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Chiral discrimination of monofunctional alcohols and amines in the gas phase

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Abstract

A methodology has been developed for enantiodiscriminating chiral monoalcohols and monoamines by mass spectrometry. The approach is based on the generation of supersonically expanded complexes of these molecules with suitable chromophores, i.e. *R*-(+)-1-phenyl-ethanol ($\mathbf{E}_R$) or *R*-(+)-1-phenyl-1-propanol ($\mathbf{P}_R$). The jet-cooled diastereomeric complexes, otherwise elusive at room temperature, have been ionized by one-color resonant two-photon absorption (R2PI) and their fragmentation pattern analyzed by time-of-flight (TOF) spectrometry. Enantiodifferentiation of the chiral monoalcohols and monoamines is based on: (1) the different spectral shifts of the band origin of their molecular complexes relative to that of the bare chromophore (Δ) and (2) the different mass spectral fragmentation patterns of the jet-cooled diastereomeric adducts. Detection of stable aggregates of methane, *n*-butane, and other simple molecules with the selected chromophores suggests that the R2PI/TOF method can be a potential tool for enantiodifferentiating chiral hydrocarbons in the gas phase. (Int J Mass Spectrom 210/211 (2001) 483–488) © 2001 Elsevier Science B.V.

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1. Introduction

Modeling chiral recognition in chemistry and biology requires the knowledge of the structure of isolated diastereomeric aggregates and of their intracomplex forces at the microscopic level. Various mass spectrometric techniques (MS) have been recently employed to this purpose [1]. The approach relies on the different thermodynamic and kinetic stability of diastereomeric pairs formed by aggregation of an enantiomeric pair (**L**) with a chiral selector (**C**). The fragmentation free energy and, therefore, the MS pattern of the corresponding diastereomeric $[\mathbf{L} \cdot \mathbf{C}]^+$ adducts depend upon the specific configuration of the **L** and **C** moieties.

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Dedicated to Nico. M. M. Nibbering, a good friend and an outstanding ion chemist.

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Enthalpy-entropy compensation is a common consequence of the weak association forces of molecular and ionic aggregates whose binding enthalpy is much lower than covalent bond strengths. In these systems, the enthalpic benefit of bonding is progressively offset by an adverse entropy of restricted motion as the temperature increases. Thus, most weakly bound aggregates are generally too elusive to be generated and characterized in low-pressure MS sources even at room temperature. On the contrary, the intense interactions between multifunctional species cannot be readily offset by entropic factors under similar conditions and, therefore, the aggregates live long enough to be detected and investigated by MS. Indeed, the recent literature reports on many examples of chiral recognition by MS based on the mass spectra of diastereomeric $[\mathbf{L} \cdot \mathbf{C}]^+$, involving at least one multifunctional component between **L** and **C**, e.g. dialkyltartrates [2], aminoacids [3], crown ethers [4a], cyclodextrins [4b], cytochrome *c* [5], etc.

This limitation prevents the MS investigation of weakly bound diastereomeric adducts between monofunctional chiral molecules, whose intracomplex forces are more easily identifiable and their relative magnitude more easily measurable [6]. However, this difficulty can be removed by generating weakly bound diastereomeric aggregates at temperatures so low to minimize the adverse entropy effects. This condition is obtained by supersonically expanding their chiral components into the source of a mass spectrometer. This work reports on the MS enantiodifferentiation of simple monofunctional ligands (**L**), i.e. chiral 2-butanols (**6**), 2-pentanols (**7**), and 2-butylamines (**8**), through the formation and the discrimination of their labile, weakly bonded diastereomeric aggregates $[\mathbf{L} \cdot \mathbf{C}]^+$ with a chiral monofunctional chromophore (**C**), i.e. *R*-(+)-1-phenylethanol $\mathbf{E}_R$ and *R*-(+)-1-phenyl-1-propanol $\mathbf{P}_R$

$$\mathbf{L} + \mathbf{C} \xrightarrow[\text{expansion}]{\text{supersonic}} [\mathbf{L}\text{–}\mathbf{C}]^\circ \xrightarrow{h\nu} [\mathbf{L}\text{–}\mathbf{C}]^* \xrightarrow[-e]{h\nu} \rightarrow$$

$$[\mathbf{L}\text{–}\mathbf{C}]^+ \longrightarrow \text{fragments} \qquad (1)$$

In order to check the potentiality of the methodology adopted, the study has been extended to complexes with even simpler achiral molecules, i.e. methane (**1**), *n*-butane (**2**), water (**3**), methanol (**4**), and diethylether (**5**).

