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The effect of halogen substitution on the aromatic ring in chiral recognition between 1-aryl-1-ethanol and butan-2-ol: Resonant Two Photon Ionization Spectroscopy and Quantum Chemical Calculations

Abstract – Non-covalent intra and intermolecular interactions account for the molecular and chiral recognition properties as well as the functionality of biomolecules.

This minireview presents the results concerning adducts between chiral aromatic alcohols, differently substituted on the aromatic ring, with the two enantiomers of butan-2-ol, which have been investigated by mass-selective resonant two-photon ionization (R2PI) and infrared depleted R2PI (IR-R2PI) techniques. The comparison of the systems allowed us to highlight the significance of specific intermolecular interactions in the chiral discrimination process. The interpretation of the results is based on theoretical predictions at the D-B3LYP/6-31++G** level of theory.

Introduction

The transmission of chiral information, the recognition properties as well as the functionality of biomolecules rely substantially on non-covalent intra and intermol-

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ecular interactions and their study is of fundamental interest and has a deep impact on chemistry, biology, pharmacology, materials science and astrophysics. In combination with stronger non-covalent interactions with high directionality, such as conventional hydrogen bonding or metal coordination, other forces such as π···π stacking, lone pair···π or weaker hydrogen bond interactions such as XH···π (X = O, N and C) or CH···X (X = O, N, halogen) interactions often play an essential role in chiral discrimination processes [1]. Indeed, the ability of halogen atoms to work as effective sites for directing molecular recognition processes long remained unexplored, despite in 1970 Hassel *et al.* [2] pointed out the key role of halogen atoms in driving molecular self-assembly processes. Then in the past decade, the effects of halogenation have received a growing interest in many different fields, and the halogen bond has been largely exploited to control the assembly of small molecules in the design of both supramolecular complexes and new materials [3].

A convenient approach to gain detailed information on the nature of the specific intervening forces is to generate tailor-made molecular adducts in the isolated state and to investigate them through high-resolution spectroscopy. Specific interactions, influencing molecular geometries, as well as the dynamics of conceivable reactive processes [4] can be studied without any interference from the environment. The results of gas phase experiments can be used by theoretical chemists as a benchmark for the validation of different approximations for quantum calculations [5].

Here, we highlight and summarize some recent results [6, 7, 8] concerning adducts containing a chiral halogenated molecule, obtained under collision-free conditions in supersonic molecular beams and investigated through resonant two-photon ionization (R2PI) and double-resonance infrared-R2PI (IR-R2PI) spectroscopy coupled with mass spectrometry. In particular, we point out results concerning the effect of the presence of a halogen atom in different positions on the aromatic ring on the structure and the conformational equilibria of the complexes between (*S*)-1-(4-chlorophenyl)ethanol (p-ClE_S), S-1-(4-fluorophenyl)ethanol (p-FE_S), (S)-1-(2-fluorophenyl)ethanol (o-FE_S), R-1-phenyl1-ethanol (E_R) with the two enantiomers of butan-2-ol (B_R and B_S). All figures are adapted from Ref. 6.7,8.

Experimental section

The experimental apparatus for the study of gas phase complexes has been described previously [6, 9] and will be briefly summarized. Neutral clusters are produced in a 10-Hz-pulsed seeded supersonic expansion of vapors of chiral molecules generated in temperature-controlled reservoirs in argon carrier gas. The clusters are ionized via one-color Resonant Two Photon Ionization (1cR2PI) process. The photoions are mass analyzed in a time-of-flight mass spectrometer and detected by a channeltron. One-color R2PI experiments are performed through the ionization of the species of interest by resonant absorption of two photons of the same energy h . The entire TOF mass spectrum is recorded as a function of ν_1. Due to the resonant

step in the two-photon process, the wavelength dependence of a given mass-resolved ion represents the excitation spectrum of the neutral precursor and contains information about its electronic excited state S_1.

The difference in the binding energies of the diastereomeric complexes has been evaluated by the measure of the product/parent dissociation ratio recorded at specific 1c-R2PI transitions.

The vibrational spectra in the OH-stretching region of the neutral precursors are recorded by IR–R2PI double resonance spectroscopy. The IR and UV lasers are counter-propagating and spatially superimposed, the IR laser pump pulse precedes the UV laser by about 100 ns. If a cluster absorbs photons with energies of one or several quanta of a high-frequency vibrational mode, it predissociates very fast by IVR resulting in a depopulation and an R2PI-ion signal depletion. An ion-dip spectrum is recorded by scanning the wavelength of the IR laser with the wavelength of the probe laser being fixed to the specific transition in the R2PI spectrum of a selected cluster. It represents part of the vibrational spectrum of the neutral precursor cluster in the electronic ground state. This methodology also allows the discrimination of different conformers present in the supersonic molecular beam [10]. The IR laser light is generated by a home-made, injection-seeded optical parametric oscillator (OPO), built according to the design developed at the University of Frankfurt [11].

