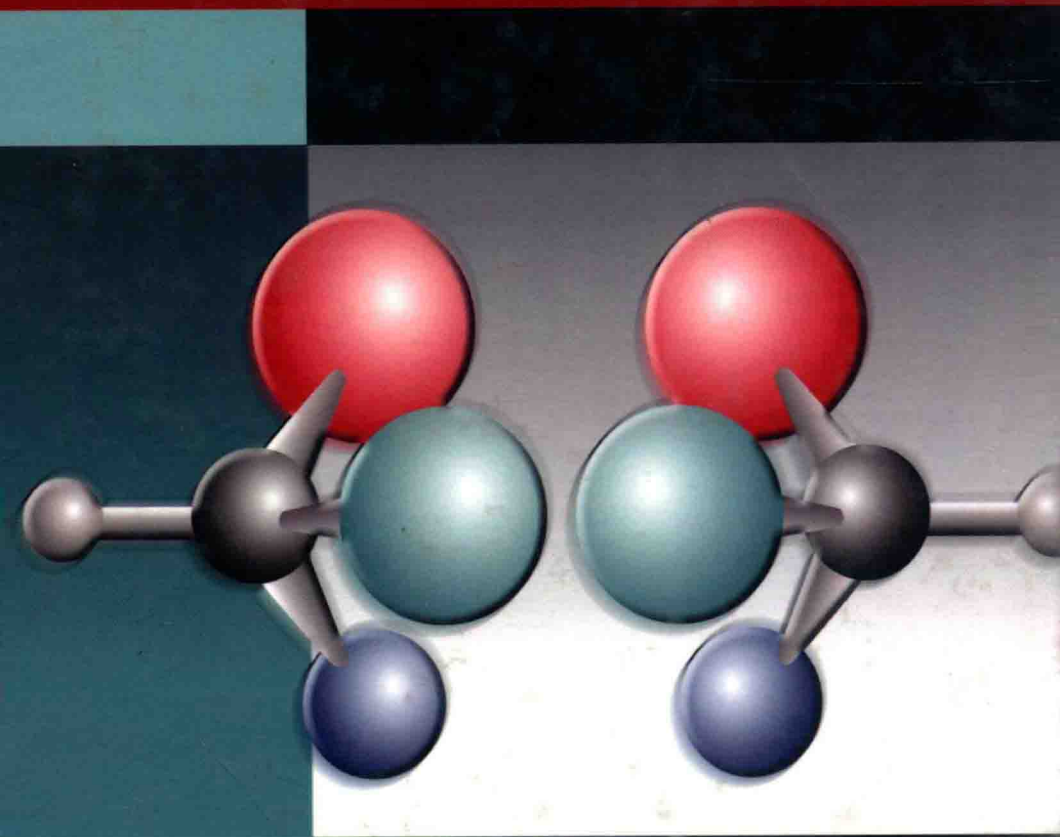
Chiral Recognition in the Gas Phase



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The Editor

Anne Zehnacker was born in 1962 and is directeur de recherche at the French Center for Scientific Research (CNRS). She began studying chemistry in Strasbourg (France) and earned a PhD in the electronic spectroscopy of aromatic molecules at the Orsay University in 1988. She spent one year in the theoretical chemistry group in CEN Saclay. Dr. Zehnacker is a member of the French Chemical Society and has been an invited scientist at several universities, including Sendai (Japan), Warsaw (Poland), Seoul (South Korea), Melbourne (Australia), Göttingen (Germany), and Toledo (Spain). She serves as a member of the advisory committee of Physical Chemistry Chemical Physics (PCCP). Her work focuses on molecular interactions and photoinduced processes in clusters. She was awarded the CNRS bronze medal in 1992 and the prize from the physical chemistry division of the French Chemical Society in 2003 for her work on chiral recognition in jet-cooled complexes.

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Introduction

Anne Zehnacker

Chirality is pervasive in nature and has long fascinated humans. The first step toward understanding chirality occurred during the nineteenth century, when French physicist J. B. Biot discovered that organic substances in solution, like tartaric acid, can rotate the polarization plane of a linear polarized light. It was only thirty-six years later when L. Pasteur related optical rotation to a molecular property. He observed that a peculiar form of tartaric acid exceptionally present in wine didn't provoke any rotation of linear polarized light. He realized that sodium ammonium salts of this para-tartaric acid, also called racemic acid, actually contained right- and left-handed crystals.[1] The optical rotation was recovered in solutions of pure left- or right-handed crystals sorted out with tweezers. What Pasteur called molecular asymmetry was a property of the molecule itself. It was only in 1873 that this molecular property was postulated to originate from stereochemical factors, when J. H. van't Hoff and J. A. Le Bel proposed the notion of an asymmetric carbon atom. The name *chirality* was proposed by Lord Kelvin, who later gave the following definition, in the Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light: "I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."[2]

