Preface

The progress in understanding protein folding and misfolding is primarily due to the development of biophysical methods, which permit to probe conformational changes with high kinetic and structural resolution. A whole battery of techniques is being used to address the fundamental problems of protein folding and misfolding. The most common approaches rely on rapid-mixing methods to initiate the folding event via a sudden change in solvent conditions. Traditionally, techniques such as fluorescence, circular dichroism or visible absorption spectroscopy are applied to study the processes. In contrast to these techniques, infrared spectroscopy came into play only very recently. The significant progress made in this field to date permits to follow folding events over the timescale from picoseconds to minutes with high structural resolution. The aim of this unique book is to provide an overview of the latest developments and applications as seen by pioneers in this burgeoning field.

The various chapters present representative examples on the sort of information which infrared techniques can provide and how this information is extracted from the experimental data. The discussion of the state-of-art technology, data evaluation strategies and representative applications on protein folding and misfolding should help the readers to estimate whether their particular systems are appropriate to be studied by infrared spectroscopy, and to assess the specific advantages the various infrared techniques have.

This book contains nine chapters. The introductory chapter by Gareth Morgan and Sheena Radford focuses on the array of experimental methods that are presently applied to the key questions of how folding, misfolding and aggregation of proteins are linked, both in vitro and in the environment of the cell. The second chapter by Joseph Brauner and Richard Mendelsohn presents a semi-empirical method of simulating the experimental amide I contour of a protein or peptide molecule whose atomic coordinates are available, and discusses the correlations between the amide I contour and the secondary structure of a protein. The adaptation of conventional mixing and temperature-jump technologies to the specific requirements of time-resolved FTIR spectroscopy, which enable to explore protein folding and misfolding events on the millisecond-to-minute timescale, together with
representative results on different proteins, is then described by Heinz Fabian and Dieter Naumann. The fourth chapter by Satoshi Takahashi and Tetsunari Kimura gives an overview on time-resolved FTIR spectroscopy based on continuous-flow rapid-mixing set-ups, which allow to follow protein folding events in the sub-millisecond-to-second time range. The authors describe practical issues in applying their devices to explore mechanism of secondary structure formation and protein main chain dehydration. Chapter 5 by Roland Winter and co-workers reports on pressure changes as an alternative trigger to unfold or refold proteins and to induce disaggregation of misfolded species. After describing the experimental techniques, examples of pressure-induced un- and refolding reactions of proteins as well as studies on enzyme reactions are presented. The use of laser-induced temperature-jump IR spectroscopy as a method to study $\alpha$-helix and $\beta$-sheet formation in the nanosecond-to-microsecond time range is presented by Karin Hauser, with emphasis on strategies to obtain insights into folding mechanism on the level of single amino acid residues. The seventh chapter by Wolfgang Zinth and Josef Wachtveitl demonstrates that photo-switches incorporated into suitably designed amino acid sequences open up numerous new applications by applying light as trigger to initiate peptide folding. Their pioneering investigations on selected light-triggered peptides demonstrate ultrafast folding reactions, and show that these processes may span the range between picoseconds and tens of microseconds. Another way to trigger unfolding and misfolding events by light is the use of caged compounds, which is described next by Andreas Barth and co-workers with special focus on the use of caged protons for time-resolved infrared spectroscopic experiments. The light-induced release of protons generates a pH jump much more rapidly than any conventional mixing technique, thus paving the way for investigating early events of aggregation processes of peptides or proteins. The final chapter by Martin Zanni and co-workers illustrates that two-dimensional infrared spectroscopy combined with isotope labelling is an elegant and powerful tool to obtain residue-specific structural information on folding and aggregation processes of peptides and proteins. A mathematical formalism to guide the interpretation of one- and two-dimensional IR spectra of amyloid fibrils is presented, which enables the design of the best isotope labelling scheme of the peptide. The chapter ends with explanatory experiments, demonstrating the specific power of the two-dimensional IR approach.

This book is the result of the work of many colleagues who generously agreed to contribute to this book by taking time away from their other responsibilities. We wish to thank all the authors for their extremely valuable contributions. We hope that their ideas and experiences will be of interest not only for those readers already familiar with infrared spectroscopic techniques, but also inspire other colleagues in the protein community to take advantage of the possibilities described herein for
their particular research in the future. Special thanks go to our co-worker Angelika Brauer for her great help and continuous encouragement during the technical preparation of the book chapters.

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