A preliminary analysis of the conformational landscape was carried out by classical molecular dynamics with the MM3 force-field. The optimized structures are classified according to their conformation and energy and the lowest energy structures for each diastereomer (relative energy lower than 2 kcal mol^{-1}) have been re-optimized with the D-DFT approach: we used the B3LYP Hamiltonian with the 6-31++G** basis set. Further details can be found in references 6,7 and 8.

The structure of the bare chromophores

The 1cR2PI excitation spectrum of the halogenated compounds pFE_S, p-ClE_S and oFE_S are characterized by the presence of low-frequency (40-50 cm-1) band progressions, which are absent in the E_R congener under similar experimental conditions. This behavior is ascribable to the fact that the S1←S0 transition in the halogenated species involves asymmetric structures of the aromatic ring in both the S_0 and S_1 states while the same electronic transition in non-halogenated E_R involves no change of the quasi-C6 symmetry of the ring. According to D-B3LYP/6-31++G** calculations, the band progression observed in the spectra of pFE_S, p-ClE_S and oFE_S can be related to the $\nu_1(C_1\text{-}C_\alpha)$ torsional mode of the most stable structure of each species, pointing out that only one predominant conformer is identified in the supersonic beam expansion. The presence of one stable conformation is found also in the case of E_R.

The most stable conformational structures of the isolated chromophores which were identified experimentally are remarkably similar. As shown in figure 1 for

p-ClE_S they are characterized by an intramolecular OH···π interaction and a weak attractive C_2H···O interaction. In the case of oFES, there is also a weak C_αH···F interaction.

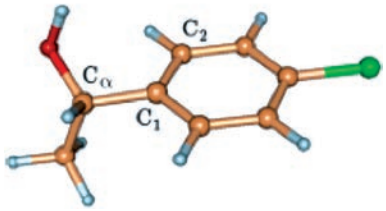

Fig. 1. D-B3LYP/6-31++G** calculated structure for the most stable conformer of isolated p-ClE_S.

Structure and stability of the para halogenated diasteromers

Fig. 2 reports as an example the 1cR2PI excitation spectra of the two complexes of p-FES with R and S-butan-2-ol [6]. Both spectra display a low frequency vibrational progression which can be assitgned to the $\nu_1(C_1\text{-}C_\alpha)$ torsional mode. A spectral chiral discrimination is evident from the spectra: each diastereomer displays distinct features shifted to the red with respect to 0_0^0 electronic transition of the chromophore [12]. The shift is greater for the homochiral complex with respect to the

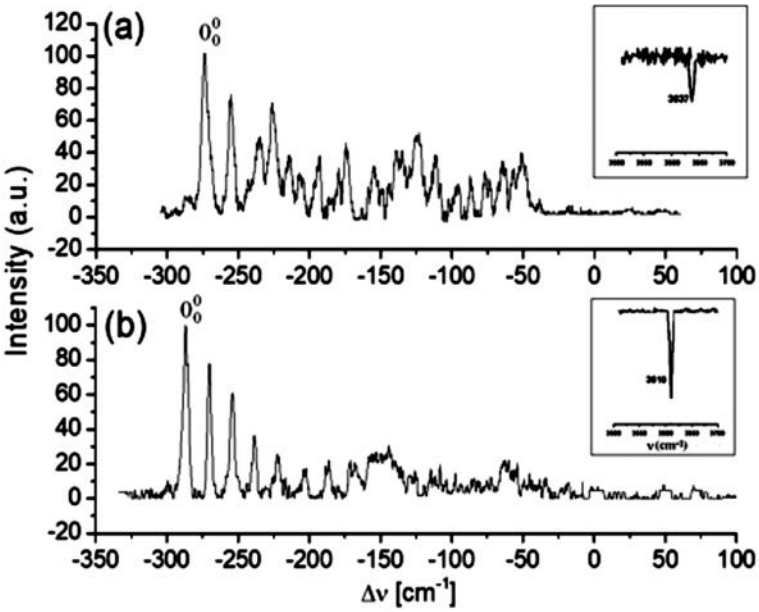

Fig. 2. R2PI excitation spectra and IR-R2PI spectra (inset) of (a) heterochiral [p-FE_S*B_R] and (b) homochiral [p-FE_S*B_S] clusters.

heterochiral complex. Similar results have been found for the non-halogenated adducts and for the para-chloro adducts with butan-2-ol [8]. The measurement of the dissociation ratios in the mass spectra indicates that the homochiral complexes are more stable than the heterochiral complexes for the non halogenated and para fluorinated diasteromers and the relative stability of the specific homo versus hetero complexes is much higher for the para substituted complexes with respect to the non-fluorinated adducts.

