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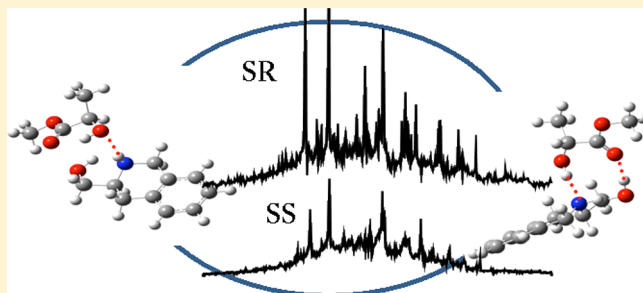
Structural Rearrangement in the Formation of Jet-Cooled Complexes of Chiral (*S*)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol with Methyl Lactate: Chirality Effect in Conformer Selection

Ahmed Mahjoub,* Katia Le Barbu-Debus, and Anne Zehnacker

Institut des Sciences Moléculaires d'Orsay (ISMO), CNRS, UMR8214, Orsay F-91405, France, and Université Paris-Sud, Orsay F-91405, France

S Supporting Information

ABSTRACT: The jet-cooled complexes between the two enantiomers of methyl lactate (ML) and (*S*)-1,2,3,4-tetrahydro-3-isoquinolinemethanol (THIQM) are studied by double resonance spectroscopy combined with ab initio calculations. Both diastereomer complexes exist in different isomers, involving either direct addition of THIQM on ML with no structural rearrangement of the subunits or formation of very stable structures involving multiple intermolecular hydrogen bonds and extensive deformation of the subunits. Competition between these two processes and its dependence upon chirality are discussed. It is shown that the most stable form of the chromophore (THIQM_I with an OH...N hydrogen bond) prefers to directly stick to ML to form the addition complex whereas the second conformer (THIQM_{II} with NH...O hydrogen bond) rearranges to form a strongly bound structure. The two structures are formed for the homochiral as well the heterochiral complex, however with different relative abundance. This shows an enantioselective binding preference of ML for one of the conformers of the chromophore.



INTRODUCTION

The selectivity with which a chiral molecule interacts with the two enantiomers of a chiral substrate, namely, chiral recognition, is one of the most important aspects of molecular recognition and lies at the basis of many life-related phenomena like drug–receptor interaction.¹ Understanding the nature of the forces responsible for chiral recognition is therefore important. However, attempts at getting information at the molecular level in solution are hampered by perturbations brought by the solvent. Moreover, the conformational wealth of biological molecules results in a plethora of conformers at room temperature, which might show different recognition phenomena. Elegant alternatives are therefore proposed in the gas phase to circumvent the difficulties met in solution, in particular those resting on mass spectrometry.^{2–8}

Isolation of ionic complexes of chiral molecules in an ion trap bring important information on thermodynamic as well as kinetic control of chiral discrimination.^{5,9} During the past decade, the relative stability of the diastereomer complexes at room temperature has been the subject of numerous studies, in particular by the kinetic method.^{10,11} More recently, these mass-spectrometry methods have been combined to laser spectroscopy or ion mobility to get structural information on chiral molecules and complexes.^{12–16} Besides this extensive work on ionic species, attention has been also paid to neutral complexes of chiral molecules.¹⁷ Supersonic expansions combined with laser spectroscopy provide a unique tool for studying neutral complexes bound by weak interactions such as

hydrogen bonds, without the competitive interactions and the perturbation brought by the solvent.^{2–4,18–29} Binding energy measurements^{26,30} as well as structural characterization by electronic as well as vibrational or rotational spectroscopy have been achieved. The spectroscopic observations have led to the conclusion that chiral recognition rests on a subtle balance between forces, among them conventional OH...O or OH...N hydrogen bonds and/or dispersion, but also forces of much lesser strength like OH... π , CH...O, or CH... π interactions.^{15,22} It has been suggested in particular that chiral recognition is due to much weaker interactions than those responsible for the stability of the complex. In this respect, weak hydrogen bonds like CH...O or CH... π are especially important. The CH...O or CH... π interactions are highly sensitive to stereochemical factors, hence their enantioselectivity.^{18,31} On the other hand, a certain extent of molecular flexibility is necessary for these contacts to be achieved. Indeed, no chiral recognition has been observed in very rigid systems like complexes of camphor.^{32,33} In multifunctional molecules, much better chiral recognition has been achieved in floppy dimers with only one intermolecular hydrogen bond than in rigid dimers with two strong intermolecular hydrogen bonds. Indeed, an additional stereoselective CH...O or CH... π interaction takes place in the former, which is responsible for chiral recognition.^{15,18,31}

