Clusters of chiral molecules in the isolated state

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Abstract – Chirality, a fundamental property present across different scales in our world, remains a captivating area of exploration. The origins of chirality and the intricate chemical pathways leading to the formation of the first replicable homochiral system are subjects of ongoing studies. This paper, dedicated to the late Prof Anna Giardini, unravels insights into chiral discrimination effects through Resonant Two-Photon Ionization (R2PI) spectroscopy on gas-phase intermolecular complexes.

Using theoretical ab-initio calculations, and a range of resonant multiphoton spectroscopic techniques, this study reports on key aspects of chirality. This involves the application of One-color R2PI Spectroscopy, where diastereomeric complexes formed by non-covalent interactions between enantiomers of chiral solvent and a chiral chromophore are discerned. Moving on, Two-color R2PI Spectroscopy is discussed as a tool to measure binding energy differences between homochiral and heterochiral adducts. After which the study of Reaction Thresholds by Two-color R2PI is reported. Here, the impact of asymmetric microsolvation on the photodissociation of C_α-C_β bonds is explored. This sheds light on how solvent molecules influence activation energies in these

processes. Lastly, the investigation into One-color R2PI and IR-R2PI focuses on the effect of fluorine substitution on chiral recognition. The interplay of CH···π, OH···π, and CH···F interactions is analyzed, highlighting the specific molecular interactions crucial in chiral discrimination.

This comprehensive exploration underscores the intricate molecular mechanisms governing chiral recognition and enantioselectivity, emphasizing the lasting impact of Prof Anna Giardini's pioneering work in this field.

Keywords: chiral discrimination, Resonant Two-Photon Ionization spectroscopy, non-covalent interactions, molecular clusters, supersonic expansion

Riassunto – La chiralità, una proprietà fondamentale presente a diverse scale nel nostro mondo, costituisce un affascinante campo di esplorazione scientifica. Questo articolo, dedicato alla memoria della Prof.ssa Anna Giardini, propone un approfondimento sulle interazioni chirali attraverso la spettroscopia di ionizzazione risonante a due fotoni (R2PI) applicata a complessi intermolecolari chirali in fase gassosa.

L'asimmetria chirale è presente a vari livelli, dalla scala subatomica a quella dell'universo. In particolare, la chiralità rappresenta un elemento essenziale della vita, sia a livello molecolare che supramolecolare. Nonostante le numerose ipotesi sull'origine abiotica della chiralità, rimangono ancora sconosciuti i meccanismi chimici che hanno portato alla formazione del primo sistema omochirale. Tuttavia, si sa che la trasmissione dell'informazione chirale e le proprietà di riconoscimento delle biomolecole dipendono ampiamente dalle interazioni intra ed intermolecolari non covalenti.

Questo articolo si concentra sullo studio di complessi intermolecolari di molecole chirali nello stato isolato, utilizzando la spettroscopia R2PI e calcoli teorici *ab initio*. Sfruttando tecniche spettroscopiche come la R2PI ad un colore, è stato possibile identificare complessi diastereomerici formati da interazioni non covalenti tra enantiomeri di un solvente chirale e un cromoforo chirale. Successivamente, la spettroscopia R2PI a due colori è stata utilizzata come strumento per misurare le differenze di energia di legame tra complessi omochirali ed eterochirali. La misura delle energie di legame si basa sull'analisi delle transizioni elettroniche dei complessi omo ed eterochirali. Questo approccio fornisce informazioni cruciali sulla enantioselettività, sottolineando l'importanza della differenza di energia di legame tra complessi omochirali ed eterochirali come parametro termodinamico fondamentale.

Un aspetto ulteriore delle ricerche riguarda la misura delle soglie di reazione attraverso la R2PI a due colori, esplorando come la microsolvatazione asimmetrica influenzi la fotodissociazione dei legami C_α-C_β. I risultati indicano che la barriera energetica per questo processo dipende dall'affinità protonica della molecola solvente e dalla sua configurazione, evidenziando come le molecole di solvente influenzino le energie di attivazione nei processi di fotodissociazione.

L'indagine prosegue focalizzandosi sull'effetto della sostituzione del fluoro sul riconoscimento chirale mediante le spettroscopie R2PI ad un colore e IR-R2PI. Quest'ultima consente la misura delle transizioni vibrazionali nello stato fondamentale dei complessi diastereomerici. L'analisi si concentra sulle interazioni di tipo CH···π, OH···π e CH···F, evidenziando come queste interazioni siano cruciali nella discriminazione chirale.

In conclusione, questo articolo offre un'ampia panoramica delle ricerche sulla discriminazione chirale e l'enantioselettività caratterizzando i complessi meccanismi molecolari e le interazioni intra ed intermolecolari non covalenti che le governano. Questo lavoro ha contribuito al progresso nella comprensione della chiralità, con implicazioni significative nei settori della chimica, biologia, farmacologia e astrofisica.

L'eredità della Prof.ssa Anna Giardini emerge come fondamentale in questo campo, rimarcando il valore essenziale della sua opera pionieristica.