The shift in the R2PI spectra is relative to the electronic transition of the isolated FE_S molecule at 37 140 cm^{-1}.

In the inset of figure 2, the IR-R2PI depletion spectra of the complexes is shown, recorded in the 3500-3700 cm^{-1} range with the probe wavelength set on the 0_0^0 origin of the complexes. The bands at 3637 and 3610 cm^{-1} correspond to the OH stretch mode of butanol in the p-$FE_S \cdot B_{R/S}$ clusters.

Figure 3 for the non halogenated and figure 4 for the para-halogenated adducts show the D-B3LYP calculated structures which have been assigned on the basis of i) the comparison between calculated and observed vibrational frequencies, ii) the analysis of the specific interactions contributing to the shift of the electronic transition, iii) the relative energy of the complexes. A complete description of all calculated complexes can be found in references 6, 7, 8. These structeres are characterized by an $O^{ch}H\cdots O$ hydrogen bond and an $O^{bu}H\cdots\pi$ interaction with the aromatic ring (O^{ch} and O^{bu} are the oxygen atoms of chromophore and butan-2-ol). The binding motif is similar, as shown in figure 4: the hydrogen atom attached to the C_2 chiral center of butan-2-ol points towards the aromatic ring, so that $C_2H\cdots\pi$ interactions are established. Other $CH\cdots\pi$ interactions can be established either by facing the ethyl or the methyl group of butan-2-ol towards the aromatic ring, yet these interactions are stronger if the ethyl points towards the aromatic ring. In the non-halogenated complexes (figure 3) and in the para fluoro or chloro substituted complexes (figure 4) the ethyl group of butan-2-ol is always bent over the aromatic ring. The conformation of butan-2-ol in the clusters is the same in all the adducts and it is

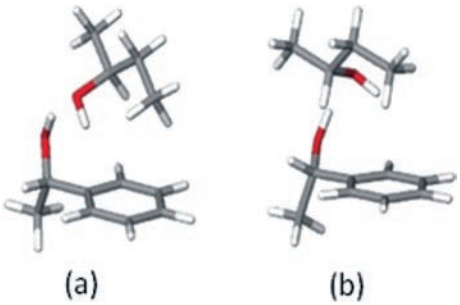

Fig. 3. D-B3LYP/6-31++G** structures of the assigned homochiral and heterochiral conformers of the complexes of of E_R with butan-2-ol. (a) homochiral (b) heterochiral.

one of the two most stable geometries that have been identified by microwave Fourier transform spectroscopy in supersonic beam expansion of isolated butan-2-ol, denoted m-ga [13]. The different chirality of the two stereoisomers of butan-2-ol involves that, in the complex, the hydrogen atom attached to the C_α chiral center of the aromatic molecule and the hydrogen atom attached to the C_2 chiral center of butan-2-ol are facing each other in the hetero complexes, (fig. 4b, as well as 4d, 3b) while they point to opposite directions in the homocomplexes (Fig. 4a as well as 4c, 3a). Consequently $C_\alpha H \cdots HC_2$ repulsive interactions in all the hetero complexes are somewhat more relevant, decreasing the overall CH···π and OH···π interactions with the aromatic ring. This is in agreement with the experimental findings that the homo complexes are more stable than the hetero complexes.

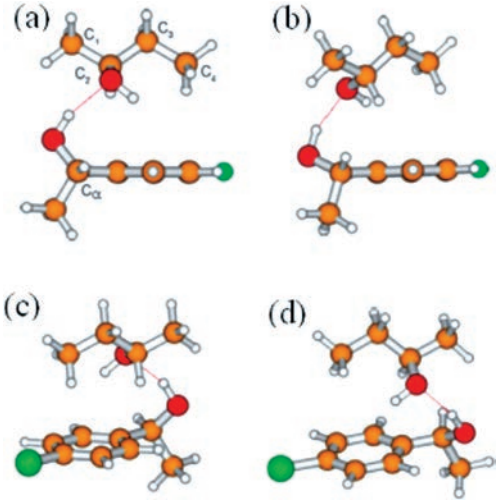

Fig. 4. D-B3LYP/6-31++G** structures of the assigned homochiral and heterochiral conformers of the complexes of p-FES and p-ClES with butan-2-ol. (a) para flluorine substituted complex, homochiral (b) para flluorine substituted complex, heterochiral (c) para chlorine substituted complex, homochiral (d) para chlorine substituted complex, heterochiral.