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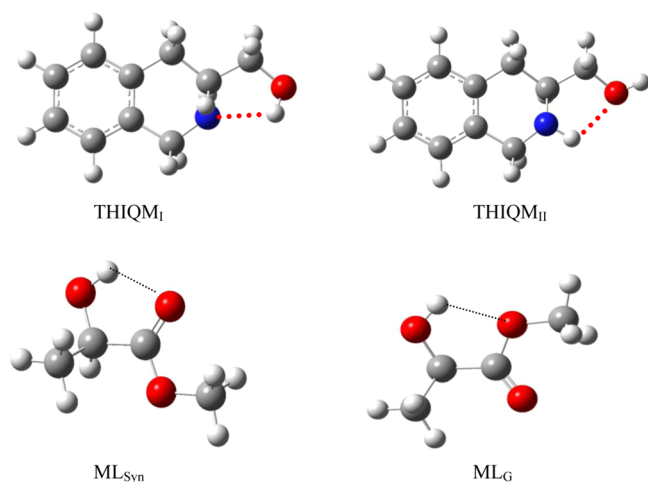
Revised: March 12, 2013

In this article, we pursue our jet-cooled studies of chiral recognition in diastereomer complexes of multifunctional molecules. The two enantiomers of methyl lactate (ML) are complexed by a chiral chromophore, (*S*)-1,2,3,4-tetrahydro-3-isoquinolinemethanol (THIQM) and studied by resonance-enhanced one-color two-photon ionization (1c-REMPI) and IR–UV double resonance vibrational spectroscopy. DFT-based calculations are conducted to assist in the interpretation of the experimental spectra. Both ML and THIQM are well characterized in supersonic expansion conditions.^{34–38} Moreover, the chirality-dependent aggregation properties of ML and its derivatives are well documented gas phase.^{20,21,39,40}

EXPERIMENTAL AND THEORETICAL METHODS

Experimental Methods. The heated THIQM chromophore was seeded in helium saturated with ML at a pressure of ~ 2 atm and expanded into vacuum through a 250 μm pulsed nozzle (General Valve). The vapor pressure of ML was controlled by cooling the sample at 10 $^{\circ}\text{C}$. (*S*)-1,2,3,4-tetrahydro-3-isoquinolinemethanol (THIQM) and (*S*)- or (*R*)-methyl lactate (Scheme 1) have been purchased by Aldrich Chemicals and used without further purification.

Scheme 1. Different Conformers of the Molecules under Study^a



^aThe intramolecular hydrogen bonds involved in each conformer are denoted by a dotted line.

based on LiNbO₃ and BBO crystals, respectively. The temporal structure of each laser pulse consisted of an about 500 ns long train, which contained about 50 micropulses separated by 10 ns. The micropulse duration was 12 ps and the spectral resolution was 3 cm^{-1} .

Depending on the temporal scheme between the pump and UV probe, one could record either the vibrational spectrum of the neutral ground state species (pump before the probe laser) or that of the ion (pump after the probe laser). Owing to the temporal structure of the lasers used in this work, it was not possible to delay electronically the UV pulse relative to the IR. We have therefore aligned the IR upstream the UV laser, in the expansion, for exciting the ground state neutral species only.

Theoretical Methods. A global exploration of the potential energy surface of the complexes has been performed by means of a semiempirical approach developed by Claverie and further developed by Brenner et al.^{48,49} It has been shown previously that gas-phase complexes can contain subunits that are not the most stable form of the bare entity.^{27,37,47,50} Different sets of exploration of the potential energy surface have therefore been launched with the three most stable forms of methyl lactate and the two most stable conformers of THIQM as input geometries. At this stage, the intramolecular coordinates were kept frozen. Then after each of them, the 20 most stable conformers have been optimized within the frame of the density functional theory at the b3lyp/6-31G(d,p) level of theory using the Gaussian 03, revision C.02 package.⁵¹ The basis-set superposition error (BSSE) has been calculated by means of the counterpoise method.⁵² The dissociation energy has then been calculated including the zero point energy (ZPE) and half the BSSE⁵³ and is given with respect to the closest fragment. The harmonic frequencies have been calculated at the same level of theory. The vibrational spectra have been simulated by convoluting the scaled calculated harmonic frequencies by a Lorentzian line shape (fwhm 3 cm^{-1}). The scaling factor has been set to 0.96 to reproduce the experimental spectra of the monomers in the 3 μm region. The frequencies given in the text as well as in the table and figures include this scaling factor of 0.96.