Parole chiave: Discriminazione chirale, spettroscopia risonante a due fotoni, interazioni non covalenti, cluster molecolari, espansione supersonica

Introduction

In our world, asymmetry can be found at various hierarchical levels, from subatomic to universe scale. Chirality is an essential element of life either at the molecular or at the supramolecular level. Various hypotheses have been proposed to explain the abiotic origin of chirality [1]. However, several evolutionary steps were required to produce, implement, and maintain chirality in the terrestrial type of life [2]. The specific chemical mechanisms that lead to the first replicable homochiral substance still remain unknown, though it is certain that the transmission of chiral information, the recognition properties as well as the functionality of biomolecules rely substantially on non-covalent intra and intermolecular interactions: their study is of fundamental interest and has a deep impact on chemistry, biology, pharmacology, materials science and astrophysics.

Precious information on the transfer of chiral information from the molecular to the supramolecular level can be gained by investigating non-covalently bound clusters of chiral molecules in the isolated state, making use of appropriate spectroscopic techniques [3]. Gas phase experiments and quantum chemical modeling allows to understand in detail the structural and energetic factors underlying chiral selectivity. Besides, it has been recognized that in complexes in solution, molecules are often extensively desolvated at active interaction sites. Hence, a proper evaluation of gas phase interactions allows also a subsequent reasonable determination of the effect of solvent firstly in hydrated complexes and then in solution [4].

Weakly bound diastereomeric complexes between chiral molecules of precisely defined configuration

Fig. 1. Prof. Anna Giardini (first on the right) with some students and researchers at the laser spectroscopy laboratory of the Rome University La Sapienza (2004).

bound to both enantiomers of another chiral molecule can be generated and isolated by supersonic expansion. The structure and energetics of gas phase diastereomeric complexes have been investigated by several spectroscopic methodologies, such as LIF (Laser Induced Fluorescence) [5], REMPI (Resonant Enhanced Multi Photon Ionization) [6], RET (Rydberg Electron Transfer) [4], FTIR (Fourier Transform Infrared) [7] and microwave spectroscopies [8].

In this paper, a tribute in memory of Prof Anna Giardini (Fig. 1) we would like to summarize some important results obtained by Resonant Two-Photon Ionization (R2PI) spectroscopy on the investigations of chiral discrimination effects in several representative gas-phase intermolecular complexes. The selected examples are extracted from the work carried out by the team of Professor Anna Giardini, who devoted a considerable part of her fruitful scientific carrier to these studies.

1. Chirality detection by one-color R2PI spectroscopy

In a one-color Resonant Two-Photon Ionization spectroscopy (1cR2PI) experiment, molecules are ionized by the absorption of two UV photons of equal frequency. The first photon ($h\nu_1$) excites a specific rovibronic tran-

sition of a molecule or cluster and then, a second UV laser photon of equal frequency ($h\nu_1$) ionizes the excited neutral species. A molecule or cluster will be ionized if the total energy of the two photons absorbed ($2h\nu_1$) exceeds its ionization energy. The formed ions are usually mass analyzed in a time-of-flight mass spectrometer. The 1cR2PI excitation spectra are obtained by recording the ion yields as a function of ν_1. Due to the resonant step in the two-photon ionization, the 1cR2PI spectrum reflects the UV excitation spectrum of the neutral molecular o cluster precursor.

If generated by seeded supersonic expansion, molecules and clusters display non-congested 1cR2PI spectra characterized by sharp signals. This comes from the efficient cooling of the translational, rotational and vibrational degrees of freedom of supersonically expanded species. Supersonic expansion stabilizes weakly bound complexes and allows for conformational/isomeric cooling into a small number of possible isomers. In a 1cR2PI process, if the excited state is much higher in energy than one-half of the ionization energy, the ion will be produced with a not negligible excess energy which results in vibrational excitation of the ionized species. Sometimes, this excitation causes the cluster ion to dissociate into its original components or give rise to

more complex fragmentation patterns. These fragments keep memory of their parent ions, which means that they have the same rovibrational electronic spectral patterns. This is an important characteristic of the 1cR2PI method, which in turn allows one to study the fragmentation and dissociation processes occurring in molecules and clusters [9].

The first application of 1cR2PI spectroscopy to discriminate chiral molecules expanded in supersonic beams concerned a study of the diastereomeric complexes formed by the noncovalent interaction between the two enantiomers of butan-2-ol (B_R or B_S) and a chiral chromophore, specifically (R)-(+)-1-phenyl-1-propanol (P_R) [6]. The homochiral [P_RB_R] and heterochiral [P_RB_S] diastereomeric complexes displayed distinguishable vibronic excitation spectra (Fig. 2a, b). Distinct vibronic spectra of non-covalently bound diastereomeric complexes had already been reported by the group of Lahmani et al [5]. for adducts between S-chloro-1-propanol and the two R and S enantiomers of α-methyl-2-naphthalenemethanol by using LIF spectroscopy.
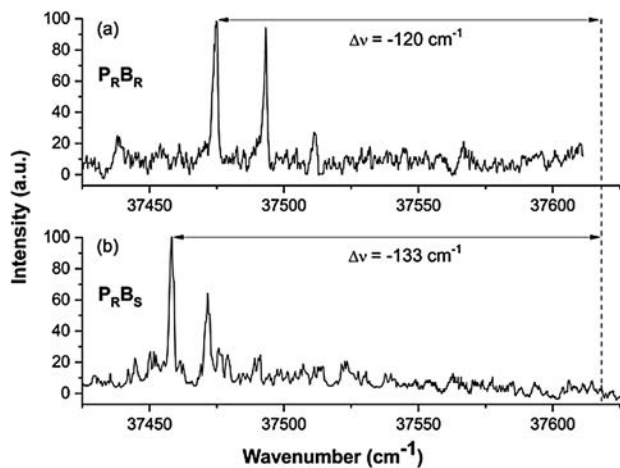
Fig. 2. 1cR2PI excitation spectra of [P_RB_R] (a) and [P_RB_S] (b) diastereomeric clusters measured at $m/z = 210$ and a total stagnation pressure 2×10^5 Pa. The dashed line refers to the electronic band origin of the $S_1 \leftarrow S_0$ transition of the bare chromophore P_R at 37618 cm^{-1}, and the reported $\Delta\nu$ values refer to the shift with respect to this transition for each cluster.