The comparison between the para halogenated and non-halogenated complexes reveals that the presence of the halogen atom in the para position of the aromatic ring does not affect the overall geometry of the complex, though in the para halogenated homo complexes a contraction of the vdW complex with a shortening of the OH···π distance is found. The strengthening of the attractive interactions in the homo para complexes can be tentatively attributed to the inductive and resonance effects of the halogen atom on the aromatic ring, which modify the distribution of the electron density. This probably leads to an extra stabilization of the homo para substituted complex with respect to the non-substituted homo adduct and could explain the fact that the experimental and theoretical binding energy difference

between the homo and hetero complexes with 2-butanol follows the order E_R*$B_{R/S}$<p-FE_S*$B_{R/S}$ <p-Cl_S*$B_{R/S}$.

Structure and stability of the ortho fluorine substituted complexes

Differently from the non halogenated and para substituted adduct, the R2PI spectrum of the homochiral complex (figure 5a) is blue-shifted with respect to the 0_0^0 transition of the bare chromophore, while in the case of the heterochiral complex (figure 5b) a red shift was measured. Both spectra display a vibrational progression spaced about 20 cm^{-1}. In their respective IR-R2PI spectra, one sharp absorption at 3636 cm^{-1} for the homochiral complex and at 3616 cm^{-1} for the heterochiral complex are measured. The dissociation ratios in the mass spectra are 51% for the homo and 62% for the hetero complex at almost equal values of total ionization energy, hence the hetero/homo ratio in the fragmentation efficiency is lower in the ortho-fluoro substituted complexes with respect to the para-fluoro substituted complexes, in agreement with the calculated binding energy differences.

In the complex formation, the fluorine atom in the ortho position is also available for the formation of an intermolecular C_2H···FC interaction. Considering a structural motif like the one described above for the para and non-fluorinated complexes (fig. 3, 4) the C_2H···FC interaction can be established only in the hetero ortho substituted complex, which indeed adopts a conformation similar to the other discussed hetero structures (figure 5b). In the ortho homo adduct, the establishment of C_2H···FC intermolecular interaction together with an $O^{bu}H$···π interaction is only possible if the conformation of butan-2-ol is different from the m-ga. The best over-

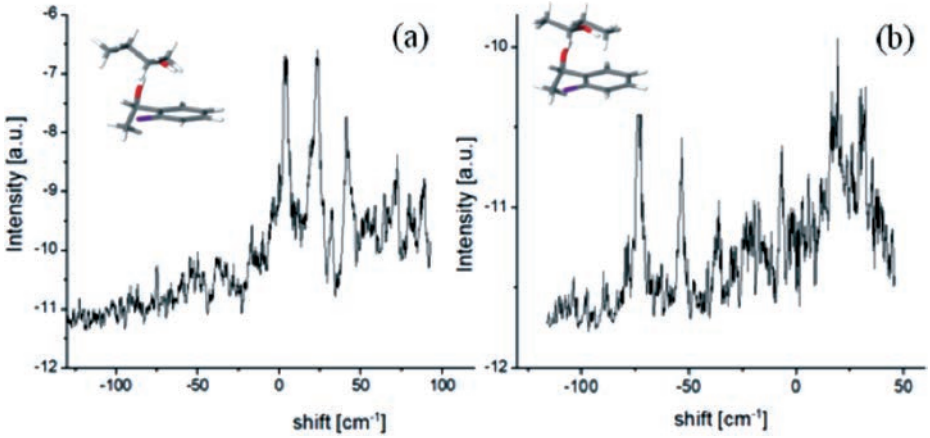

Fig. 5. R2PI excitation spectra and D-B3LYP/6-31++G** structures of (a) homochiral [o-FE_S*B_S] and (b) heterochiral [o-FE_S*B_R] clusters. The shift in the R2PI spectra is relative to the 0_0^0 electronic transition of the isolated o-FE_S molecule at 37587 cm^{-1}.

all agreement with the experimental data is in fact obtained if the spectrum of the homo adduct is assigned to the structure reported in the inset of figure 5a, where the conformation of butan-2-ol is e-ga [13], with the methyl (instead of the ethyl) group interacting with the aromatic ring. The different spectroscopic behavior of this complex acknowledges the role and the importance of CH···F interactions in molecular and chiral recognition processes. While the ortho hetero complex is structurally analogous to the hetero para and non-fluorinated structures, butan-2-ol in the ortho homo adduct adopts a different conformation in order to establish a CH···F intermolecular interaction.