It has been shown that molecular rearrangement of the subunits upon complex formation results to barrier to complexation. We have proposed to estimate this barrier with the deformation energy, which is the difference in energy between the most stable geometry of a bare molecule and that which is adopted in the complex.^{31,54} Deformation energies have been calculated for all the obtained structures.

EXPERIMENTAL AND THEORETICAL RESULTS

Mass Spectra. THIQM and its complexes undergo extensive fragmentation in the ionic state, which correspond to the loss of a neutral CH₃OH fragment.³⁸ In the case of the THIQM/ML complexes (m/z 267), the fragmentation efficiency amounts to 90%. Their REMPI S_0 – S_1 spectra must therefore be recorded at the mass of the m/z 235 fragment.

Electronic Spectroscopy. The REMPI S_0 – S_1 spectra of a mixture of (*S*)-THIQM with the two enantiomers of ML are shown in Figure 1a,b. At first sight, the two spectra are very similar to each other. They both display two strong bands in the low-energy region, located at -29 and -6 cm^{-1} for the heterochiral complex, and -24 and -5 cm^{-1} for the homochiral complex. A third intense band appears at 47 cm^{-1} in both spectra. Last, bands of medium intensity appear in the SR spectrum at 29 and 79 cm^{-1} , which have their counterpart at

Mass-resolved S_0 – S_1 spectra were obtained by means of one-color resonance-enhanced two-photon ionization (1c-REMPI) using a nanosecond frequency-doubled dye laser (Sirah) equipped with C540A and pumped by the second harmonic of a YAG laser (Spectra Physics). The supersonic beam was intersected by the laser in the ion-source region of a linear one meter time-of-flight mass spectrometer (RM Jordan). The ions were detected by a microchannel plate detector (RM Jordan, 2.5 cm). The ion signal was averaged by an oscilloscope (Tektronix) and processed through a PC. The laser fluence was kept as low as possible to minimize fragmentation.

Mass-resolved vibrational spectra were recorded by means of IR–UV ion-dip double resonance spectroscopy.^{41–43} The experimental setup has been described in details and only a brief overview is given here.^{28,44–47} The IR and UV light sources were provided by two OPOs synchronously pumped by the fundamental and the third harmonic a 20 Hz YAG laser and

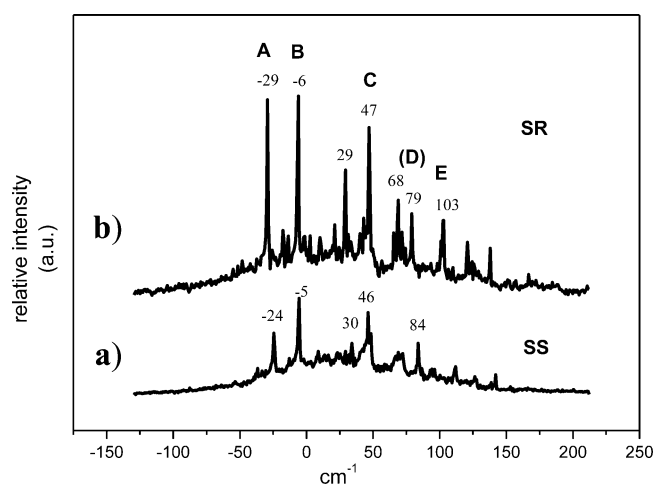


Figure 1. REMPI spectrum of the THIQM/ML complexes (m/z 267), recorded at the mass of the fragment (m/z 235): (a) SS complex; (b) SR complex. The zero of the scale is set at the transition origin of the most stable conformer THIQM_I of the chromophore, located at 36 894 cm^{-1} .

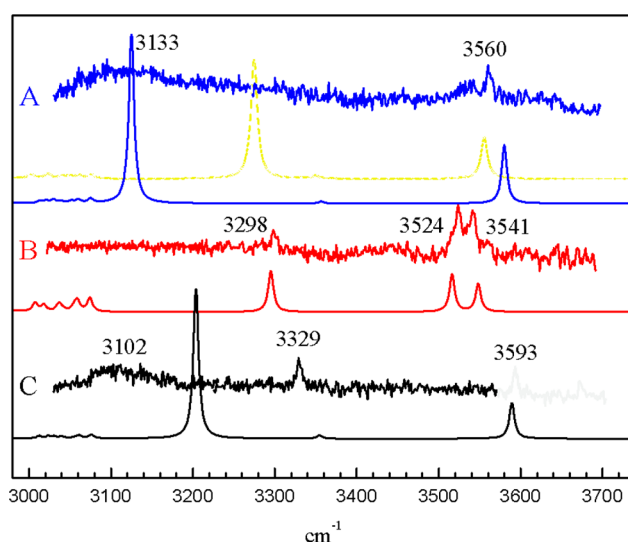


Figure 2. Vibrational spectra of the SR complex, with the probe set at (a) -29 cm^{-1} , (b) -6 cm^{-1} , and (c) $+47 \text{ cm}^{-1}$ together with the simulated spectra.