The 1cR2PI technique demonstrated several advantages over LIF, related to the ionization process and to mass resolution. The homochiral [P_RB_R] and heterochiral [P_RB_S] complexes displayed different fragmentation efficiencies in the 1cR2PI process. The distinct difference between the ion yields in the mass spectra of the diastereomers (Fig. 3a, b) provided a further tool for their
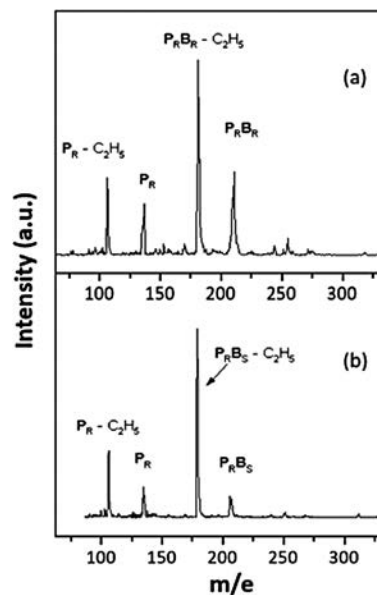
Fig. 3. 1cR2PI mass spectra of [P_RB_R] (a) and [P_RB_S] (b) diastereomeric clusters at $\lambda = 266.68$ nm and $\lambda = 266.77$ nm, respectively, and a total stagnation pressure 2×10^5 Pa. The mass peak labels in the spectra refer to the cluster [$P_RB_{R/S}$], the bare chromophore P_R, and the fragments due to ethyl loss from the clusters ($P_RB_{R/S}$ - C_2H_5) and from the chromophore ($P_R - C_2H_5$).

discrimination and also indicated a higher stability of the homochiral complex. These results also pointed out that the R2PI process could be applied to enantiomerically enrich a racemate with the same approach used for isotope-enrichment procedures [10].

2. Binding energy measurements by two-color R2PI spectroscopy

The difference between the dissociation energy of the heterochiral and homochiral adducts is an important thermodynamic parameter, defined as chiral discrimination energy or chirodiastaltic energy. Binding energy differences between diastereomeric complexes may lead to privilege binding of one enantiomer over the other, which is the basis of thermodynamic enantioselectivity, still lacking a detailed theoretical description.

From the experimental perspective, binding energy measurements in isolated neutral clusters rest on the measurement of the ionization energy of the isolated molecule and on the dissociation threshold of the diastereomeric ions and can be performed in a two color Resonant Two-Photon Ionization (2cR2PI) experiment.

The complexes can be discriminated since their electronic transition is different in the homo and heterochiral complexes.

Fig. 4 reports a scheme of the experiment for the adduct of the chromophore C and a solvent molecule, Solv. A laser of frequency ν_1 is fixed on the electronic origin of the isolated chromophore ($h\nu_1$) or on the electronic origin of the cluster ($h\nu_3$), in different threshold measurements. The ion yield at the mass of the chromophore C is measured as a function of the energy $h\nu_2$ or $h\nu_5$ of a second spatially and temporally overlapped laser. The ground state binding energy D_0" of the cluster is obtained by the equation:

$$D_0\text{"} = AE(C^+) - IP(C)$$

where $IP(C)$ is the ionization energy of the chromophore ($h\nu_1 + h\nu_2$) and $AE(C^+)$ is the appearance threshold of the ionized chromophore ($h\nu_3 + h\nu_5$) with excitation step fixed on the electronic origin of the cluster. When considering the two enantiomers of a chiral Solv, the difference between the dissociation energy of the heterochiral and homochiral adducts is therefore $\Delta D_0\text{"} = AE(C^+)_{homo} - AE(C^+)_{hetero}$.

Prof. Anna Giardini has been a pioneer in the binding energy measurements of diastereomeric adducts. The first of such measurements was between P_R and the R and S enantiomers of butan-2-ol [11]. Their homochiral complex resulted to be more stable than the heterochiral adduct by 1.1±0.4 kcal/mol in the ground state (see Fig. 5).

Similar measurements have been made also on adducts of P_R with the two enantiomers of pentan-2-ol and by employing 1-phenyl-1-ethanol as chromophore.

For these adducts between chiral benzylic alcohol derivatives and chiral secondary alcohols, the binding energy differences have been calculated in the range 0.7-1.6 kcal/mol, with the homochiral complexes always being more stable than the corresponding heterochiral complexes [11-14] (Table 1).