The importance of Pasteur's discovery was not only the existence of molecular asymmetry, but its intimate relation to life chemistry. Indeed, chiral tartaric acid was produced during wine fermentation, a process driven by bacteria. Most of the bricks of life are chiral, and nature has, one does not know how, made a choice between the two enantiomers. From Pasteur's intuition about "dissymmetry of the cosmic forces" to the discovery of parity violation in cesium atoms, physicists and chemists seek to understand chirality. They follow different approaches, however. Physicists search for the consequences of parity violation of weak electron-nucleus interactions, which must result in an absolute energy difference between enantiomers, with spectroscopic consequences.[3] The other physically based method for probing molecular chirality, namely, chiroptical spectroscopy, rests on the interaction between polarized light and chiral molecules. Recent books have been devoted to the principles of optical activity and its application.[4,5] In particular, circular dichroism relies upon differential interaction with a circular polarized light and consists in measuring the difference in absorption by a chiral molecule of a right and a left circular beam. Thought very small, this effect is well documented in the range of both electronic and vibrational transitions. Because of their limited magnitude (10^{-6} to 10^{-2} of the absorption), these methods are mostly limited to a condensed phase. More recent is the observation, in the gas phase, of the photoelectron circular dichroism (PECD) spectroscopy effect, which will be described in Chapter 1. Notwithstanding its magnitude (several orders of magnitude greater than conventional absorption), PECD is exquisitely sensitive to stereochemical factors. It therefore has the long-term capability of studying chiral

recognition in molecular pairs isolated in the gas phase. Moreover, there are attempts to explain life's homochirality by asymmetric processes induced by astronomical sources of circular polarized light. PECD, as an asymmetric photon-induced process, could play a role in the origin of life's homochirality, which will also be discussed in Chapter 1.

The chemist does not intervene at the atomic scale or at a single molecule, but at molecular interaction. Indeed, all the chemical approaches rest on chiral discrimination, i.e., the difference in behavior of the two enantiomers of a chiral molecule when interacting with a chiral surrounding. This phenomenon plays a key role in life chemistry: it is, for example, well recognized that the biological activity and bioavailability of enantiomers often differ. This is true for the activity of drugs, but also for smell and taste.[6] The enantiomers of carvone have characteristic odors, caraway for (S)-(+)-carvone and spearmint for (R)-(–)-carvone.

The marked enantioselectivity characterizing most of the processes involving the interaction of a chiral ligand, like a drug with enzymes or protein receptors, has been explained in terms of formation of weakly bound contact pairs involving specific interactions.

The economic importance of enantiomerically pure compounds has prompted growing development and application of chiral chromatographic methods, especially in pharmaceutical sciences.[7] Here again, specific interactions between the chiral stationary phase and the enantiomers to separate are invoked.[8] However, the interaction energy at stake is often weak, i.e., of the same order as the thermal energy at room temperature; the contact pairs responsible for chiral recognition are difficult to isolate and study in solution. It is therefore of prime importance to find a means of studying them at the molecular level, in order to cast some light on the molecular interactions responsible for chiral discrimination in isolated molecular pairs. Gas-phase experiments, on either neutral or ionic adducts of chiral molecules, allow studying the intrinsic properties of chiral recognition in solvent-free conditions. Two directions have been explored so far: the structural and the energetic aspects. Structural aspects have been studied mainly by optical spectroscopy in jet-cooled conditions, in neutral complexes.[9] The combination of supersonic expansion and electronic, vibrational, or microwave spectroscopy has led to a flurry of experimental results that, in conjunction with quantum chemical calculations, brings information on the structure of weakly bound complexes of chiral molecules and the nature of the interactions responsible for chiral recognition. Electronic spectroscopy is limited to complexes containing an aromatic chromophore and only brings indirect structural information, even when mass resolved by using resonance-enhanced multiphoton ionization (REMPI) methods.[9–12] More information is brought by vibrational spectroscopy, which can be obtained, on the one hand, by IR-UV double resonance experiments. In this case, however, an aromatic chromophore is necessary as the method is based on the depletion of a fluorescence or ion signal due to IR absorption. More universal is direct Fourier-transformed infrared (FTIR) absorption or Raman scattering from species cooled down in a slit jet,[13] because these techniques do not require the presence of an aromatic chromophore. Clusters of small molecules can be studied, which are amenable to high-level quantum chemistry calculations. By this way, subtle effects like those related to transient chirality or chirality linked to the nonequivalence of