175 $+30$ and $+84 \text{ cm}^{-1}$ for SS. The S_0 – S_1 spectra of the homo- and
176 heterochiral complexes differ in intensity. In identical
177 experimental conditions, the spectrum of the heterochiral
178 complex is more intense (Figure 1a). Bands of weaker intensity
179 appear in the high-energy region (above 100 cm^{-1} to the blue)
180 in the spectrum of the SR complex, which are hardly discernible
181 in that of the SS complex. Moreover, several congested bands
182 are observed at $+68 \text{ cm}^{-1}$ in the spectrum of the SR complex,
183 which has a weak counterpart for the SS complex. Because of
184 their dependence as a function of the ML partial pressure, they
185 are assigned to clusters of larger size.

186 Last, it is worth noting that the two red-shifted bands, which
187 are of similar intensity for SR, show very different relative
188 intensity for SS.

189 **Vibrational Spectroscopy.** As the spectra of the SR and SS
190 complexes are very similar to each other, we will focus on the
191 SR complex and simply mention the differences observed in the
192 SS complex. The vibrational spectra of the SR complex, with the
193 probe set on the most red-shifted band located at -29 cm^{-1}
194 (band A) is shown in Figure 2a. It shows two intense bands, a
195 narrow band located at 3560 cm^{-1} and a broad band centered at
196 3133 cm^{-1} . The latter is typical of a strong $\text{OH}\cdots\text{N}$ hydrogen
197 bond whereas the former corresponds to an interaction of
198 lesser strength. The spectrum of the SS complex with the probe
199 set at -24 cm^{-1} is the same within the experimental resolution,
200 which confirms that the two bands correspond to identical
201 geometries. The spectrum obtained with the probe located at
202 the $+29 \text{ cm}^{-1}$ band of the SR complex (not shown) is identical
203 to that of band A which shows that this band belongs to the
204 same species.

205 The vibrational spectra of the SR complex, obtained with the
206 probe set on the red-shifted band located at -6 cm^{-1} (band B)
207 is shown in Figure 2b. It displays a doublet at 3524 and 3541
208 cm^{-1} , characteristic of $\nu(\text{OH})$ stretches located on OH groups
209 involved in a weak interaction, as well as a narrow band typical
210 of a $\nu(\text{NH})$ stretch at 3298 cm^{-1} . The spectrum of the SS
211 complex probed at -5 cm^{-1} is similar, with a minor shift of the
212 frequencies (3300 , 3514 , and 3535 cm^{-1}). The similarity of the
213 homochiral complex spectroscopy with that of the heterochiral
214 complex reflects the resemblance of their structure. The

spectrum of the band at $+103 \text{ cm}^{-1}$ is identical to that
215 recorded with the probe at band B, which indicate that they are
216 due to the same species.

217 When the probe is set on the blue-shifted band of the SR
218 complex, located at $+47 \text{ cm}^{-1}$ (band C), the vibrational
219 spectrum (Figure 2c) strongly differs from the previously
220 mentioned spectra. It shows two narrow bands located at 3593
221 and 3329 cm^{-1} , as well as a diffuse feature centered at 3102
222 cm^{-1} . The same spectrum is obtained for the SS complex with
223 bands at 3330 and 3596 cm^{-1} .

224 The bands located at $+79$ (SR complex) or $+84 \text{ cm}^{-1}$ (SS
225 complex) are shown to belong to the same isomer as band C.