3. Reactions Thresholds by 2cR2PI: Effect of asymmetric microsolvation

Spectral studies on P_R and several hydrogen-bonded adducts showed that, after photoionisation, their clusters may fragment by homolytic C_α-C_β bond cleavage (see Fig. 6). The relevant energy barriers for this reaction are much lower in the radical ionic states than in the neutral electronic states. The minimum energy required to cleave the C_α-C_β bond in the isolated $[P_R]^{\bullet+}$ ion has been measured to be 7470 cm^{-1} (21.4 kcal/mol) [15] and the values are lowered in hydrogen bonded clusters [16, 17]. This low C_α-C_β bond dissociation energy was ascribed to an intersection between the potential energy surfaces of the lowest energy electronic states of the radical cations, which are perturbed by the interaction with a solvent molecule, as shown in Fig. 6. Therefore, this means that hydrogen-bond interaction between the chromophore and the solvent molecules substantially alters the topology of the intersection region of the two ionic potential energy surfaces involved in the dissociation, resulting in much lower values of activation energy (E_{act}) in H-bonded clusters. The effects of microsolva-
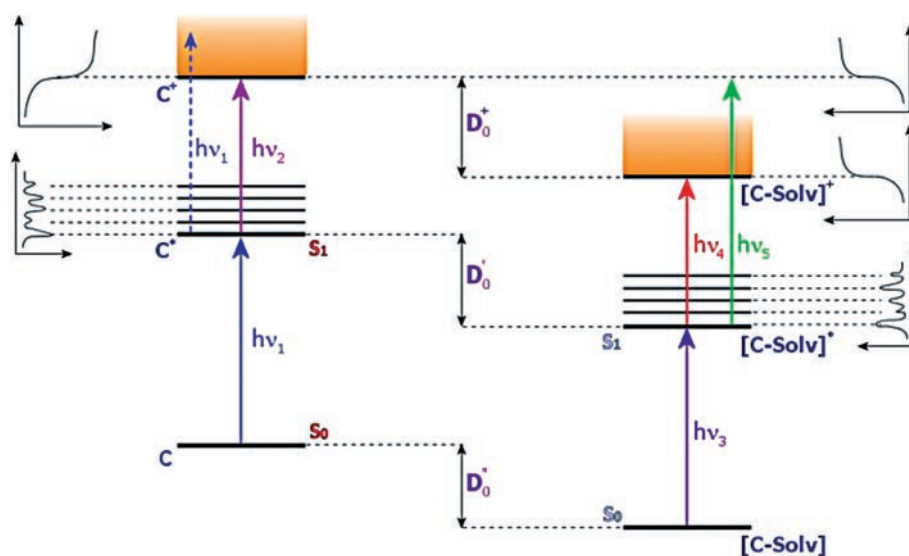

Fig. 4. 1c and 2cR2PI scheme for the spectroscopic investigation of a chromophore, C, and its adduct with a solvent molecule, Solv. D_0", D_0' and D_0^+ are the binding energies of the cluster for the ground, excited and ionic state, respectively.

Table 1 – Experimental binding energies in diastereomeric complexes of the chromophores (R)-1-phenyl-1-propanol and (R)-1-phenyl-1-ethanol with (R)- and (S)-butan-2-ol and (R)- and (S)-pentan-2-ol. D_0" is the binding energy of the cluster in the ground state and ΔD_0" is the difference of the binding energies of the diastereomeric complexes.

Chromophore	Solvent molecule	Binding energy D_0" (kcal/mol)	ΔD_0" (kcal/mol)	Reference
(R)-1-phenyl-1-propanol	(S)-butan-2-ol	4.8±0.2	1.1	11
	(R)-butan-2-ol	5.9±0.2		
(R)-1-phenyl-1-propanol	(S)-pentan-2-ol	3.1±0.2	1.6	12
	(R)-pentan-2-ol	4.7±0.2		
(R)-1-phenyl-1-ethanol	(S)-butan-2-ol	0.9±0.5 – 1.29±0.46	1.0±0.7	13
	(R)-butan-2-ol	1.9±0.5 – 2.0±0.4		

tion by water, chiral diols (2R,3R) and (2S,3S)-2,3-butanediol), and (R) and (S)-3-hydroxy-tetrahydrofuran ($Th_{R/S}$) on the energetics and dynamics of photodissociation of C_α-C_β bond in $[P_R \, Solv]^{\bullet+}$ were analyzed by measuring their fragmentation thresholds in a 2cR2PI experiment [15-17]. It was evidenced that the energy barrier for this process depends on the proton affinity of the solvent molecule and also on its configuration. Moreover, in the case of $[P_R \, Th_R]$ and $[P_R \, Th_S]$, three different hydrogen-bonded isomers have been recovered in the supersonic expansion of each cluster (Fig. 7). The isolation of different isomers within the same diastereoisomer suggests that enantioselectivity is conformation dependent and that the molecules involved in the complexation process obey to largely different arrangements of dispersive intermolecular interactions. It was found that the magnitude of the activation energies for the ethyl radical loss from the $[P_R Th_{R/S}]^{\bullet+}$ ions depends upon the configuration of the solvent molecule as well as its specific H-bonded structure of the specific isomer (Table 2).

4. 1cR2PI and IR-R2PI: the effect of fluorine substitution on chiral recognition: interplay of CH⋯π, OH⋯π and CH⋯F interactions.

