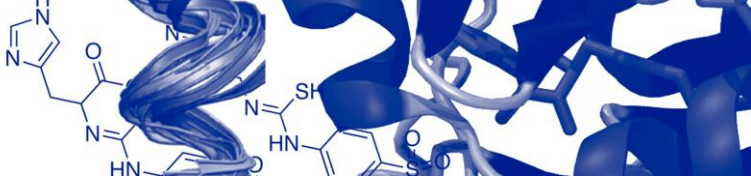
Computational Chemistry Group

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

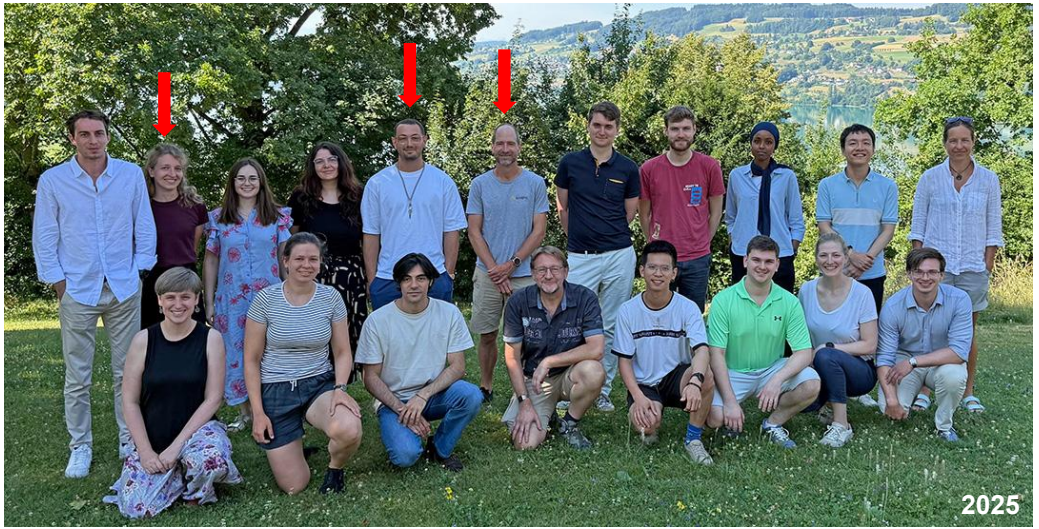


Better Informed Distance Geometry: 10 Years Anniversary of ETKDG

Prof. Sereina Riniker

14th RDKit UGM, September 10, 2025

Acknowledgements



Current: **Jessica Braun**, Domen Pregeljc, Enrico Ruijsenaars, Riccardo Solazzo, Carl Schiebroek, Patricia Brandl, **Niels Maeder**, Lucija Glazer, Jakob Teetz, Antonia Kuhn, Eva Hermann, Dr. Shu-Yu Chen, **Dr. Greg Landrum**

Alumni: **Jagna Witek**, Annick Renevey, Dominik Sidler, Dr. Patrick Bleiziffer, Dr. Gerhard König, Dr. Carmen Esposito, Dr. Gregor Weiss, **Shuzhe Wang**, Lennard Böselt, Benjamin Ries, Salomé Rieder, Dr. Albert Hofstetter, Thomas Stadelmann, Dr. Anna Sophia Kamenik, Stephanie Linker, Dr. Emilia Pécora de Barros, Dr. Marta Brucka, Moritz Thürlemann, Marc Lehner, Candide Champion, Dr. Felix Pultar, Paul Katzberger, Dr. Franz Waibl, Dr. Idil Ismail