lone pairs can be studied. An example of such an approach is given in Chapter 3, which describes how infrared and Raman spectroscopy can be used to evidence transient torsional chirality in ethanol derivatives. The two *gauche* forms of ethanol are transient enantiomers, which interconvert on a timescale of the order of 1 ps. Hydrogen bond formation from a donor to ethanol quenches the stereomutation. Another method for detecting quenching of stereomutation by hydrogen bonding is microwave spectroscopy, as shown in Chapter 2. The individual conformers of transient chiral molecules, like the gauche form of ethanol, are discriminated by formation of a complex with a permanently chiral species, like *R,R*-dimethyloxirane. Despite microwave spectroscopy being applicable to any molecular system with permanent dipole moment, it meets difficulties when applied to larger systems. The dimers of 2-butanol, which can be seen as the smallest truly chiral organic molecule, are already challenging in terms of the interpretation of experimental spectra.[14]

Larger molecular systems demand different approaches. The experiments often rest on medium-resolution infrared spectroscopy combined with theoretical methods with decent computational time, like those resting on the density functional theory. In this respect, numerous complexes of an aromatic chiral chromophore with chiral solvating agents have been studied.[10,15] These studies resort to electronic spectroscopy, by either laser-induced fluorescence (LIF) or REMPI. In both cases, the spectroscopy of the S_0-S_1 transition is the signature of chiral recognition and is necessary for further investigation, either energetic or structural. From an energetic point of view, REMPI experiments allow measuring the binding energy of the diastereomeric complexes, thanks to a two-color dissociative ionization scheme. The appearance threshold of the fragment resulting from photodissociative ionization of the complex, AP, is related to the binding energy of the complex BE and the adiabatic ionization potential of the chromophore IP_{ad} by the simple equation $BE = AP(Rs^+ \rightarrow R^+) - IP_{ad}(R)$.[16,17] From a structural point of view, the knowledge of the S_0-S_1 spectroscopy is a prerequisite for recording vibrational spectra via double resonance experiments. Besides its sensitivity, this method has the advantage of being isomer selective, as it allows recording separately the spectra of different species, which absorb in the same energy range. It has been applied to complexes of a chiral alcohol chromophore with aminoalcohols, in which a conformation-dependent interaction site (NH_2 or OH) has been observed.[18] More recently, it has been used to compare the efficiency of different chiral chromophores in discriminating between the enantiomers of methyl-lactate.[19,20] It has been shown that the interaction that ensures the stability of the complex (strong conventional hydrogen bonds) is not the same as the one that is responsible for chiral recognition. Indeed, minor CH ... π or dispersive interactions play a decisive role in chiral recognition,[20] a hypothesis that has been postulated already in complexes of chiral alcohols.[10] Some of these topics have been reviewed already.[9,12,21] An important issue is that supersonic expansions are not a medium in thermodynamic equilibrium. The formation of complexes is mainly governed by kinetic factors, which in turn play an important role in the chiral recognition efficiency. These aspects have been studied in detail thanks to IR-UV double-resonance spectroscopic studies accompanied by quantum chemical calculations, with either *ab initio* or density functional theory (DFT) methods. They will be illustrated with

the example of complexes involving molecules with an intramolecular hydrogen bond in Chapter 4.

Mass spectrometry approaches of chiral recognition in ionic complexes have grown in number during the last decades and have been the subject of several review articles.[22–25]

As for neutral species, chiral recognition in ionic systems rests on the formation of complexes involving enantiospecific interactions. These diastereoisomeric adducts are endowed with different stability, which leads to thermodynamic enantioselectivity ($\Delta\Delta G \neq 0$). They also show different activation barrier to reactivity, which results in kinetic enantioselectivity ($\Delta\Delta G^* \neq 0$). All the methods at the basis of mass spectrometry study of chiral recognition rest on one of these properties. They are basically classified in terms of the following three approaches.