226 **Calculated Structures.** We will first recall the structural
227 characteristics of the two subunits (Scheme 1). Only one
228 conformer of ML is observed in supersonic expansion
229 conditions, namely a syn structure showing an $\text{OH}\cdots\text{O}=\text{C}$
230 intramolecular hydrogen bond.^{35,39,55} Its $\nu(\text{OH})$ stretch
231 frequency is measured at 3571 cm^{-1} . It will be noted ML_{syn}
232 in what follows. Gauche conformers displaying an $\text{OH}\cdots\text{OCH}_3$
233 intramolecular hydrogen bond are observed in matrix isolation
234 conditions.⁵⁶ However, they are located $\sim 2 \text{ kcal/mol}$ higher in
235 energy. Their population is therefore below 5% of that of the
236 main conformer at room temperature according to a Boltzmann
237 distribution. They will be denoted ML_{G} and $\text{ML}_{\text{G}'}$ in what
238 follows.

239 THIQM exists in two distinct conformers that are cooled in
240 the supersonic expansion. Conformer THIQM_I displays an
241 intramolecular $\text{OH}\cdots\text{N}$ bond with an experimental $\nu(\text{OH})$
242 stretch frequency at 3566 cm^{-1} . This conformer shows a free
243 $\nu(\text{NH})$ stretch whose oscillator strength is too low to be
244 observed. THIQM_{II} shows the opposite $\text{NH}\cdots\text{O}$ configuration;
245 hence two bands in its IR spectrum that correspond to a free
246 $\nu(\text{OH})$ stretch (3686 cm^{-1}) and a $\nu(\text{NH})$ stretch at 3366 cm^{-1} ,
247 which gains intensity through the formation of the intra-
248 molecular hydrogen bond.^{36,38}

249 A wealth of stable calculated structures has been obtained for
250 the complexes. They can be described in terms of four different
251 families, which are classified according to the nature of the
252 hydrogen bonds ($\text{OH}\cdots\text{O}$, $\text{OH}\cdots\text{N}$, $\text{NH}\cdots\text{O}$) and their intra- or
253 intermolecular character. For each family, diversity is
254

introduced by the variety of the hydrogen bond donor (THIQM or ML) and the conformers of the subunit contained in the complex (THIQM_I or THIQM_{II}, as well as ML_{syn}, ML_G or ML_C). The different families are shown schematically in Figure 3. For the sake of simplicity, the OH or NH group of the

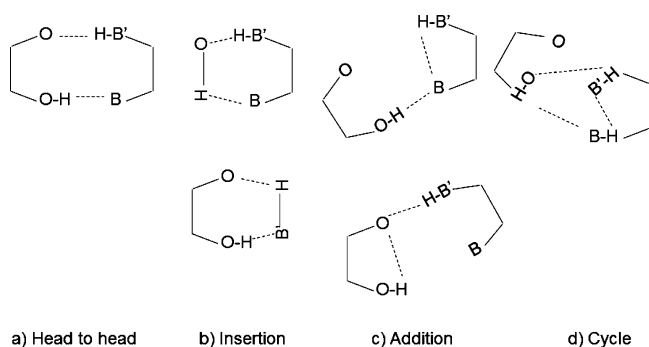


Figure 3. Schematic description of the most stable structures obtained for the THIQM/ML complexes. ML is systematically drawn on the left-hand side. The structures of THIQM_I and THIQM_{II} are abbreviated by replacing the O and N atoms by B or B', where B and B' stand for the hydrogen bond acceptor or donor, respectively. In THIQM_I, B stands therefore for N and B' for O, whereas it is the opposite in THIQM_{II}. (a) *Head-to-head* structure. (b) *Insertion* structure, with either OH_{ML} group inserted in the intramolecular hydrogen bond of THIQM (top) or the THIQM hydrogen bond donor (B'H) inserted in the intramolecular bond of ML (bottom). (c) *Addition* structure with ML added to THIQM (top) or THIQM added on ML (bottom). (d) *Cycle* structure.

subunit X will be noted OH_X or NH_X. For example, OH_{ML} corresponds to the hydroxyl substituent of methyl-lactate.

- **Head-to-head** structures (Figure 3a): In this case, the two intramolecular hydrogen bonds open up to form a double hydrogen bond bridge, as often observed in dimers of carboxylic acids or bifunctional molecules.^{47,57–61} This strongly bound structure involves partial intramolecular reorganization for THIQM as well as ML, resulting in high deformation energies. When not obvious from the context, the *Head-to-head* nomenclature will be followed by the name of the subunit it contains. For example, *Head-to-head* (THIQM_I-ML_{syn}) corresponds to a *Head-to-head* complex containing THIQM_I and ML_{syn}.
- **Insertion** structures (Figure 3b): The hydrogen bond donor of one of the subunits is inserted in the intramolecular hydrogen bond of the other one. A large variety of insertion structures can be formed. For example OH_{ML} can be inserted in the intramolecular bond of either THIQM_I or that of THIQM_{II}. This structure will be called Insertion of OH_{ML}. Conversely, the OH_{THIQM} or NH_{THIQM} can be inserted in the intramolecular bond of one of the conformers of ML. These structures will be called *Insertion of OH_{THIQM}* and *Insertion of NH_{THIQM}*, respectively. Insertion structures are often observed when the molecule to be inserted is small, for example, in the case of hydrates of bifunctional molecules.^{36,37,62,63} However, some amino alcohol hydrates show no insertion structure.⁶⁴
- **Addition** structures (Figure 3c): In this type of complex, the intramolecular hydrogen bond of one of the partners opens up so that its hydrogen bond donor can bind to an

