

PART A

General Issues

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INTRODUCTION

Usually, a book like this would start with a statement regarding the importance of its contents. However, if one considers where non-covalent interactions, the topic of the present book, play a role, the answer is quite brief and simple: almost everywhere. On the simplest level, hydrogen bonding makes water a liquid under normal conditions—a fundamental basis for life on our planet. In everyday life, detergents form micelles that solubilize greasy dirt in water and help to wash it away. In chemistry, intermolecular forces modulate reactivity. The solvent dependence of nucleophilic substitution is only one of many prominent examples, some of which even made it into the basic organic chemistry textbooks. Non-covalent interactions are widely utilized by the organic chemist in templated synthesis and catalysis [1–3]. Displays based on liquid crystalline material [4] and the wetting behavior of surfaces mimicking Lotus leaves [5] are only two examples from material sciences. Weak intermolecular forces organize cell membranes, help in the precise information read-out during DNA replication, control the secondary and tertiary structures of proteins, and mediate the formation of multiprotein complexes in biochemistry. For a well-functioning metabolism, a precise recognition of the substrates in enzymes is of utmost importance. But, on even higher levels of complexity, non-covalent interactions mediate the interplay of organs

within the body through hormone regulation. Molecular recognition of the hormones on specific cell receptors is the chemical basis. Viruses dock to cells and infect them by the operation of multiple weak forces [6]. Even ant nests are organized through pheromones that need to be distinguished by the ants to be effective and thus require molecular recognition. Some researchers even believe that the likes and dislikes between humans may be controlled through our sense of smell [7, 8]—again molecular recognition through non-covalent forces is involved here. Finally, weak interactions make geckos capable of effortlessly hanging head-over from a glass ceiling, seemingly defying gravity [9]. To conclude this diverse and certainly incomplete choice of examples, one might say that non-covalent interactions organize matter, thereby creating structures of increasing complexity and function without which life as we know it would not be possible.

What then makes non-covalent forces omnipresent? Why do such weak forces have so much control about all the processes that happen around us? Probably, there is more than one answer to this question. Maybe the most obvious one would be: Because they are so weak. As we will see below, self-organization is one of the most powerful concepts to explain how simple building blocks are able to create highly complex structures with new, emergent properties on a higher level of complexity. However, self-organization requires reversibility, providing the capability to adapt to changes in the environment. In terms of reversibility, weak forces are clearly advantageous. Even though the strength of non-covalent bonds is a thermodynamic property while reversibility is a kinetic term and means that barriers are low, the approximation generally holds that species organized through weak bonds are usually highly dynamic. In contrast, a purely covalent world—if it could exist at all—would be almost completely static under the conditions encountered on earth. The term *reversibility* is intimately connected with the time scales on which changes happen, and we will call processes *quickly reversible* when they are fast on the human time scale. Non-covalently driven processes can operate on a large range of time scales, but most processes going on in our metabolism occur on very short time scales. Some enzyme reactions, which always involve a more or less reliable substrate recognition step, can even be diffusion-controlled.

From a historical perspective, it is quite astonishing that supramolecular chemistry developed into an independent field of research not before the late 1960s. The DNA double helix [10] was already known for more than a decade at that time, so that chemists probably had recognized the importance of intermolecular forces. The late advent of supramolecular chemistry is even more surprising when one becomes aware that several very fundamental principles were already formulated at the end of the 19th century [11]: Villiers and Hebd discovered cyclodextrin inclusion complexes in 1891 [12], Werner introduced the concept of coordination chemistry two years later [13]. Fischer formulated the key-lock principle in 1894 [14, 15], and in 1906 Ehrlich invented the concept of substrate–receptor interactions as expressed in his statement “*corpora non agunt, nisi fixata*” [16]. During the following decades, intermolecular interactions always

played a role in chemical research and many of the above concepts have seen revisions and extensions. Koshland's induced-fit model [17] for guest binding to a receptor molecule is one of the most prominent examples providing an important revision of the rather static key-lock principle.

Given the early existence of so many concepts fundamental to supramolecular chemistry, why didn't people fully acknowledge the importance of intermolecular forces earlier? Jean-Marie Lehn, one of the founders [18] of today's supramolecular chemistry [11, 19–21], provides two answers: The first answer is that chemists weren't really prepared to think about non-covalent forces that way. As a first approximation, the strong covalent bonds would be more decisive for a molecule's properties. Non-covalent interactions would merely bias these properties a bit, and one would be able to say that the properties of the molecule are by and large its inherent properties. It needed a paradigm shift to appreciate that non-covalent forces alter the features of a given molecule significantly. Therefore, a detailed understanding of these intermolecular interactions is indeed required. In several fields other than supramolecular chemistry, mass spectrometry contributed to this development at about the time when supramolecular chemistry became a research field in its own right. For example, solvent-dependent acidity and basicity scales were not always satisfying, and mass spectrometry could provide gas-phase acidities (i.e., proton affinities) in order to make an absolute scale of intrinsic acid–base properties available [22, 23]. Similarly, a double-minimum potential explained the fact that S_N2 reactions proceed up to 10^{15} times faster in the gas phase as compared to the same reactions in solution [24, 25]. In the gas phase, no solvent shell needs to be stripped off. Consequently, no barrier comes from solvent reorganization. Instead, ions and dipoles attract each other, making nucleophilic substitutions. Mass spectrometry thus had its share in making chemists aware of the extreme effects that solvation can indeed have. Nevertheless, it took another 20 years for mass spectrometry to study weakly bound complexes more or less routinely.