The role of non-covalent bonding interactions in stabilizing specific molecular conformations and molecular
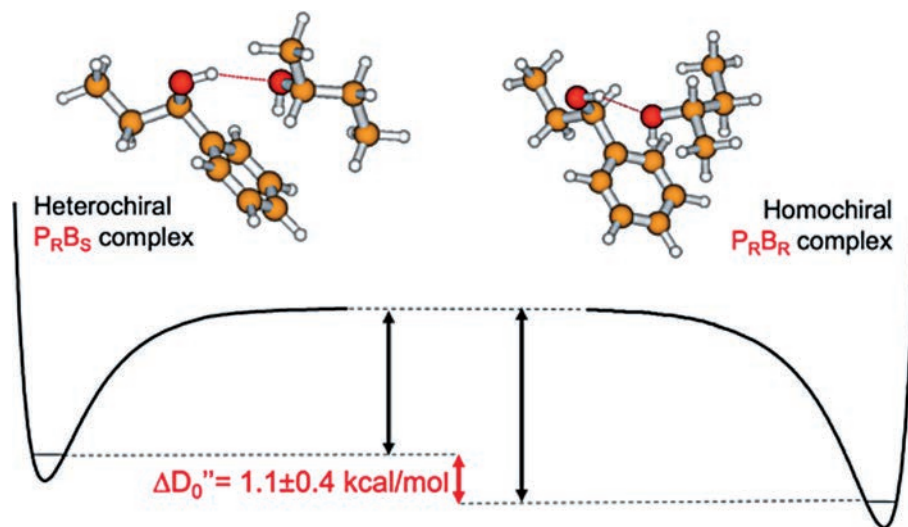

Fig. 5. Pictorial view of the binding energy difference in diastereomeric clusters $[P_R B_R]$ and $[P_R B_S]$ measured by 2cR2PI spectroscopy in supersonic beam. The D-B3LYP/6-31++G** structures of the most stable homochiral and heterochiral conformers are also reported.
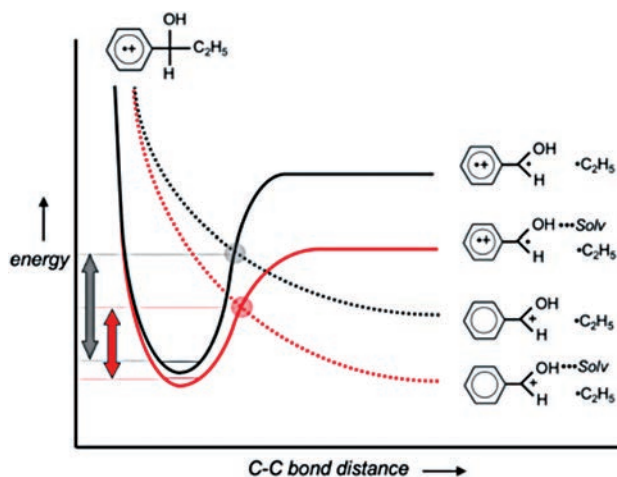
Fig. 6. Pictorial crossing between the two lowest-energy electronic states of the radical cations $[P_R]^{\bullet+}$ (black full and broken lines) and $[P_R\,Solv]^{\bullet+}$ (red full and broken lines), where Solv is a solvent molecule hydrogen-bonded to P_R.

complexes involving chiral molecules was explored using 1cR2PI and infrared depleted R2PI (IR-R2PI) with the aid of theoretical predictions at the D-B3LYP level of theory [18].

IR-R2PI double resonance spectroscopy allows to measure the vibrational transitions in the electronic ground state of the diastereomeric complexes and also to discriminate different stable conformations present in the supersonic molecular beam [19]. This methodology requires a tunable infrared laser, which fires ahead of the UV probe laser utilized for R2PI. If the IR laser is at resonance with vibrational transitions of the ground state

of the cluster, the ground state population is depleted, and the cluster can predissociate by absorption of one or several energy quanta. This results in a reduction of the number of ions produced by 1cR2PI. By measuring the ion signal while tuning the IR wavelength, the so-called IR-R2PI depletion spectrum can be recorded, which represents the vibrational transitions of the neutral precursor in the S_0 ground state.

Three systems have been investigated, in particular the molecular diastereomeric complexes between (R) and (S)-butan-2-ol and the chromophores (R)-1-phenyl-1-ethanol, (S)-1-(2-fluorophenyl)ethanol and (S)-1-(4-fluorophenyl)ethanol. The comparison of these three systems allowed us to highlight the significance of specific intermolecular interactions in the chiral discrimination process. In particular, in combination with hydrogen bonding, CH···π and OH···π interactions, in the ortho and para fluorine substituted adducts we have investigated the role of CH···F interactions in stabilizing specific molecular assemblies involving the chiral molecules. Structural assignment is based on the experimental results aided by theoretical predictions mainly at the D-B3LYP/6-31++G** level of theory. It results that the homo and heterochiral complexes between ortho, para and non-substituted 1-aryl-1-ethanol and butan-2-ol are characterized by the same binding motif. Fig. 8 shows an example for the most stable homo and hetero isomers of the parasubstituted adducts [17].

Fig. 9 reports, in a histogram, the contribution of the specific intermolecular interactions for the assigned structures, which were calculated with a classical force field (MM3) at the D-DFT geometries. The homo and

Table 2 – Ethyl-loss fragmentation thresholds and activation energies for the ethyl radical loss from the $[P_R\,Solv]^{\bullet+}$ ions.

