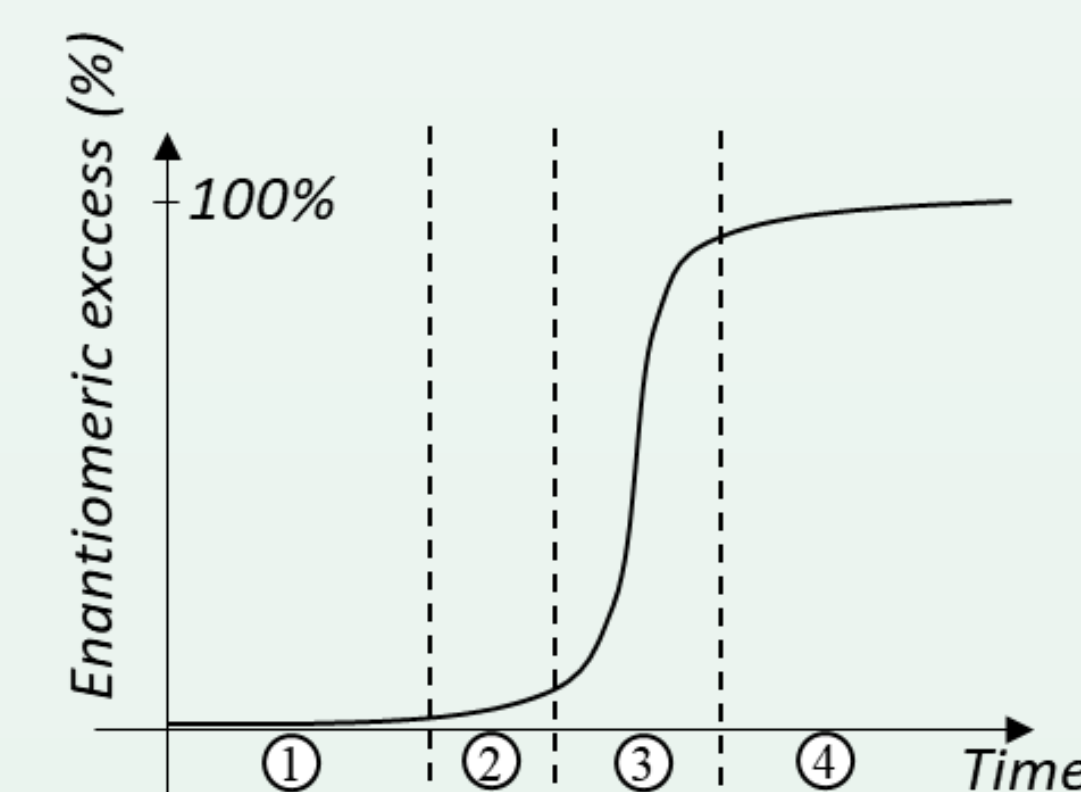


✓ **Dissolution - Crystallization**



THE PROCESS OF DERACEMIZATION

- ① A **racemic mixture** is in suspension with a racemizing agent.
- ② Once an **imbalance** is created between
- ③ both enantiomers, an **autocatalytic process** begins. Only one population of enantiomer increases in the solid phase.
- ④ With a step of filtration, the **enantiopure solid** is isolated.

