# Chemical Shift Calculations in Proteins with a Fragment-Based Quantum Chemical Approach

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The determination of 3D structures based on NMR techniques is an emerging alternative to X-ray crystallography even for larger proteins. Nevertheless, there is still debate about the reliability of these models since in some cases wrong folds were proposed [**1**]. Therefore there is the need for independent evaluations tools to identify problematic parts in the strutures. We describe here attempts for the quantum chemical calculation of NMR chemical shifts of proteins. Since these are only indirectly used in the structure determination, the comparison of these with the experimental values could identify local inconsistency in the models.

To be able to calculate chemical shift also for large proteins, the fragment-based Adjustable Density Matrix Assembler (ADMA) [**2, 3**] is applied. This methode combines electron density matrices for fragments to approximate the electron density matrix of the complete macromolecule, resulting in a linear-scaling quantum chemical approach.

AMDA-based NMR calculations were performed in vacuo and with an implicit water model. The implitict solvent model largely increases the accuracy of the chemical shifts. Only groups directly involved in hydrogen bonding with the solvents show large diviations to the experiment and cannot be used for the validation of experimental structures. Additionally, we show with the trp-cage miniprotein as test cases that relatively small fragment sizes are sufficent for good agreement with the full calculation on the complete molecule.

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[3] Exner, T. E.; Mezey, P, *J.Comp.Chem.*, **2003**, *24*, 1980-1986.