Ionic species	Isomeric structure	Experimental C_α–C_β fragmentation threshold $^{exp}AE^{-C_2H_5}$ (cm^{-1})[a]	Calculated ionization potential $^{exp/th}IP$ (cm^{-1})[b]	Activation energy E_{act} (cm^{-1})[b,c]	Relative stability in the ionic state $^{th}AE_+$ (cm^{-1})[b]
[P_R Th$_R$]	I$_{homo}$ (β_R)	72500	68942	3558	819
	II$_{homo}$ (α_R)	71385	67270	4115	0 (most stable)
	III$_{homo}$ (γ_R)	72185	68507	3678	752
[P_R Th$_S$]	I$_{hetero}$ (β_S)	72435	68499	3936	535
	II$_{hetero}$ (α_S)	71585	67830	3755	392
	III$_{hetero}$ (γ_S)	71960	68331	3629	552

[a] Uncertainty level: ±100 cm^{-1}; [b] uncertainty level: ±140 cm^{-1}; [c] $E_{act} = {}^{exp}AE^{-C_2H_5} - {}^{exp/th}IP(cluster)$
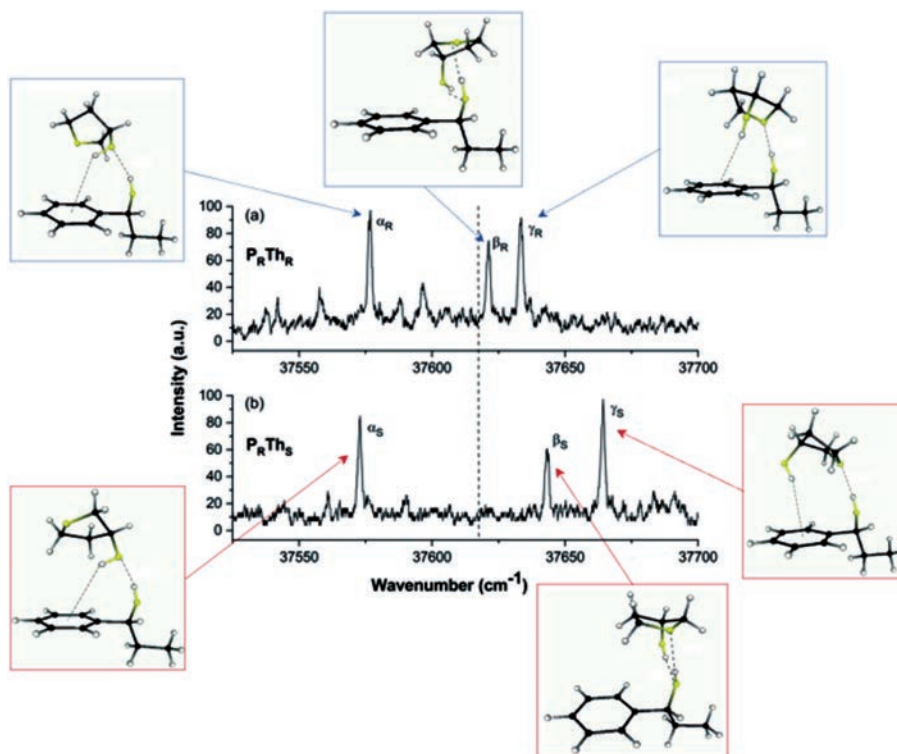
Fig. 7. 1cR2PI excitation spectra of $[P_R Th_R]$ (a) and $[P_R Th_S]$ (b) diastereomeric clusters measured at $m/z = 218$ and a total stagnation pressure 2×10^5 Pa, and structural assignment of the cluster isomers (B3LYP/6-31++G** level of theory). The dashed line refers to the electronic band origin of the $S_1 \leftarrow S_0$ transition of the bare chromophore P_R at 37618 cm^{-1}.

heterochiral complexes of these molecules are endowed with very fine, subtle differences in the CH···π, OH···π and CH···F interactions and in the strength of the hydrogen bond.

This model evaluates that the homo para and non-fluorinated complexes are characterized by somewhat stronger CH···π, OH···π and CH···F (in para fluoro substituted complexes) interactions with respect to the hetero complexes. The intermolecular interactions in turn affect the strength of the hydrogen bond which is some-
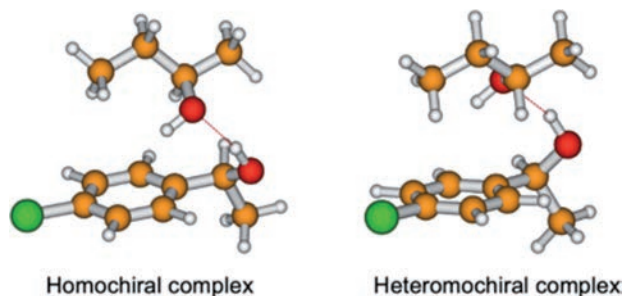
what larger in the homo clusters with respect to the hetero complexes. These differences in the contributions make the total binding energy of the homo complexes higher compared to the binding energy of the hetero structures. It also results that in the homo ortho-fluorinated complex, CH···F interactions are established at
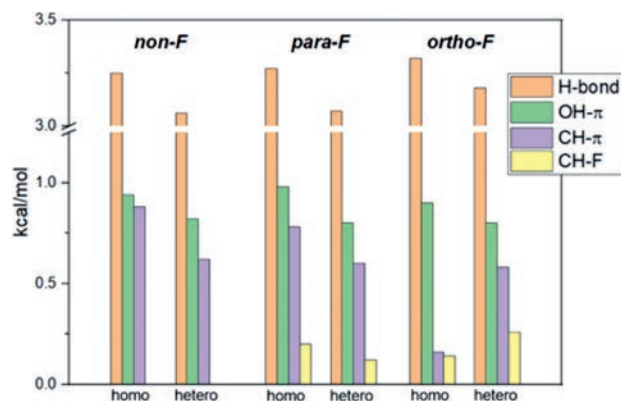

Fig. 8. D-B3LYP/6-31++G** structures of stable isomers of the homo and heterochiral adducts of (S)-1-(4-fluorophenyl)ethanol with butan-2-ol.