Conclusions

This mini-review resumes the results of a systematic investigation aimed at clarifying, at the molecular level, the potential of the halogen substitution on the aromatic ring to alter the type and magnitude of non-covalent interactions as well as to modify the spectroscopic properties of the adducts. 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.

REFERENCES

[1] (a) J. Bella, M. Eaton, B. Brodsky and H.M. Berman, Crystal and molecular structure of a collagen-like peptide at 1.9 A resolution. Science, 1994, 266, 75; (b) H.C. Chang, J.C. Jiang, C.M. Feng, Y.C. Yang, C.C. Su, P.J. Chang and S.H. Lin, Evidence of charge-enhanced C-H-O interactions in aqueous protonated imidazole probed by high pressure infrared spectroscopy. Chem. Phys., 2003, 118, 1802; (c) S. Scheiner, T. Kar and J. Pattanayak, Comparison of Various Types of Hydrogen Bonds Involving Aromatic Amino Acids. J. Am. Chem. Soc., 2002, 124, 13257; (d) P. Milko, J. Roithová and K.A. Schug, Impact of long-range van der Waals forces on chiral recognition in a *Cinchona* alkaloid chiral selector system. Phys. Chem. Chem. Phys., 2013, 15, 6113.

[2] Hassel, O. Structural Aspects of Interatomic Charge-Transfer Bonding. Science 1970, 170, 497-502.

[3] (a) a) Rissanen, K. Halogen Bonded Supramolecular Complexes and Networks. CrystEngComm 2008, 10, 1107-1113. (b) Bouchmella, K.; Boury, B.; Dutremez, S.G.; van der Lee, A. Molecular Assemblies from Imidazolyl-Containing Haloalkenes and Haloalkynes: Competition between Hydrogen and Halogen Bonding. Chem. - Eur. J. 2007, 13, 6130. (c) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. Halogen Bonding in Supramolecular Chemistry. Angew. Chem., Int. Ed. 2008, 47, 6114-6127 and references therein.

[4] B. Brutschy, Reactions in molecular clusters following photoionization J. Phys. Chem., 1990, 94, 8637-8647.

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

[6] Rondino, F.; Paladini, A.; Ciavardini, A.; Casavola, A.; Catone, D.; Satta, M.; Dieter Barth, H.; Giardini, A.; Speranza, M.; Piccirillo, S. 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.

[7] Ciavardini, A.; Rondino, F.; Paladini, A.; Speranza, M.; Fornarini, S.; Satta, M.; Piccirillo, S. 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, 19360-19370.

[8] F. Rondino, M. Satta, S. Piccirillo, A. Ciavardini, A. Giardini, M. Speranza, L. Avaldi, A. Paladini Chlorine Para-Substitution of 1 Phenylethanol: Resonant Photoionization Spectroscopy and Quantum Chemical Calculations of Hydrated and Diastereomeric Complexes J. Phys. Chem. A 2016, 120, 5023-5031.

[9] Piccirillo S., Coreno M., Giardini-Guidoni A., Pizzela G., Snels M., Teghil R. (1993). Spectroscopy of 4-fluorostyrene clusters. J Mol Struct 293, 197.

[10] Riehn C., Lahmann C., Wassermann B., Brutschy B. (1992). IR depletion spectroscopy. A method for characterizing a microsolvation environment. Chem Phys Lett 197:443-450.

[11] Reimann B., Buchhold K., Barth H.D., Brutschy B., Tarakeshwar P., Kim K.S., Anisole-(H2O)n(H2O)n (n=1-3)(n=1-3) complexes: An experimental and theoretical investigation of the modulation of optimal structures, binding energies, and vibrational spectra in both the ground and first excited states. J Chem Phys 117, 2002,1.

[12] Speranza, M.; Rondino, F.; Giardini, A.; Paladini, A.; Hortal, A.R.; Piccirillo, S.; Satta, M., Conformational landscape of supersonically expanded 1-(fluorophenyl)ethanols and their monohydrated clusters. ChemPhysChem 2009, 10, 1859-1867.

[13] King, A.K.; Howard, B.J., An investigation into the relaxation of the conformers of butan-2-ol in a supersonic expansion J. Mol. Spectrosc. 2009, 257, 205-212.