The first one rests on the comparison of the relative peak intensity of diastereoisomeric adducts in a single-stage mass spectrometry experiment. As the two adducts must be measured during the same experiment to avoid artifacts, one of the enantiomers of either the reference compound or the analyte must be mass tagged, usually in a substituent remote to the chiral center, so that the mass of the molecule can be correlated with its absolute configuration. A way of doing that rests on the use of isotopically labeled species, so that the corresponding mixture of the diastereoisomeric adducts can be mass resolved. This approach is valid provided that the stereochemical effect is not altered by isotope effects and is described in Chapter 5. This chapter describes how the intensity of the ions produced by fast atomic bombardment (FAB) nicely reflects the composition of the matrix. By means of a temperature-controlled probe, it is therefore possible to deduce the thermodynamic parameters of the enantioselective host-guest complexation. Mass tagging can be also obtained resorting to what are called quasi-enantiomers, i.e., molecules that would be enantiomers if it were not for a minor chemical substitution, supposed to be ineffective in the reaction or complex formation process. This technique, pioneered by Horeau and Nouaille[26] and Guo et al.,[27] is described in Chapter 9. It has been applied successfully for screening asymmetric catalysts based on the detection of the catalytic intermediates rather than that of the products.[28]

The second method rests on ion/molecule reactions, mainly exchange reactions. A chiral analyte incorporated in a complex with a chiral host undergoes an exchange reaction by a nonchiral reference. The kinetics of displacement of the guest by the nonchiral reference is an indication of the difference in interaction energy between the two enantiomers of the analyte with the host. This method is illustrated in Chapter 7 in the example of crown-ether as chiral hosts. The enantioselectivity of oligosaccharides like cyclodextrins or their linear analogues, namely, maltose-based oligomers, toward amino acids and pharmacologically important molecules has been probed by the same method and described in Chapter 6.[29] More recently, more complex macrocycles have been used as chiral hosts.[30] Recognition by calixarenes and resorcinarenes grafted with chiral substituents at their upper or lower rim has proven to depend on the binding site of the chiral guest. Because of the complexity of these guest-host systems, molecular dynamics calculations are necessary for getting information on their molecular structure. As pointed out in Chapter 6, different isomeric forms of the host-guest adduct coexist in the experimental conditions, which can

show different enantioselectivity. This points out the fact that the strongest binding sites do not correlate with the strongest enantioselectivity; this observation has also been made for neutral complexes in the gas phase[20] as well as in solution.[31]

The last methods rest on collision-induced dissociation (CID) of trimeric ionic clusters. The widespread kinetic method (KM) pioneered by R. G. Cooks and his group consists of comparing the efficiency of dissociation of the chiral reference (ref*) and the analyte (A) from the trimeric cationic complex, $M^{II}(A_R)(ref^*)_2 - H^+$, for the two enantiomers of the analyte.[32] It has proven to be a very efficient method for enantiomeric excess measurements, in particular when using transition metal cations, which provide multiple interaction for chiral recognition.[25] The chiral recognition ratio (CR) introduced by the group of Che[33,34] is also based on dissociation of diastereoisomeric complexes, but measures the ratio of the intensity of one fragment ion, $M^{II}(A_R)(ref^*) - H^+$, to that of the parent ion, $M^{II}(A_R)(ref^*)_2 - H^+$. These dissociation-based methods also apply to anionic complexes, as illustrated in Chapter 8. The conformational wealth of oligonucleotide sequences used as aptamers prompted their use as stationary phase in chiral chromatography.[35] In this context, Chapter 8 describes the use of small DNA sequences as auxiliaries for discriminating the enantiomers of amino acids.

The experiments described above must satisfy the same conditions as extensively discussed for measurements of binding affinities scales in general,[36–39] like reaching the Bolztmann equilibrium in a collision-free environment and defining an effective temperature, studying systems with a dominant unimolecular dissociation pathway in CID, and understanding the role of flexibility, i.e., entropy in the studied processes. These issues are beyond the scope of this book, but one should notice that in the case of chiral recognition, the different complexes at play only differ in the configuration of one of the subunits, in the case of real or pseudo enantiomers, or in a substituent remote to the chiral center, in the case of isotope-labeled or quasi-enantiomers. The similarity of the systems therefore makes the comparison between them pretty safe.[38] However, a strong limitation is that the ionic clusters must retain their original configuration; racemization is, of course, strongly undesirable. Moreover, the interpretation of the information obtained by the kinetic method rests on the assumption that no isomeric form of the complex complicates the analysis of the data. This assumption might be wrong in clusters of complex chiral molecules, which can show multiple binding sites, as described in Chapter 4.