Lehn's second answer is a technical one. Each research field requires its own methods—some adapted from outside to the problems of the field, some newly developed. In its infancy, supramolecular chemistry suffered from the lack of easy-to-handle, reliable methods to examine, for example, host–guest complexes on a general basis. Lehn's argument is applied here to the introduction of mass spectrometric experiments to supramolecular chemistry. It is a textbook example for a mutually fruitful process. Supramolecular chemistry provided new, highly intriguing samples and challenging scientific problems, which, however, required the improvement of, for example, ionization methods or the development of new ones. In turn, the new options offered by mass spectrometry made it possible to address new aspects of supramolecular chemistry.

However, this process did not always occur in this ideal manner. Supramolecular chemists did not know enough about the potential of mass spectrometry, and not all mass spectrometrists recognized the interesting problems at hand in supramolecular chemistry. Most often, supramolecular chemists saw the harshness of electron ionization and the need to vaporize a sample before ionization

and abandoned the method without a closer look. Mass spectrometry was thought to be merely useful for a characterization of the building blocks, but not suitable to take a look at the complexes thereof. In turn, many mass spectrometrists were focusing on metastable ions and an analysis of their fragmentation pathways—almost completely neglecting the aspects of intermolecular forces unless they played a significant role in the fragmentation of metastable ions. With soft ionization methods such as electrospray ionization, time has come to bring both intimately together and bridge the gap. This is the intention of the present book.

How can mass spectrometry contribute to the investigation of non-covalent complexes? The primary information is the relative abundance of an ion at a certain mass-to-charge (m/z) ratio. Although this seems not to be much, a mass spectrometer offers quite significant advantages: The amount of sample can be small, because mass spectrometry is a quite sensitive method. Since the ions generated in the ion source are separated according to their m/z ratios, a mass spectrometer is a multichannel sensor providing an extreme degree of specificity. Finally, most simple mass spectrometric experiments can be done within minutes. Consequently, this method also offers high speed. Sensitivity, specificity, and speed are the three “S” advantages introduced by McLafferty [26]. But there is much more, if one thinks in terms of scientific problems that can be solved regarding non-covalent complexes in particular. The following list provides a collection of the potential data provided by mass spectrometric experiments. It should be noted that the list is somewhat idealized. Mass spectra need to be interpreted carefully, and it is not always possible to provide all the information for every single sample under study.

- From the exact m/z ratio and the isotope pattern, the *elemental composition* of an ion under study can be determined. Mass spectrometry thus offers access to *stoichiometry* data on weakly bound complexes.
- Ions with m/z ratios different from that expected for the complex may appear, thus yielding *information on impurities and defects*.
- Through structure-sensitive experiments—in particular, collision-, photon-, or electron-induced fragmentation reactions—information may be gained on the *secondary structure* of complexes. We borrow the term “secondary structure” from protein chemistry here in order to stress that we do not refer to atom connectivity in the individual building blocks, but instead to the arrangement of non-covalently bound subunits in the complex. Ion mobility and H/D exchange experiments even provide some ideas on the *conformations* of non-covalent complexes and biomolecules in the gas phase.
- Methods have been devised to take a closer look at *chiral recognition processes* that involve chiral receptors and chiral guests—even though mass spectrometry is an inherently achiral method.
- A mass spectrometer can be used as a detector for solution-phase processes. The *dynamic processes* occurring in non-covalently bound complexes can thus be monitored.

- In the gas phase, the ions do not interfere with each other chemically. Consequently, dynamic processes do not play a role anymore, and completely new insights are obtained from the examination of their *gas-phase reactivity*. Experiments can be designed in a way that only *unimolecular fragmentations* occur, but they can also be specifically used to address *bimolecular reactions* such as H/D exchange in the absence of a solvent.
- There are several methods available for the *determination of binding energies* of non-covalent complexes in solution. If one extends them to small libraries of guests that can interact with a host in a competition experiment, at least qualitative rankings of the guests can be obtained.
- Similarly, several methods exist to derive *relative and absolute binding energies in the gas phase*. A comparison of the gas-phase binding energies with those obtained in solution may provide detailed insight into the effects of solvation.

This list is probably still incomplete, but it sketches the research program that can be carried out by applying mass spectrometry to non-covalent species—and it defines a program for this book.

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