2. Methodology

The methodology used in the present work is based on the generation in the source of a time-of-flight (TOF) mass spectrometer of the fragile molecular complexes $[\mathbf{L} \cdot \mathbf{C}]$ by supersonic expansion of their components.

Adducts $[\mathbf{L} \cdot \mathbf{C}]$ are produced in their electronic ground state S_0 {$[\mathbf{L} \cdot \mathbf{C}]^\circ$ in Eq. (1)} with translational and vibrational temperatures of few degrees Kelvin [7]. Their ionization is obtained by resonance-enhanced two-photon absorption (R2PI), i.e. one photon ν is used to excite the chromophore in the complex, i.e. $\mathbf{E}_R$ or $\mathbf{P}_R$, from its ground state to its first electronically excited S_1 state {$[\mathbf{L} \cdot \mathbf{C}]^*$ in Eq. (1)} and a second photon ν leads it to the continuum {$[\mathbf{L} \cdot \mathbf{C}]^+$ in Eq. (1)}. It should be noted that the $[\mathbf{L} \cdot \mathbf{C}]^\circ$ and $[\mathbf{L} \cdot \mathbf{C}]^*$ binding energies may depend upon the nature and the configuration of their moieties and, therefore, each complex is characterized by a different resonant ν absorption. This may allow the selective ionization of a specific adduct even in a complex mixture and in the presence of its diasteroisomeric form. In the R2PI experiments, some excess energy may be imparted to the ionized complexes to an amount that is related to the overall energy absorbed ($2h\nu$). As a consequence, fragmentation of $[\mathbf{L} \cdot \mathbf{C}]^+$ may take place to an extent which again depends upon the resonant ν excitation. On these grounds, the discrimination of diastereomeric complexes is based on the resonant absorption ν value and the corresponding fragmentation pattern.

3. Experimental

The experimental setup for the generation of $[\mathbf{L} \cdot \mathbf{C}]^\circ$ and their spectral analysis was described previously [8]. Supersonic beam production of $[\mathbf{L} \cdot \mathbf{C}]^\circ$ was

Table 1
Resonant frequencies ν of complexes [**L**·**C**] and their shifts Δ relative to the band origin ν^0 of the bare chromophore **C**

Chromophore, **C**	Ligand, **L**	ν (cm^{-1})	Δ (cm^{-1})
R-(+)-1-phenyl-1-propanol, $\mathbf{P}_R$	None	$\nu^0 = 37\,577 \pm 1$	
	Methane, **1**	$37\,541 \pm 1$	-36 ± 2
	n-Butane, **2**	$37\,557 \pm 1$	-20 ± 2
	Water, **3**	$37\,665 \pm 1$	$+88 \pm 2$
	Methanol, **4**	$37\,575 \pm 1$	-2 ± 2
	Diethyl ether, **5**	$37\,533 \pm 1$	-44 ± 2
	R-(−)-2-Butanol, $\mathbf{6}_R$	$37\,498 \pm 1$	-79 ± 2
	S-(+)-2-Butanol, $\mathbf{6}_S$	$37\,485 \pm 1$	-92 ± 2
	R-(−)-2-Pentanol $\mathbf{7}_R$	$37\,513 \pm 1$	-64 ± 2
	S-(+)-2-Pentanol, $\mathbf{7}_S$	$37\,602 \pm 1$	$+25 \pm 2$
	R-(−)-2-Butylamine, $\mathbf{8}_R$	$37\,468 \pm 1$	-109 ± 2
	S-(+)-2-Butylamine, $\mathbf{8}_S$	$37\,450 \pm 1$	-127 ± 2
R-(+)-1-phenyl-ethanol, $\mathbf{E}_R$	None	$\nu^0 = 37\,618 \pm 1$	
	Water, **3**	$37\,672 \pm 1$	$+54 \pm 2$
	R-(−)-2-Butanol, $\mathbf{6}_R$	$37\,499 \pm 1$	-119 ± 2
	S-(+)-2-Butanol, $\mathbf{6}_S$	$37\,487 \pm 1$	-131 ± 2
	R-(−)-2-Butylamine, $\mathbf{8}_R$	$37\,474 \pm 1$	-144 ± 2
	S-(+)-2-Butylamine, $\mathbf{8}_S$	$37\,457 \pm 1$	-161 ± 2