Fig. 9. Contribution of the OH···O, CH···π, OH···π and CH···F interactions to the total potential energy of the assigned structures, calculated with an MM3 force field at the D-B3LYP/6-31++G** geometries.

the expense of CH···π interactions, the latter resulting stronger in the heterochiral adduct, which has the ethyl group pointing towards the aromatic ring.

Our results confirm at the molecular level that chiral recognition is a process that involves the conformational adjustments of the partners in order to achieve the best efficacy of non-covalent interactions.

Conclusions

In this paper, a tribute in memory of Prof Anna Giardini, we have highlighted some relevant results obtained by the application of mass resolved R2PI spectroscopy and related double resonance IR-R2PI spectroscopy for investigating chiral recognition and enantioselectivity at the molecular level.

The possibility to determine the configuration of a chiral molecule and to possibly enrich a racemic mixture, the structural characterization on non-covalently bound diastereometric complexes, information on the role of specific electrostatic and dispersive interactions in chiral recognition, the experimental measurement of the chirodiastaltic energy and the characterization of enantiospecificic chemical reactivity in ion complexes are some salient results which have been outlined in this paper.

REFERENCES

[1] (a) M. Quack. How Important is Parity Violation for Molecular and Biomolecular Chirality? Angew. Chem., Int. Ed., 2002, 41, 4618-4630. DOI: 10.1002/anie. 200290005; (b) U. J. Meierhenrich and W. H. -P. Thiemann. Photochemical Concepts on the Origin of Biomolecular Asymmetry. Origins Life Evolution Biosphere 2004, 34, 111-121; (c) D. K. Kondepudi, R. J. Kaufman and N. Singh. Chiral symmetry breaking in sodium chlorate crystallization. Science 1990, 250, 975–976. DOI: 10.1126/science.250.4983.975; (d) M. Musigmann, A. Busalla, K. Blum and D. J. Thompson. Asymmetries in collisions between electrons and oriented chiral molecules. J. Phys. B: At., Mol. Opt. Phys., 1999, 32, 4117-4128. DOI 10.1088/0953-4075/32/16/311; (e) W. A. Bonner, J. M. Greenberg and E. Rubenstein. The Extraterrestrial Origin of the Homochirality of Biomolecules – Rebuttal to a Critique. Origins Life Evolution Biosphere, 1999, 29, 215-219.

[2] R. Popa. Between Necessity & Probability: Searching for the Definition and Origin of Life, Advances in Astrobiology & Biogeophysics Series, Springer, Berlin Heidelberg, Germany, 2004.

[3] (a) J. P. Simons. Good Vibrations: Probing Biomolecular Structure and Interactions through Spectroscopy in the Gas Phase, Mol. Phys. 2009, 107, 2435; (b) T. S. Zwier. Laser Probes of Conformational Isomerization in Flexible

Molecules and Complexes, J. Phys. Chem. A, 2006, 110, 4133. DOI: 10.1021/jp056390z; (c) B. Brutschy. Reactions in molecular clusters following photoionization, J. Phys. Chem. 1990, 94, 8637-8647. DOI: 10.1021/j100387a006.

[4] J. P. Shermann. Spectroscopy and modelling of biomolecular building blocks, Elsevier, Amsterdam, 2007.

[5] A. R. Al Rabaa, E. Breheret, F. Lahmani and A. Zehnacker. Enantiodifferentiation in jet-cooled van der Waals complexes of chiral molecules, Chem. Phys. Lett. 1995, 237, 480. DOI: 10.1016/0009-2614(95)00329-3.

[6] S. Piccirillo, C. Bosman, D. Toja, A. Giardini, M. Pierini, A. Troiani and M. Speranza. Gas phase enantiodifferentiation of chiral molecules: Chiral recognition of 1-phenyl-1-propanol/2-butanol clusters by resonance enhanced multiphoton ionization spectroscopy, Angew. Chem., Int. Ed. Engl., 1997, 36, 1729. DOI: 10.1002/anie.199717291.

[7] N. Borho and M. Suhm. Glycidol dimer: anatomy of a molecular handshake, Phys. Chem. Chem. Phys., 2002, 4, 2721. DOI: 10.1039/B111123J.

[8] (a) A. K. King and B. J. Howard. A microwave study of the hetero-chiral dimer of butan-2-ol, Chem. Phys. Lett. 2001, 348, 343-349. DOI: 10.1016/S0009-2614(01)01121-6; (b) Z. Su, N. Borho and Y. Xu. Chiral Self-Recognition: Direct Spectroscopic Detection of the Homochiral and Heterochiral Dimers of Propylene Oxide in the Gas Phase, J. Am. Chem. Soc. 2006, 128, 17126-17131. DOI: 10.1021/ja066128j.

