

Chirality Assignment of Organic Molecules

Determination of the Absolute Configuration of Chiral Organic Molecules using a Combination of Anisotropic NMR Spectroscopy and Molecular Dynamics Simulations

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In Short

- Method development for determination of the absolute configuration of small molecules
- Hybrid approach of molecular dynamics simulations and anisotropic nuclear magnetic resonance spectroscopy
- Prediction of the orientation of organic molecules in the liquid crystalline phase using molecular dynamics simulations

Assigning the correct relative and absolute configuration and 3D conformation to new molecules is of pivotal importance in organic chemistry. The by far most important source of information for molecules in solution stems from nuclear magnetic resonance (NMR) data, but despite some progress in computer-assisted structure elucidation (CASE) protocols and chemical shift analysis by DP4 methods, there is still no rigorous means to tackle the "growing and general problem of structural mischaracterization".^[1–3] With the known constitution of a compound, isotropic NMR parameters such as chemical shifts, scalar couplings and cross-relaxation (NOE or ROE) derived interproton distances provide valuable structural information for establishing the relative configuration and conformation of organic molecules. With the remarkable progress made in last 20 years, anisotropic NMR data such as residual dipolar or quadrupolar couplings (RDCs/RQCs) and residual chemical shift anisotropies (RCSAs) acquired in weakly aligning media become essential for solving challenging structural problems.^[4–6] In this regard, anisotropic NMR data complement valuable angular information that is able to correlate distant molecular fragments or describe the conformational space of highly flexible molecules.

While nowadays anisotropic NMR allows to assign the relative configuration of challenging chiral organic molecules more precisely and rapidly than ever before, determination of the absolute configuration using NMR spectroscopy^[7] poses a major challenge, as generally both enantiomers do not show difference in their NMR spectra. Only when enantiomers are derivatized into diastereomers, they can be distinguished and their absolute configuration

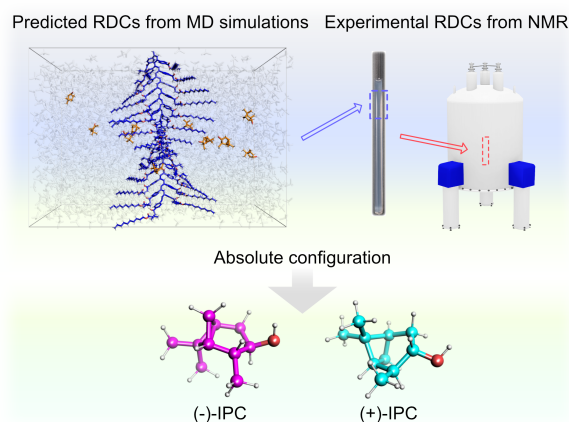


Figure 1: Determination of the absolute configuration (e.g. (-)-IPC and (+)-IPC in the lower panel) by comparison of predicted RDCs from MD simulations (left panel) and experimental RDCs from anisotropic NMR measurements (right panel).

is able to be assigned. With the recent remarkable progress in the development of new chiral alignment media,^[8–10] distinct anisotropic NMR data can be measured for both enantiomers, relying on the fact that both enantiomers show different orientational preference in these media due to the diastereomorphous interactions. Nevertheless, until now there is still no satisfactory method for interpreting these anisotropic NMR data that can be finally used for assigning the absolute configuration.

In an ongoing study, we proposed and pioneered the usage of atomistic MD simulations for predicting the orientational property of the analyte molecule in the chiral aligning media, which can be then translated into the NMR observables residual dipolar coupling (RDC) (Figure 1). Comparison of the predicted and experimental RDC data allows to assign the absolute configuration of chiral organic molecules. So far, we demonstrated this approach on the L-valine-derived poly(phenylacetylene) (PPA-L-Val, in short PPA), which revealed large enantiodiscriminating property for a number of chiral small molecules.^[8,9] We performed MD simulations of both enantiomeric forms of analytes in explicit solvent together with the PPA, where M and P conformations of PPA^[11–13] were employed as starting structures in the MD simulations. Using a number of microsecond MD simulations, we could show that the P conformation of PPA-L-Val enabled the correct assignment of a number of chiral analytes such as isopinocampheol (IPC) and menthol. In contrast, the M conformation results

in an opposite assignment of the absolute configuration. This result is in a very good agreement with experimental findings, revealing that the backbone helicity of the polymer determines the enantiodiscriminating property. Within this project, we plan to extend the application of this new approach into a more general scope.

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<https://www.leibniz-fmp.de/sun>

More Information

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Project Partners

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