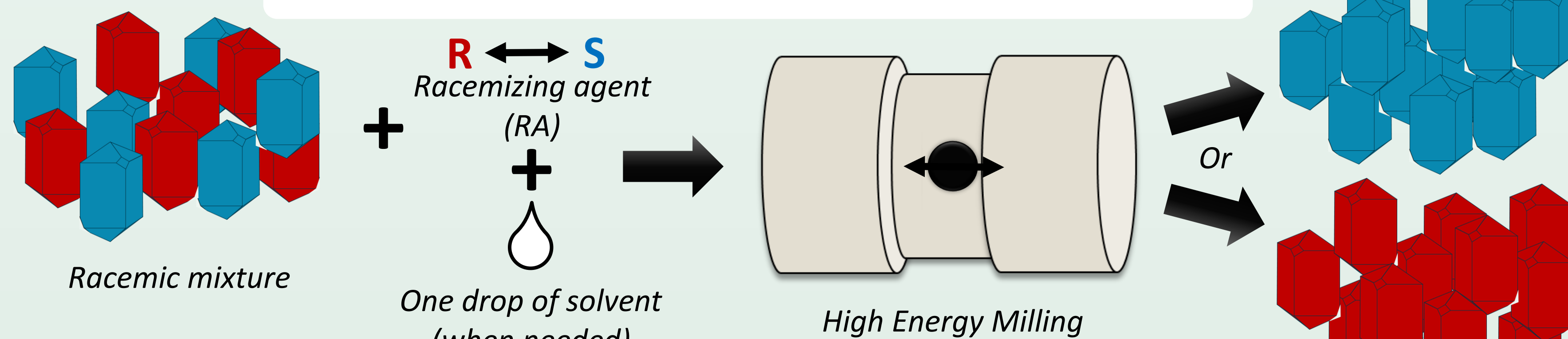


Schematic representation of the solid *e.e.*

MAJOR DRAWBACK : NECESSITY TO USE SOLVENT

TRANSFERRING THE PROCESS TO MECHANOCHEMISTRY

CONCEPT OF MECHANOCHEMICAL DERACEMIZATION



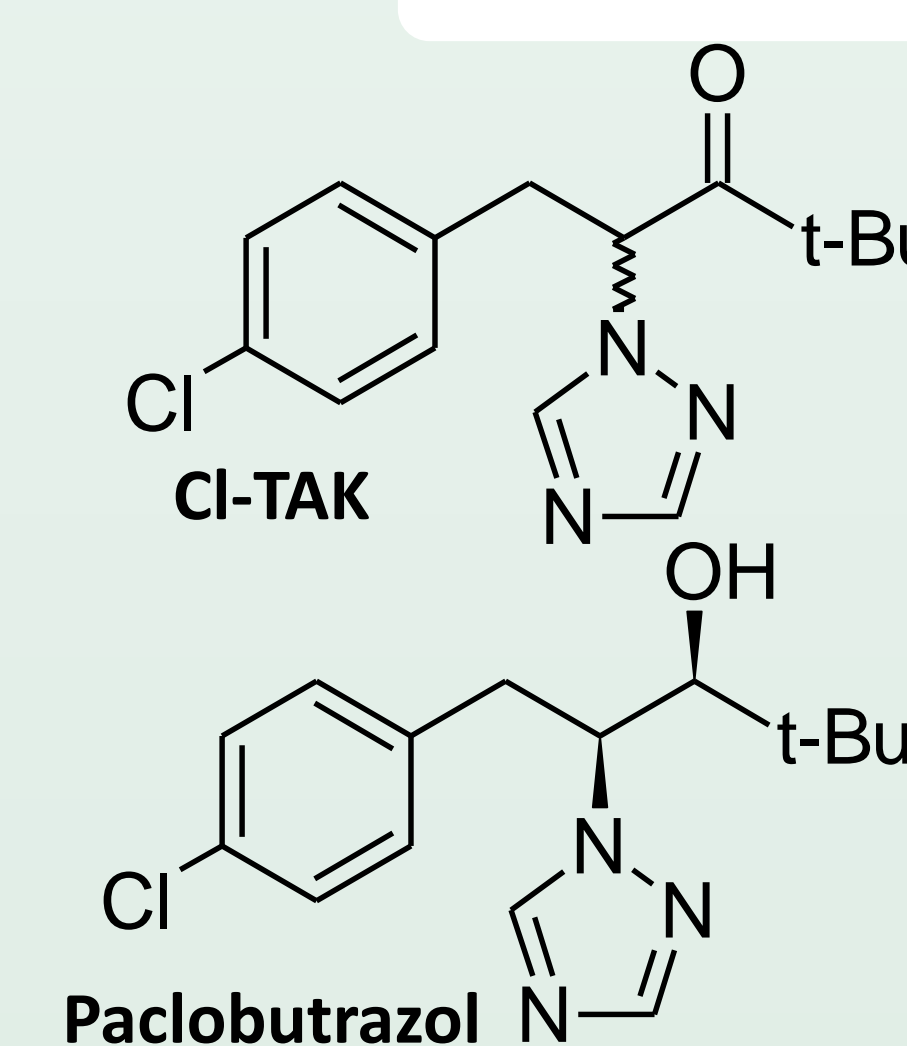
The conglomerate and the racemizing agent are gathered in the jar (solvent is added if needed).