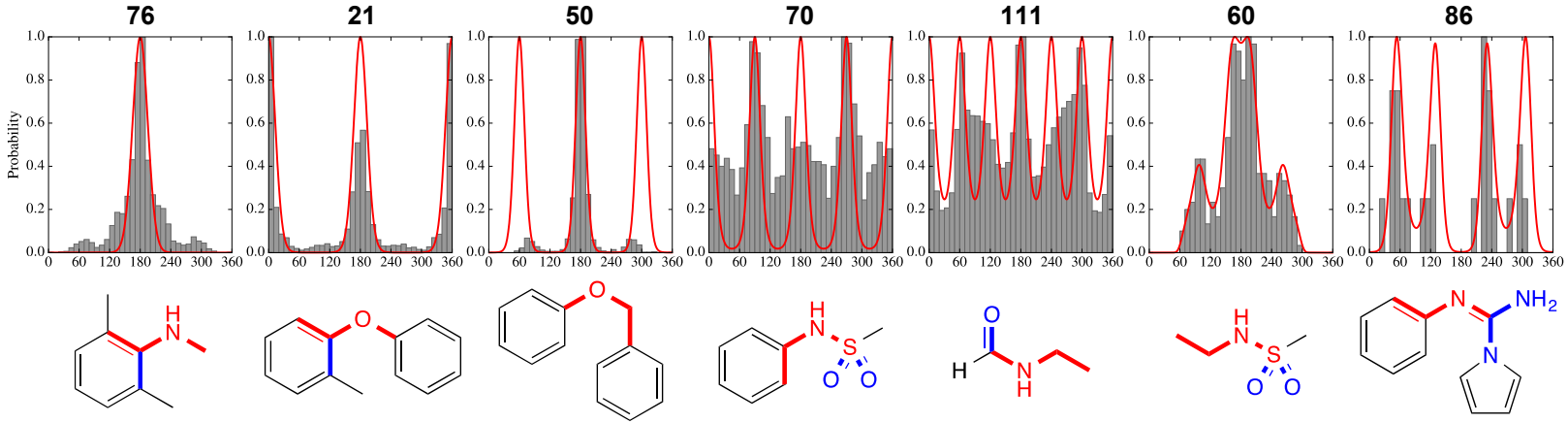
What is ETKDG?

ETKDG = Experimental torsions – knowledge (terms) – distance geometry

Experimental torsional-angle preferences from CSD

Examples of fitted torsion potentials:

$$V_{tors}(x) = \sum_{i=1}^{6} K_i \left(1 + \cos(\delta_i)\cos(m_i x)\right)$$



387 SMARTS patterns (acyclic) from:

- **Version 1**: Schärfer et al., *J. Med. Chem.*, 56, 2016 (2013).
- **Version 2**: Guba et al., *J. Chem. Inf. Model.*, 56, 1 (2016).

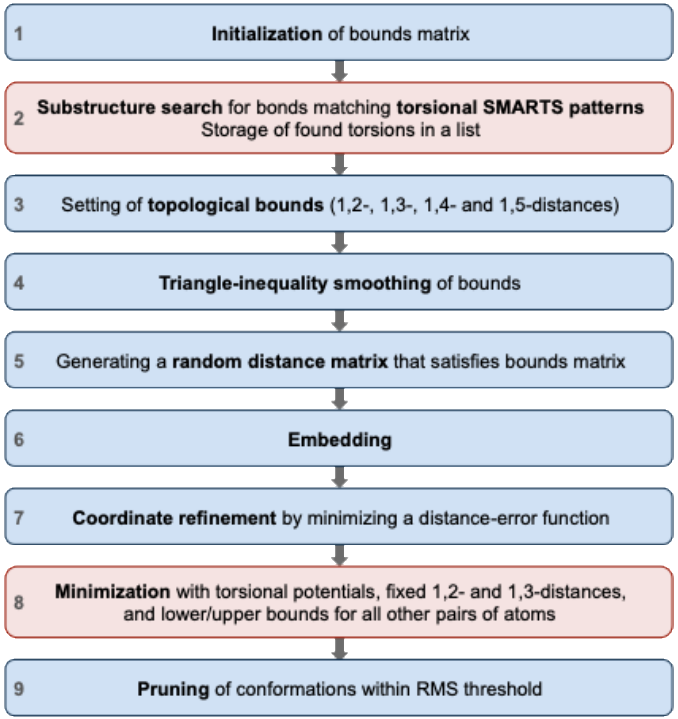
Knowledge terms: Flat sp2 atoms, torsion for aromatic rings, straight triple bonds

Riniker, Landrum, *J. Chem. Inf. Model.*, **55**, 2562 (2015).