acceptor site of the other moiety, whose structure is not modified. Addition structures show less deformation energy than the ones described above as the intramolecular bond of one of the subunits is kept intact. They will be called *Addition of OH_{ML} to THIQM* when it is the intramolecular hydrogen bond of ML that opens up, and *Addition of OH_{THIQM} to ML* or *Addition of NH_{THIQM} to ML* when it is the internal hydrogen bond of THIQM that opens up to allow its OH or NH group to bind to ML.

- **Cycle** structures: These structures are derived from the *Addition of OH_{ML} to OH_{THIQM}* or *Addition of OH_{ML} to OH_{THIQM}*. Like in the *Addition* structures, the intramolecular hydrogen bond of THIQM still exists and an intermolecular H bond is formed from OH_{ML} to the available acceptor site of THIQM (O for THIQM_I and N for THIQM_{II}). However, an additional hydrogen bond is formed from the available donor site of THIQM (NH for THIQM_I and OH for THIQM_{II}) toward OH_{ML}.

All the complexes mentioned above have been calculated; only those which are energetically favorable will be described in detail.

Table 1 displays the binding energy of the most stable complex of each previously described family, built from one of the three different conformers of R-ML and one of the two conformers of S-THIQM, together with the deformation energy of each entity. The equivalent table for the SS complex is given in the Supporting Information. We will discuss hereafter only the case of the SR complex as the results for the SS complex parallel those for SR.

DISCUSSION

Assignment of the Observed Complexes to Calculated Structures. Assignment of the calculated structures to the observed ones rests on three criteria: spectroscopy (i.e., good agreement between experimental and theoretical spectra), thermodynamics (i.e., calculated binding energy), and kinetics (i.e., deformation energy). Indeed, results on both neutral and ionic complexes have shown that the most thermodynamically favored complex was not always formed under supersonic expansion conditions and that barriers on the complexation path, i.e., too large a deformation energy, prevents the complex to be formed.

Complexes Built from THIQM_I. We will first focus on the complexes built from the most stable forms of the two subunits, namely, THIQM_I and ML_{syn}. As described in our previous work, the complexes displaying too large a deformation energy (about 2 kcal/mol and more) are not expected to be observed in our experimental conditions.^{31,54} On the basis of this hypothesis, the *Head to head* complex as well as the *Insertion of ML* complex or the *Addition of OH_{ML} to OH_{THIQM}* are not expected to be observed. The *Insertion of OH_{THIQM}* complex shows deformation energy of the ML part of 2.15 kcal/mol, which would be acceptable. However, two strong hydrogen bonds should then be expected, which do not manifest themselves in the experimental vibrational spectrum. The last complex is the *Addition of NH_{THIQM} to OH_{ML}* with a binding energy of 4.10 kcal/mol. In this structure, NH_{THIQM} is involved in an intermolecular hydrogen bond, acting as a donor towards OH_{ML}. This involves a large increase of the oscillator strength localized on the NH mode. Its spectrum, displayed in Figure 2b, matches that of band B very satisfyingly. Combining