The milling will ensure : (i) Overcoming the **energy barrier** for chemical racemization.

(ii) A **dynamic exchange** of matter between a racemic phase (likely amorphous and/or liquid) and the enantiopure solid.

THREE REQUIREMENTS ARE FULLFILLED WITH A LOWER QUANTITY OF SOLVENT

STUDIED COMPOUND



CI-TAK is a **conglomerate forming system**.

This molecule is the precursor of **Paclobutrazol**: a plant growth inhibitor.

It is known to be **easily racemized and deracemized** by using NaOH as racemizing agent.^[3]

No polymorph or solvate is known.

GOOD CANDIDATE FOR MECHANOCHEMICAL DERACEMIZATION

FROM THEORY TO PRACTICE

KINETICS STUDY

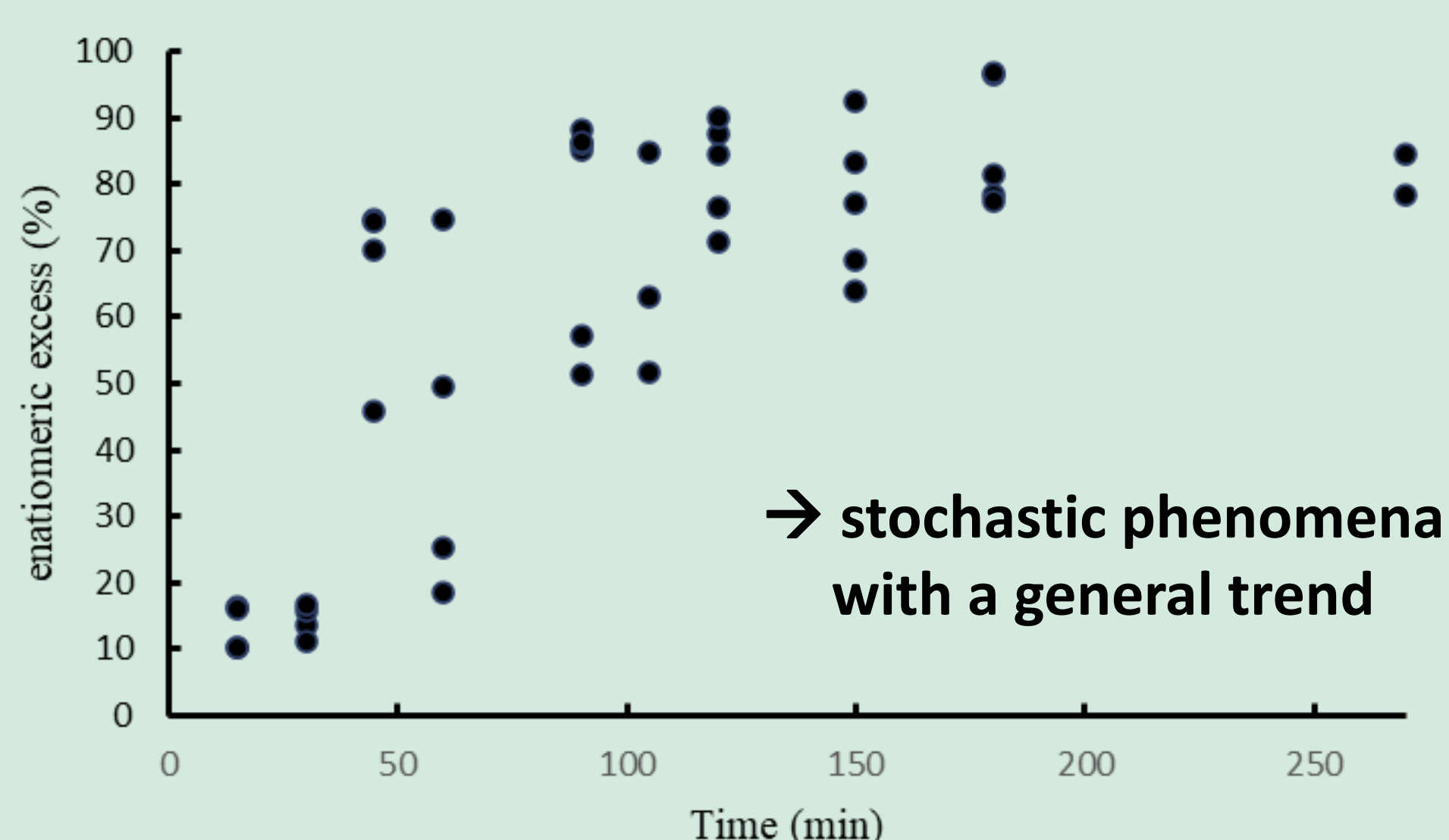
Operatory conditions:

- 100mg of solid + 2.5eq of NaOH + 10 μ L of water.

STARTING WITH AN INITIAL *e.e.*

- The starting solid is **slightly enriched (10% *e.e.*)** to reduce the time required to create an imbalance between the two populations of enantiomeric crystals.

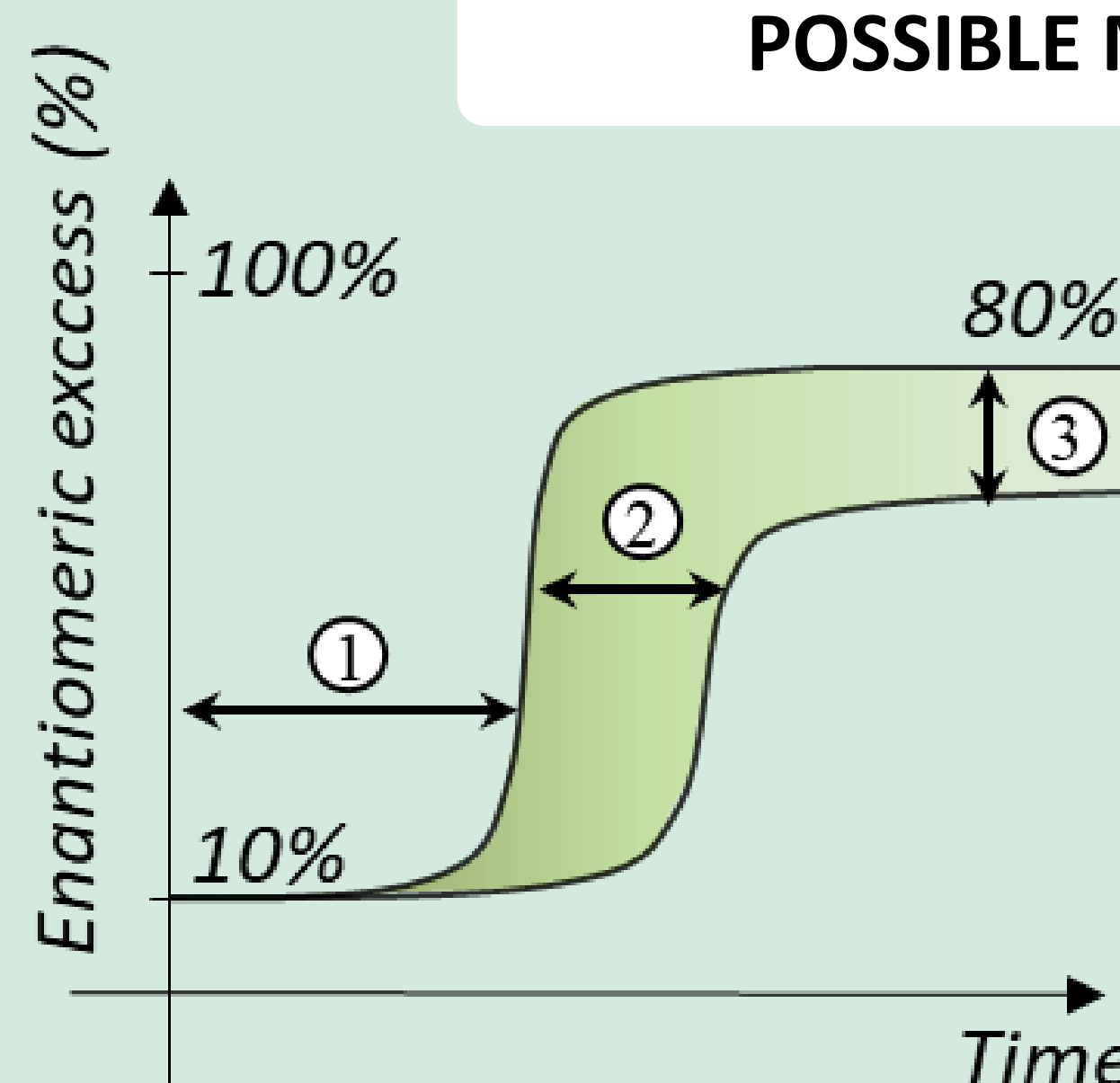
→ for each milling time, each experiment is **stopped and analyzed**. All the results are obtained by starting again the experiments **from the initial *e.e.***