What is ETKDG?

ETKDG = Experimental torsions – knowledge (terms) – distance geometry

Conformer generation workflow



Riniker, Landrum, *J. Chem. Inf. Model.*, **55**, 2562 (2015).

ETKDG version 3

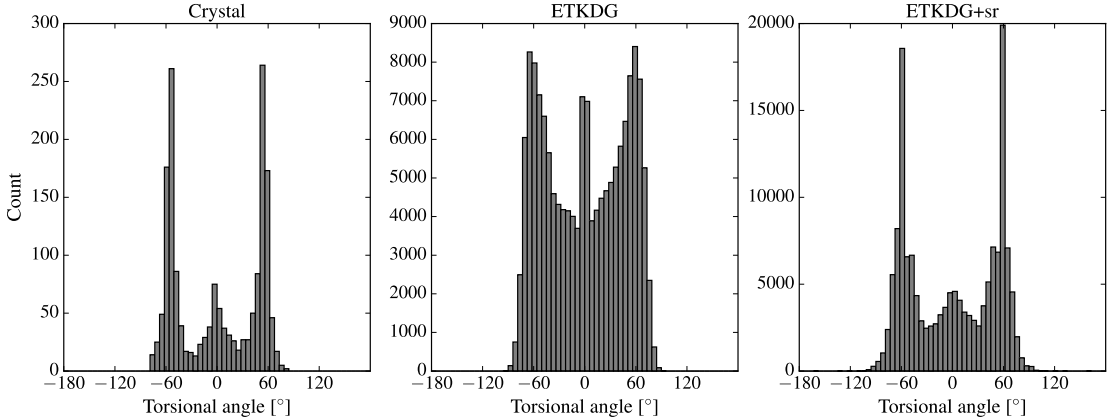
What about aliphatic cyclic bonds?

Distinguishing between small rings and macrocycles

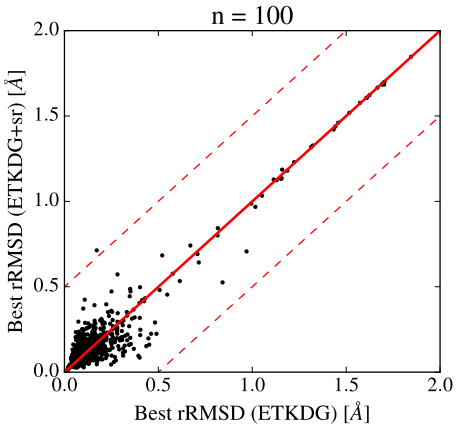
Small rings:

- New torsion SMARTS pattern derived (105 in total)
- Maximum ring size = 8
- Bridged systems: Bonds in >1 SSSR ring excluded, if ring shares >2 bonds with another ring → excluded

Six-membered rings



Best rRMSD on CSD test set



Wang, Witek, Landrum, Riniker, *J. Chem. Inf. Model.*, **60**, 2044 (2020).