obtained by adiabatic expansion of a carrier gas (Ar), seeded with the ligand **L** (**1**–**8**) and the chromophore **C** [$\mathbf{E}_R$ or $\mathbf{P}_R$); Aldrich Chemical Co.], through a pulsed 400 μm nozzle kept at ∼ 85 °C. The molecular beam was allowed to pass through a 1 mm skimmer into a second chamber equipped with a TOF spectrometer. The laser system consisted of a Nd: YAG doubled in frequency (λ=532 nm) which pumps two dye lasers. The dye frequencies were doubled and, when necessary, mixed with residual 1064 nm radiation. The ions formed by R2PI ionization in the TOF source are mass discriminated and detected by a Channeltron after a 50 cm flight path. The R2PI/TOF ion fragmentation patterns of all of the [**L** · **C**] adducts investigated are reproducible within 5% and are insensitive to a three-fold increase of the stagnation pressure.

4. Results and discussion

Table 1 reports the resonant ν frequencies for the [**L** · **C**]°→[**L** · **C**]* transition and their shifts Δ relative to the band origin of the bare chromophore **C**. As pointed out in previous papers [9–14], a negative Δ value (redshift) reflects an increase of the binding energy of [**L** · **C**]* relative to [**L** · **C**]°, whereas a positive value (blueshift) indicates a decrease. The redshifts observed for the complexes with **L**=hydrocarbons **1** and **2** are the result of dispersive (polarization, charge exchange, etc.) interactions stabilizing the adduct more in the excited than in the ground state. The blueshifts measured for the complexes with water **3** reflect instead the operation of the O–H$^{\cdot\cdot\cdot}\pi$ electrostatic interaction between the ligand and the chromophore [13,14]. Cooperative dispersive and electrostatic interactions are responsible of the redshifts observed for the remaining complexes (except [$\mathbf{7}_S$ · $\mathbf{P}_R$], vide infra). In them, the chromophore **C** acts as a hydrogen-bond donor to the ligand **L**, whose alkyl group points toward the π system of the chromophore [9–13].

Comparison of the Δ values of diastereomeric complexes with 2-butanols **6**, 2-pentanols **7**, and 2-butylamines **8** indicates that relative extent of electrostatic and dispersive forces depends upon the nature, the bulkiness, and the configuration of both the chromophore **C** and the ligand **L**. Analysis of Table 1 reveals that, in general, the heterochiral complexes

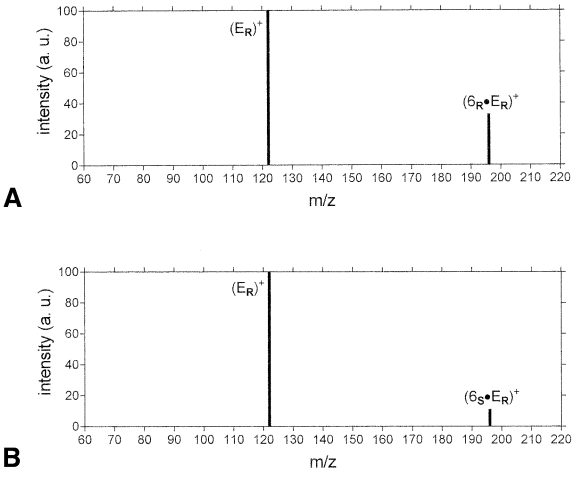

Fig. 1. Schematized R2PI-TOF spectra of (a) [$\mathbf{6}_R \cdot \mathbf{E}_R$], taken at λ=266.669 nm and (b) [$\mathbf{6}_S \cdot \mathbf{E}_R$], taken at λ=266.759 nm, at a total stagnation pressure of 2×10^5 Pa.