Kinetics monitoring of CI-TAK mechanical deracemization^[4]

DERACEMIZATION PROCESS CAN BE TRANSFERRED TO MECHANOCHEMISTRY

POSSIBLE MECHANISM ENVISAGED FOR THE PROCESS

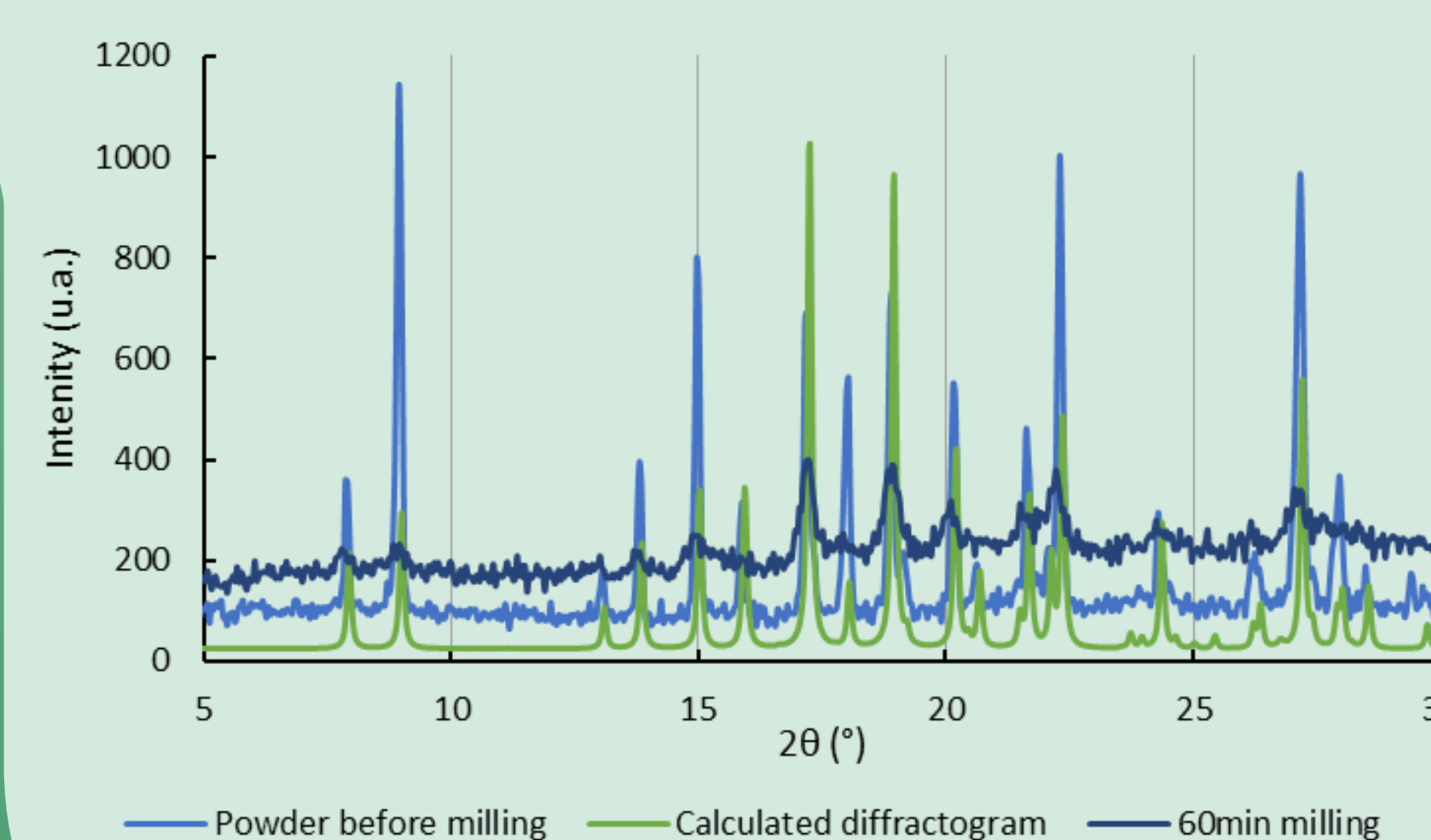


STARTING WITH A RACEMIC MIXTURE

Total deracemization by starting with a **racemic mixture** has been performed in less than **390min**. Comparing to classical deracemization, the process is **faster** (generally in the order of hours).

- ① Deracemization begins after an **equilibration time** which is typical of mechanochemistry.^[5]
- ② Once the deracemization starts, a global trend is observed : the **enantiomeric excess increases**. The stochasticity of the process explains the spread of the results.
- ③ Enantiomeric excesses are all reaching a value around 80% instead of 100%. As the racemic and enantiopure phases are solid, **no separation is possible** inducing a decrease of the *e.e.*

Similarly to classical deracemization, a **sigmoidal trend** is obtained possibly highlighting a similar mechanism.



After milling, XRPD reveals **lower intensities and broader peaks**.
→ **Reduction of the crystal size distribution ?**
→ Presence of a transient **amorphous phase ?**

DERACEMIZATION PROCESS PRESENTS SIMILARITIES WITH THE "CLASSICAL" PROCESS

CONCLUSION & PERSPECTIVES

This study is a proof that deracemization process can be conducted by mechanochemistry with improved kinetics (deracemization of a compound takes less than 3 hours). As for deracemization in solution, this process seems **stochastic**.

Even if it represents a scientific advance in the field of chiral discrimination and mechanochemistry, **many questions are remaining concerning the mechanism**. Is there an **intermediate phase** that allows the racemization ? Is it possible to reach this phase **without any solvent**, and if yes, which parameters must be changed? Does the **temperature** have an influence on the results ?

The next step of this work is the study of **mechanochemical racemization** in order to better understand the deracemization.

References

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