Towards a standardized characterization of solution phase protein structure using Raman optical activity

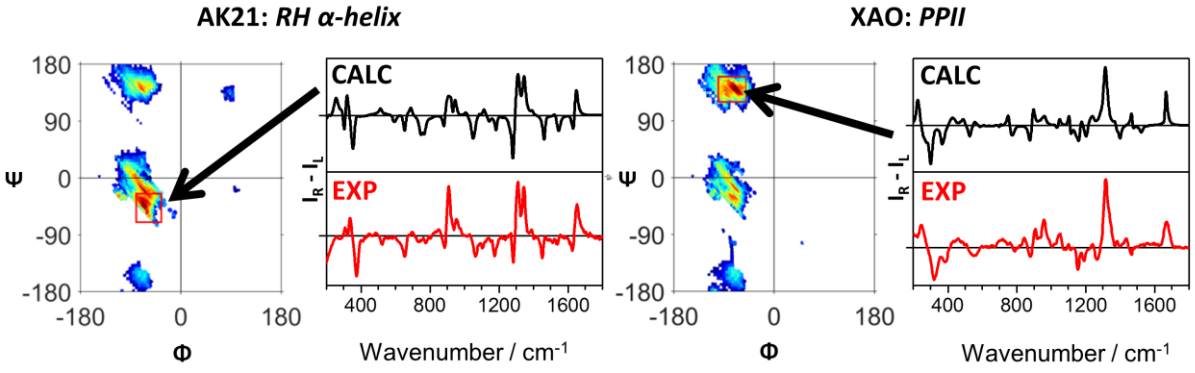
Carl Mensch[a,b], Laurence D. Barron[c], Christian Johannessen[a]

[a]Department of Chemistry, University of Antwerp, 2020 Antwerp, Belgium; [b]Department of Inorganic and Physical Chemistry, Ghent University, 9000 Ghent, Belgium; [c]School of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK

contact: carl.mensch@uantwerpen.be

Over the past 20 years, Raman optical activity (ROA) has shown much promise as a strong technique to elucidate the structure and dynamics of proteins in solution. ROA is measured as the small difference in the right and left circularly polarised components in the Raman scattered light by chiral molecules. This technique is uniquely sensitive to local conformational propensities of peptides and proteins. While the ROA spectrum of a protein gives rich information on the secondary structure of a protein, the biggest and most urgent challenge is to understand the relation between the ROA patterns and the protein structure in detail. Because of important advances in computational chemistry and computer power, it is now possible to use quantum chemical calculations to simulate ROA spectra of peptides.

Here, we present the first large scale study on the relation between the ROA patterns and protein conformation.[1] By creating a large library of peptide models with systematically varying conformations and calculating the ROA signatures quantum mechanically, we are developing an approach to characterise the solution structure of peptides and proteins with unprecedented detail. By using similarity indices, experimental Raman and ROA spectra can be compared to the simulated spectra in the database, which allows an objective and detailed assignment of the experimental spectra.



Using this approach, the experimental spectra of different peptides with diverse but known conformational preferences were studied. The newly developed database correctly assigns the solution structure of these peptides. Furthermore, the results demonstrate the strong conformational sensitivity of ROA, as very slight changes in protein structure result in specific changes in the ROA patterns. The database characterises these differences in the spectra to structural differences.

While structural biology relies on the powerful techniques of NMR and crystallography, complementary methods are necessary to provide additional information on protein structure and dynamics where the former techniques fall short. ROA has a unique structural sensitivity to protein structure and the database developed in this work is a strong tool to assign preferential conformations and changes of proteins based on the ROA spectrum.

[1] Mensch, C., Barron, L. D., Johannessen, C. *Phys. Chem. Chem. Phys.*, **2016**, *18*, 31757–31768.