[9] (a) B. Brutschy. Reactions in molecular clusters following photoionization. J. Phys. Chem. 1990, 94, 8637-8647. DOI: 10.1021/j100387a006; (b) S. Piccirillo, M. Coreno, C. Bosman, A. Giardini-Guidoni, A. Mele, A. Palleschi. Resonant two-photon ionization of van der Waals adducts of 4-fluorostyrene with monomethylamine and monoethylamine: intracluster chemical reactions. Chem. Phys. Lett. 1995, 247, 577-583. DOI: 10.1016/S0009-2614(95)01232-X; (c) M. Speranza, M. Satta, S. Piccirillo, F. Rondino, A. Paladini, A. Giardini, A. Filippi, D. Catone. Chiral recognition by mass-resolved laser spectroscopy, Mass. Spectrometry Rev. 2005, 24, 588-610. DOI: 10.1002/mas.20040

[10] R. Fantoni, E. Borsella, A. Palucci, A. Giardini. Laser e molecole: la stagione dei multifotoni a Frascati negli anni 70 e 80 Energia, Ambiente e Innovazione 2015, 6, 29. DOI: 10.12910/EAI2015-091.

[11] A. Latini, M. Satta, A. Giardini Guidoni, S. Piccirillo, M. Speranza. Short-Range Interactions within Molecular Complexes Formed in Supersonic Beams: Structural Effects and Chiral Discrimination, Chemistry-A European Journal 2000, 6, 1042-1049. DOI: 10.1002/(SICI)1521-3765(20000317) 6:6< 1042::AID-CHEM1042>3.0.CO;2-W

[12] A. Giardini Guidoni, S. Piccirillo, D. Scuderi, M. Satta, T. M. Di Palma, M. Speranza, A. Filippi, A. Paladini. R2PI Study of Intermolecular Hydrogen Bond in Solvent-Free Chiral Complexes, Chirality 2001, 13, 727–730. DOI: 10.1002/chir.10010.

[13] M. Mons, F. Piuzzi, I. Dimicoli, A. Zehnacker, F. Lahmani. Binding energy of hydrogen-bonded complexes of the chiral 1-phenylethanol molecule by 2C-R2PI: comparison between diastereoisomeric complexes with butan-2-ol and the singly hydrated complex, Phys. Chem. Chem. Phys. 2000, 2, 5065–5070. DOI: 10.1039/B005660J.

[14] S. Piccirillo, M. Satta, D. Catone, D. Scuderi, A. Paladini, F. Rondino, M. Speranza and A. Giardini Guidoni. Mass resolved laser spectroscopy of micro-solvated R-(+)-1-phenyl-1-propanol: A chiral molecule of biological interest. Phys. Chem. Chem. Phys. 2004, 6, 2858-2862. DOI: 10.1039/B316737B.

[15] D. Catone, A. Giardini Guidoni, A. Paladini, S. Piccirillo, F. Rondino, M. Satta, D. Scuderi, M. Speranza. Homolytic C - C bond cleavage in a chiral alkylarene radical cation: effects of asymmetric microsolvation, Angew. Chem. Int. Ed 2004, 43(14), 1868-1871. DOI: 10.1002/anie.200353462.

[16] S. Piccirillo, F. Rondino, D. Catone, A. Giardini Guidoni, A. Paladini, M. Tacconi, M. Satta, M. Speranza. Excitation, Ionization, and Fragmentation of Chiral Molecules in Asymmetric Microenvironments: A Mass-Resolved R2PI Spectroscopic Study, J. Phys. Chem. A. 2005, 109(9), 1828-1835. DOI: 10.1021/jp044510h.

[17] (a) F. Rondino, A. Paladini, A. Ciavardini, A. Casavola, D. Catone, M. Satta, H. D. Barth, A. Giardini, M. Speranza and S. Piccirillo. Chiral recognition between 1-(4-fluorophenyl) ethanol and 2-butanol: higher binding energy of homochiral complexes in the gas phase, Phys. Chem. Chem. Phys. 2011, 13, 818–824. DOI: 10.1039/c0cp01401j; (b) A. Ciavardini, F. Rondino, A. Paladini, M. Speranza, S. Fornarini, M. Satta and S. Piccirillo. The effect of fluorine substitution on chiral recognition: interplay of CH···π, OH···π and CH F interactions in gas-phase complexes of 1-aryl-1-ethanol with butan-2-ol, Phys. Chem. Chem. Phys., 2013, **15**, 19360. DOI: 10.1039/C3CP53215A.

[18] (a) Page R. H., Shen Y. R. and Lee Y. T. Local modes of benzene and benzene dimer, studied by infrared–ultraviolet double resonance in a supersonic beam. J. Chem. Phys. 1988, 88, 4621-4636. DOI: 10.1063/1.453775; (b) Page R. H., Shen Y. R. and Lee Y. T. Infrared–ultraviolet double resonance studies of benzene molecules in a supersonic beam. J. Chem. Phys. 1988, 88, 5362-5376. DOI:10.1063/1.454574; (c) Riehn C., Lahmann C., Wassermann B., and Brutschy B. IR depletion spectroscopy. A method for characterizing a microsolvation environment. Chem. Phys. Lett. 1992, 197, 443-450. DOI: 10.1016/0009-2614(92)85798-F.

[19] Bakker J.M., Compagnon I., Meijer G. Von Helden G., Kabela M., Hobzac P., De Vries M. The mid-IR absorption spectrum of gas-phase clusters of the nucleobases guanine and cytosine, Phys. Chem. Chem. Phys. 2004, 6, 2810-2815. DOI: 10.1039/b316158g.