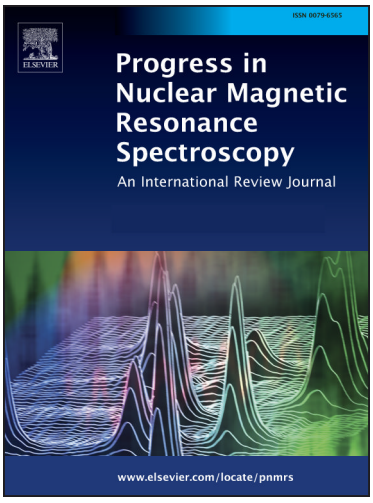

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Chemical shift-based methods in NMR structure determination

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Abstract

Chemical shifts are highly sensitive probes that can be harnessed by NMR spectroscopists and structural biologists as conformational parameters to characterize a range of biological molecules. Traditionally, assignment of chemical shifts has been a labor-intensive process requiring numerous samples and a suite of multidimensional experiments. Over the past two decades, the development of complementary automated and computational approaches has bolstered the analysis, interpretation and utilization of chemical shifts for elucidation of high-resolution protein and nucleic acid structures. Here, we review the development and application of chemical shift-based methods for structure determination with a focus on *ab initio* fragment assembly, comparative modeling, oligomeric systems, and automated assignment methods. Throughout our discussion, we point out practical uses, as well as advantages and caveats, of using chemical shifts in structure modeling. We additionally highlight *(i)* hybrid methods that employ chemical shifts with other types of NMR restraints (residual dipolar couplings, paramagnetic relaxation enhancements and pseudocontact shifts) that allow for improved accuracy and resolution of generated 3D structures, *(ii)* the utilization of chemical shifts to model the structures of sparsely populated excited states, and *(iii)* conformational modeling of protein sidechains. Finally, we briefly discuss the advantages of contemporary methods that employ sparse NMR data recorded using site-specific isotope labeling schemes for chemical shift-driven structure determination of larger molecules. With this review, we hope to emphasize the accessibility and versatility of chemical shifts for structure determination of challenging biological systems and point out emerging areas of development that lead us towards the next generation of tools.