Table 1. Most Stable Calculated Structure for Each Family of the SR Complex^a

	$D_0 + 1/2\text{BSSE}$	$E_{\text{def}} \text{THIQM}$	$E_{\text{def}} \text{ML}$	scaled calculated frequencies (cm^{-1})	experimental frequencies (cm^{-1})
(S) $\text{THIQM}_{\text{I}}(\text{R}) \text{ML}_{\text{syn}}$					
Insertion of OH_{ML}	-7.30	2.79	2.77		
Head to head	-5.97	2.92	2.76		
Insertion of OH_{THIQM}	-5.46	0.63	2.15		
Addition of OH_{ML} to OH_{THIQM}	-4.96	0.35	2.68		
Addition of NH_{THIQM} to OH_{ML}	-4.10	0.22	0.59	3295	3298
				3516	3524
				3548	3541
(S) $\text{THIQM}_{\text{I}}(\text{R}) \text{ML}_{\text{G}}$					
Insertion of OH_{ML}	-7.02	2.81	1.75		
Insertion of OH_{THIQM}	-5.35	0.30	0.90		
Head to head	-5.30	1.26	1.38		
(S) $\text{THIQM}_{\text{I}}(\text{R}) \text{ML}_{\text{G}'}$					
Insertion of OH_{ML}	-7.07	2.49	1.25		
Insertion of OH_{THIQM}	-5.76	0.46	1.00		
Addition of OH_{ML} to OH_{THIQM}	-5.21	0.27	1.33		
Head to head	-4.90	1.12	0.84		
(S) $\text{THIQM}_{\text{II}}(\text{R}) \text{ML}_{\text{syn}}$					
Head to head	-9.44	1.19	3.60	3125	3133
				3357	3560
				3580	
Cycle	-7.85	1.29	2.96		
Insertion of OH_{THIQM}	-6.74	1.26	2.70		
Addition of OH_{ML} to NH_{THIQM}	-5.95	0.19	2.13		
Addition of OH_{THIQM} to OH_{ML}	-5.93	1.13	0.23		
(S) $\text{THIQM}_{\text{II}}(\text{R}) \text{ML}_{\text{G}}$					
Head to head	-8.64	1.22	2.23	3204	3102
				3355	3329
				3589	3593
Addition of OH_{ML} to NH_{THIQM}	-6.70	0.25	1.33		
Addition of OH_{THIQM} to OH_{ML}	-6.19	0.32	0.43		
(S) $\text{THIQM}_{\text{II}}(\text{R}) \text{ML}_{\text{G}'}$					
Cycle	-7.42	1.48	1.49	3275	3133
				3350	3560
				3555	
Addition of OH_{ML} to NH_{THIQM}	-6.44	0.26	1.11		

^aBinding energy including ZPE and BSSE corrections (D_0), as well as deformation energy of the chromophore ($E_{\text{def}} \text{THIQM}$) and the solvent ($E_{\text{def}} \text{ML}$). The energies are given in kcal/mol. Experimental and calculated frequencies of the experimentally observed complexes (cm^{-1}). The calculated frequencies have been scaled by 0.96 (see text). The complexes assigned to the observed species are in bold.

the three above-mentioned criteria allow us to assign the complex responsible for band B to *Addition of NH_{THIQM} to OH_{ML}* . *Complexes Built from THIQM_{II}* . THIQM_{II} is observed as a bare molecule under our experimental conditions. Moreover, complexes containing THIQM_{II} are globally more stable than those obtained from THIQM_{I} . We will therefore take them into account too. Among those made from THIQM_{II} and ML_{syn} , two addition complexes display reasonable deformation energy and large binding energy (around 5.9 kcal/mol). However, their vibrational spectrum does not match any of the experimentally observed ones. The *Head-to-head* complex has frequencies with perfect match with the experimental spectrum observed when probing band A. However, the deformation energy seems to be by far too high for this structure to be taken into account. We will therefore consider as an alternative the complexes built from THIQM_{II} and ML_{G} or $\text{ML}_{\text{G}'}$, even if they are not formed from the subunits present in the supersonic expansion as isolated species. The most stable complexes built from THIQM_{II} and ML_{G} or $\text{ML}_{\text{G}'}$, respectively have

deformation energies small enough to be taken into consideration. The most stable $\text{THIQM}_{\text{II}}\text{-ML}_{\text{G}}$ complex is a *Head to head* structure. Its calculated spectrum is displayed in Figure 2c. It shows a large red shift of the $\nu(\text{OH})$ stretch of ML that is bonded to the N atom of THIQM_{II} ; the $\nu(\text{OH})$ stretch frequency localized on THIQM_{II} shows moderate shift which perfectly fits that observed for band C at 3593 cm^{-1} . It seems therefore that the *Head to head* structure involving THIQM_{II} and ML_{G} obeys the three above-mentioned criteria and can be safely assigned to band C. The most stable complex built with $\text{ML}_{\text{G}'}$ is the *Cycle* structure. Here again, OH_{ML} acts as a hydrogen bond donor toward the nitrogen atom of THIQM whereas OH_{THIQM} acts as a donor toward OH_{ML} . This leads again to a very red-shifted band and a band characteristic of a slightly bonded OH group. The corresponding calculated spectrum displayed in Figure 2a can reproduce that experimentally observed for band A in an acceptable way. However, though the frequencies of the $\nu(\text{OH})$ and $\nu(\text{NH})$ stretch vibrations of medium oscillator strength are well reproduced by the calculations, the latter fail to reproduce