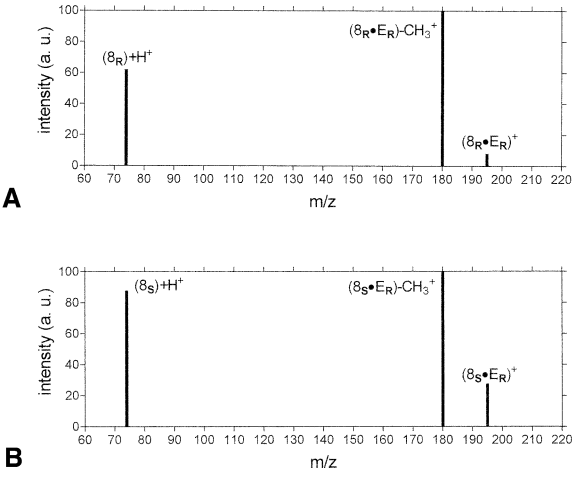

Fig. 2. Schematized R2PI-TOF spectra of (a) [$\mathbf{8}_R \cdot \mathbf{E}_R$], taken at λ=266.851 nm and (b) [$\mathbf{8}_S \cdot \mathbf{E}_R$], taken at λ=266.972 nm, at a total stagnation pressure of 2×10^5 Pa.

display a larger redshift (Δ_{hetero}) than their homochiral homologs (Δ_{homo}). Indeed, the shift difference $\Delta\Delta=(\Delta_{homo}-\Delta_{hetero})$ amounts to +12 (**C**=$\mathbf{E}_R$; **L**=**6**); +13 (**C**=$\mathbf{P}_R$; **L**=**6**); +17 (**C**=$\mathbf{E}_R$; **L**=**8**), and +18 cm^{-1} (**C**=$\mathbf{P}_R$; **L**=**8**). These $\Delta\Delta$ values indicate that the size of the **C** sidechain and the configuration of the **L** moiety determine the intensity of the attractive interactions and therefore the energy gap between [**L** · **C**]° and [**L** · **C**]*. In the extreme, configurational constraints may even subvert the nature and the intensity of the intracomplex forces, as demonstrated by the opposite shifts exhibited by the homochiral and the heterochiral complexes of 2-pentanols **7** with $\mathbf{P}_R$ (-64 ± 2 versus $+25\pm2$ cm^{-1}, respectively). This marked spectral diversity is indeed attributed to a considerable steric congestion in the heterochiral [$\mathbf{7}_S \cdot \mathbf{P}_R$], which may modify the mutual orientation of the two moieties or even invert their H-bond donor/acceptor role.

Configurational effects are also visible in the highly reproducible R2PI/TOF mass spectra of diastereomeric complexes. The mass spectra of diastereomeric [$\mathbf{6}_R \cdot \mathbf{E}_R$] and [$\mathbf{6}_S \cdot \mathbf{E}_R$] are schematized in Fig. 1(a) and (b), respectively. Fig. 2(a) and (b) reproduces those concerning the diastereomeric pair [$\mathbf{8}_R \cdot \mathbf{E}_R$] and [$\mathbf{8}_S \cdot \mathbf{E}_R$], respectively. The R2PI/TOF mass spectral patterns of the selected adducts, taken at the corresponding resonant frequencies ν (Table 1), are summarized in Table 2.

Abundant signals corresponding to the protonated ligand ($[\mathbf{L}+H]^+$) are observed in the mass spectra of the complexes with amines **8**, whereas the corresponding fragment is completely absent in the spectra with alcohols **6** and **7**. This indicates that, in the [**L** · **C**]$^+$ complex or, more likely, in its [(**L** · **C**)–C_xH_{2x+1}]$^+$ fragments (Table 2), the charged moiety is able to transfer a proton to the highly basic 2-butylamine **8** moiety [proton affinity (PA)=222.2 kcal mol^{-1}) and not to the less basic alcohols [PA (kcal mol^{-1})=195.0 (**6**); 195.6 (**7**)] [15].