ETKDG version 3

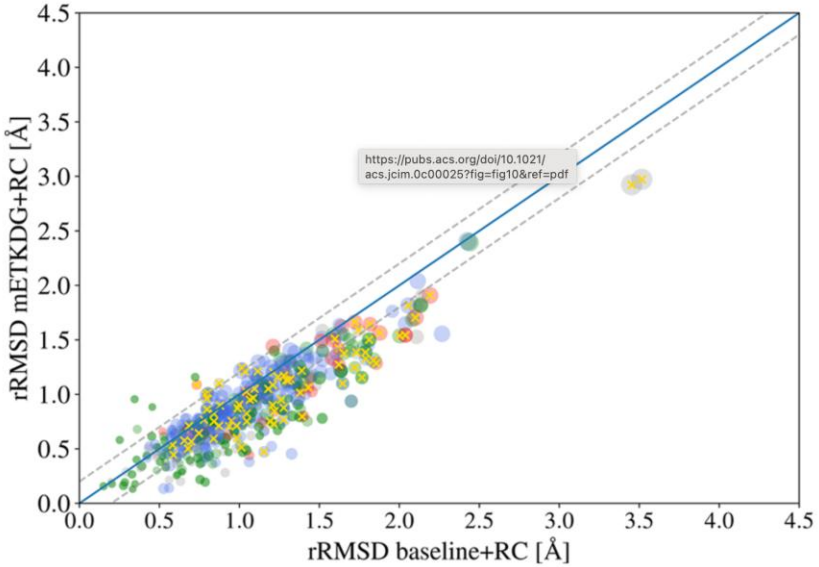
What about aliphatic cyclic bonds?

Distinguishing between small rings and macrocycles

Macrocycles:

- Cyclic bonds in rings > 8 behave similar to acyclic bonds (in terms of torsions)
- SMARTS patterns from version 2 adapted for macrocyclic bonds
- Changes to existing 1,4-bounds subroutines to treat macrocyclic bonds as acylic

mETKDG versus ETKDGv2 (random coordinates)



Size of markers = macrocyclic ring size
Colours = source of the macrocycles:
blue = CSD
green = Prime
red = BIRD
grey = Mac10
Blue solid lines: y = x; gray dotted lines: ±0.20 Å deviation
Golden crosses on a marker = compounds for which the experimental structure has a flatness value of <0.85

Wang, Witek, Landrum, Riniker, *J. Chem. Inf. Model.*, **60**, 2044 (2020).

Versions, Variants, and Parameters

ETKDG, version 3 (default) – `AllChem.ETKDGv3()`
- *Knowledge terms* ON (`useBasicKnowledge = true`)
- *Acyclic bonds*: torsions ON (`useExpTorsionAnglePrefs = true, ETVersion = 2`)
- *Macrocyclic bonds*: torsions ON (`useMacrocycleTorsions = true, useMacrocycle14config = true`)
- *Small ring bonds*: torsions OFF (`useSmallRingTorsions = false`)

ETKDG, version 3 (small rings) **– `AllChem.srETKDGv3()`**
- *Knowledge terms* ON (`useBasicKnowledge = true`)
- *Acyclic bonds*: torsions ON (`useExpTorsionAnglePrefs = true, ETVersion = 2`)
- *Macrocyclic bonds*: torsions OFF (`useMacrocycleTorsions = false, useMacrocycle14config = false`)
- *Small ring bonds*: torsions ON (`useSmallRingTorsions = true`)

ETKDG, version 2 – `AllChem.ETKDGv2()`
- *Knowledge terms* ON (`useBasicKnowledge = true`)
- *Acyclic bonds*: torsions ON (`useExpTorsionAnglePrefs = true, ETVersion = 2`)
- No torsions for cyclic bonds (`useMacrocycleTorsions = false, useSmallRingTorsions = false`)

ETKDG, version 1 – `AllChem.ETKDG()`
- *Knowledge terms* ON (`useBasicKnowledge = true`)
- *Acyclic bonds*: torsions ON (`useExpTorsionAnglePrefs = true, ETVersion = 1`)
- No torsions for cyclic bonds (`useMacrocycleTorsions = false, useSmallRingTorsions = false`)

KDG – `AllChem.KDG()`
- All torsions OFF, but knowledge terms ON (`useBasicKnowledge = true`)
- Faster than ETKDG; no bias from crystal structure preferences that might not apply in gas phase
- Useful when subsequent optimization performed anyway (classical force field and/or QM)