The approaches resting on mass spectrometry (MS) only, as described in review articles[40] or in this book, do not reach the outstanding efficiency of HPLC coupled with MS/MS detection, which affords sensitivity down to 0.0025% of the minor enantiomer.[41] However, it makes possible fast and direct analysis of enantiomeric composition down to 0.5% enantiomeric excess.[40] An important issue related to analytical applications is whether the gas-phase results mimic those observed in solution, in the case of electro-sprayed solutions, or in the matrix, in the case of fast atomic bombardment. In some cases, different ionization methods give rise to contrasted differences in the enantioselectivities, a case where FAB was supposed to match the solution results in a more quantitative way.[42] The comparison between the selectivity observed in solution and that in the gas phase has been discussed in Chapter 10. Indeed, comparison between gas-phase properties and what is observed

in solution helps us to understand the mechanism responsible for the separation of enantiomers and fathom the relative importance of dispersion vs. purely electrostatic interactions, as those observed in ion exchange mechanisms. In this respect, it brings interesting information on the chiral recognition mechanisms at play when cinchona alkaloid carbamates or antimony (III) tartrates are used as stationary phases for chiral stationary phase chromatography.

Last, it is impossible to describe chiral recognition phenomena without mentioning homochirality of life. R. G. Cooks has proposed that homochirality of life results from three successive processes: chiral selection of a single enantiomer via symmetry breaking, chiral accumulation, and chiral transmission.[43] The observation of an especially stable protonated homochiral serine octamer strengthens the case that serine could play a key role in chiral accumulation and chiral transmission. Moreover, the L-serine cluster can accommodate a D-sugar molecule, which in turn dimerizes within the cluster to form a life-related C6 sugar. The symmetry-breaking step could be achieved either through parity violation effects or via irradiation by a circular polarized light, as proposed in Chapter 1.

Among the promising new methods, which are still under development, one can mention the use of ion mobility, to observe either the difference of mobility between diastereoisomeric adducts or the difference of mobility of enantiomers in a drift gas seeded with a chiral molecule.[44,45]

Coupling laser spectroscopy techniques and ion traps has been applied widely to the study of biologically relevant molecules by infrared multiphoton dissociation (IRMPD). Amino acids[46,47] and peptides[48] have been the subject of particular interest. So far, the only application to adducts of chiral molecules has been limited to protonated serine clusters, with sizes ranging from the dimer to the famous octamer.[49] The vibrational spectra in the range of 3 μ are compatible with the structure proposed for the octamer. However, no attempt for chirality-dependent spectroscopic fingerprint has been made, probably because the width of the spectra obtained at room temperature wipes out the subtle chirality effects. The use of cold ion trap combines the advantages of mass spectrometry and resolved spectra as obtained at low temperature, which makes spectroscopic measurements as precise as in supersonic expansions.[50] Besides the fact that supersonic expansions are meant mainly to study neutral species, the lack of thermodynamic equilibrium is one of the main points differentiating them from ion traps. It would be promising to perform experiments in a temperature-controlled ion trap to assess the relative importance of the most stable adducts and those of lesser binding energy in chiral recognition. Last, comparison of the chiral recognition efficiency in neutral, ionic, protonated, or cationized complexes of the same molecules is made possible thanks to the always broader range of experimental techniques available. This comparison would cast light on molecular and chiral recognition processes in different solvent conditions, or environment related to life chemistry.

Experiments resting on electron capture dissociation (ECD) have been reported very recently and compared to collision-activated dissociation (CAD) results in terms of fragmentation specificity. ECD experiments have proven to be much more sensitive to hydrogen bonding patterns than CAD. For this reasons, they are a precious tool for studying the stereochemistry of peptides, which can profoundly influence

their biological activity, as observed in the case of opioids. Indeed, changing the chirality of a single amino acid strongly modifies the pharmaceutical activity of the peptide, which makes peptide stereoisomers interesting candidates for new drugs. The study by ECD of the consequences of changing the chirality of a single amino acid in a peptide, as described in Chapter 11, opens the way to promising, highly stereoselective experiments.

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Contents

1 Valence Photoelectron Circular Dichroism of Gas Phase Enantiomers

Laurent Nahon and Ivan Powis

CONTENTS

1.1 INTRODUCTION

To those broadly familiar with the theory or practice of chiral molecular spectroscopies, one of the more recently investigated chiroptical phenomena, photoelectron circular dichroism[1] (PECD), may nevertheless be surprising when first encountered because from randomly oriented, noninteracting molecular enantiomers it routinely yields asymmetry factors ranging from 0.01 to 0.3. Asymmetries of this magnitude exceed those encountered in more traditional circular dichroism (CD) measurements by several orders of magnitude, and so promise a number of advantages associated with the potentially greater ease of detecting such large effects.

Foremost among these is the ability (indeed, in practice a necessity) to work with dilute gas phase samples. In this manner one both removes restrictions imposed by