The homochiral adducts containing 2-butylamines **8** undergo more extensive fragmention than their heterochiral homologs (95% versus 87% for [$\mathbf{8} \cdot \mathbf{E}_R$]; 91% versus 84% for [$\mathbf{8} \cdot \mathbf{P}_R$]). This is probably the result of the larger excess energy imparted to the homochiral adducts by the two-photon ionization (Table 1). The reverse situation is met with the adducts with 2-butanols **6**. Here, the homochiral adducts undergo less extensive fragmentation than the heterochiral ones (75% versus 90% for [$\mathbf{6} \cdot \mathbf{E}_R$]; 81% versus 93% for [$\mathbf{6} \cdot \mathbf{P}_R$]), despite ionisation imparts more excess energy to the homochiral complexes than the heterochiral ones (Table 1). This opposite fragmentation extent can be rationalized only by assuming

Table 2
Relative ion abundance from the R2PI-TOF mass spectra of the supersonically expanded complexes [**L**·**C**]

Chromophore, **C**	Ligand, **L**	$[\mathbf{L}\cdot\mathbf{C}]^+$	$[(\mathbf{L}\cdot\mathbf{C})–C_xH_{2x+1}]^+$	$[\mathbf{C}]^+$	$[\mathbf{C}–C_xH_{2x+1}]$	$[\mathbf{L}+\mathbf{H}]^+$
R-(+)-1-phenyl-1-propanol, $\mathbf{P}_R$						
	Methane, **1**	3	...	100	6[a]	...
	n-Butane, **2**	77	...	100	11[a]	...
	Water, **3**	58	56[a]	100	17[a]	...
	Methanol, **4**	8	86[a]	100	4[a]	...
	Diethyl ether, **5**	57	96[a]	100	40[a]	...
	R-(−)-2-Butanol, $\mathbf{6}_R$	41	100[a]	28	42[a]	...
	S-(+)-2-Butanol, $\mathbf{6}_S$	11	100[a]	15	35[a]	...
	R-(−)-2-Pentanol, $\mathbf{7}_R$	70	100[a]	13	96[a]	...
	S-(+)-2-Pentanol, $\mathbf{7}_S$	17	45[a]	58	100[a]	...
	R-(−)-2-Butylamine, $\mathbf{8}_R$	18	100[a]	27	...	53
	S-(+)-2-Butylamine, $\mathbf{8}_S$	41	100[a]	59	3[a]	45
R-(+)-1-phenyl-ethanol, $\mathbf{E}_R$						
	Water, **3**	73	...	100	...	...
	R-(−)-2-Butanol, $\mathbf{6}_R$	33	...	100	...	...
	S-(+)-2-Butanol, $\mathbf{6}_S$	11	...	100	...	...
	R-(−)-2-Butylamine, $\mathbf{8}_R$	8	100[b]	...	...	62
	S-(+)-2-Butylamine, $\mathbf{8}_S$	28	100[b]	...	...	88

[a] $X = 2$.
[b] $X = 1$.

a higher probability of populating dissociative states in $[\mathbf{6}_R \cdot \mathbf{E}_R]^+$ (or $[\mathbf{6}_R \cdot \mathbf{P}_R]^+$) than in their heterochiral homologs. The largest difference in the fragmentation pattern is observed for diasteromeric $[\mathbf{7}_R \cdot \mathbf{P}_R]^+$ (75%) and $[\mathbf{7}_S \cdot \mathbf{P}_R]^+$ adducts (91%). Besides the higher excess energy imparted to the heterochiral $[\mathbf{7}_S \cdot \mathbf{P}_R]^+$ complex (Table 1), this marked diversity likely reflects the strong repulsive interactions operating in the highly congested heterochiral $[\mathbf{7}_S \cdot \mathbf{P}_R]^+$ adduct which instead are strongly reduced in the less congested homochiral $[\mathbf{7}_R \cdot \mathbf{P}_R]^+$ form.

5. Conclusions

Supersonic beams allow the synthesis of otherwise fragile molecular complexes in quantities suitable for their spectroscopic characterization.

R2PI/TOF spectroscopy of supersonically expanded adducts provides information on their structure and the stability in their ground, excited, and ionic states and allow the determination of the intramolecular forces responsible of their behavior.

R2PI/TOF spectroscopy proved the technique of choice for enantiodifferentiating monofunctional chiral species **L** by aggregation with simple chromophores **C** in the isolated state.

Enantiodifferentiation is based on both the different resonant ν frequencies for the excitation of the diastereomeric [**L** · **C**] complexes and their different R2PI/TOF fragmentation patterns.

The spectroscopic detection of relatively intense $[\mathbf{L} \cdot \mathbf{C}]^+$ signals in the R2PI/TOF mass spectra of the [**L** · **C**] adducts with **L**=hydrocarbon (Table 2) suggests the possible extension of the technique even to the discrimination of chiral compound with no functionalities.

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