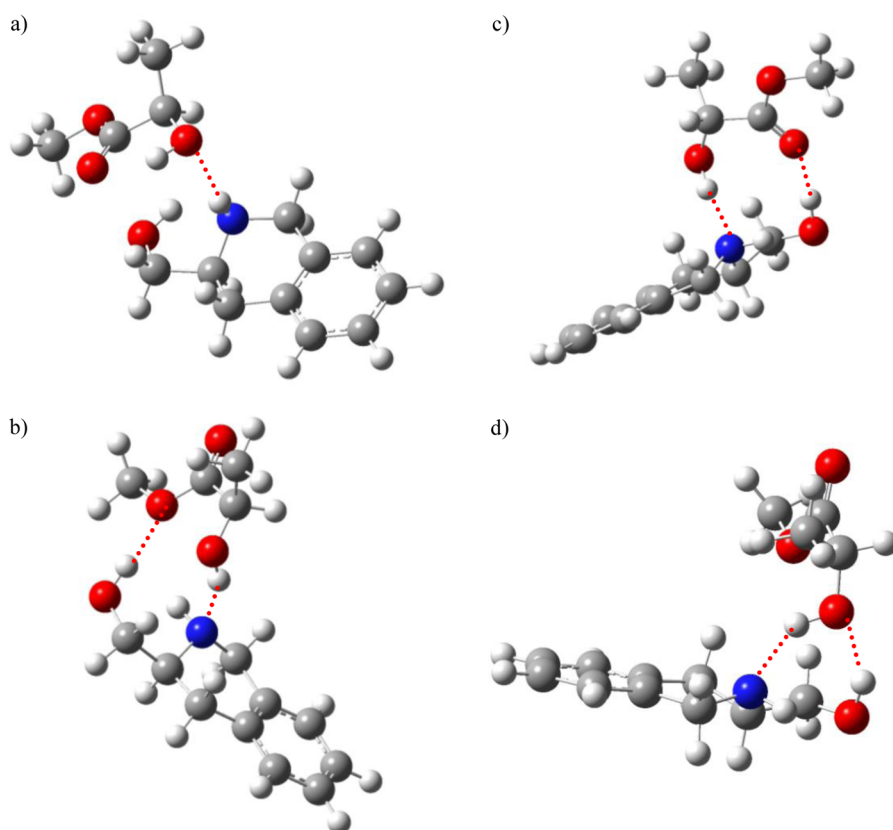


Figure 4. Most stable calculated structures of the SR complex: (a) Addition of NH_{THIQM} to OH_{ML} ($\text{THIQM}_{\text{I}} - \text{ML}_{\text{syn}}$); (b) Head to head ($\text{THIQM}_{\text{II}} - \text{ML}_{\text{G}}$); (c) Head to head ($\text{THIQM}_{\text{II}} - \text{ML}_{\text{syn}}$); (d) Cycle ($\text{THIQM}_{\text{II}} - \text{ML}_{\text{G}}$).

correctly the strong bonded OH involved in an $\text{OH} \cdots \text{N}$ interaction.

We are therefore facing a dilemma; either the calculated complex shows a good match between observed and calculated frequencies and is formed from conformers of the subunits observed in our experimental conditions, but its deformation energy is not satisfying. This is the case for the *Head to head* structure formed from THIQM_{II} and ML_{syn} . Or it shows no deformation but obeys the spectroscopic criterion in a much less satisfying way; this is the case for the *Cycle* structure formed from THIQM_{II} and ML_{G} . In the following discussion, we shall balance the pros and cons of the assignment of band A to one of these structures and see that isomerization in the early stage of the supersonic expansion can explain the observed results.

Mechanism of Formation of the Complexes. Only one of the three observed complexes, namely *Addition of NH_{THIQM} to OH_{ML}* formed between THIQM_{I} and ML_{syn} , is assigned to a structure involving the most stable form of the subunits, despite being not the most stable complex built from these most stable conformers. The two other observed complexes have to involve both subunits in less stable form but could correspond to the most stable complex formed from these conformers. The formation of the complexes seems therefore to result from a subtle compromise between direct sticking leading to complexes that are not necessary among the most stables, and reorganization of the subunits resulting in the most stable complex of their family. This behavior can be explained through a mechanism analogous to solvent-assisted conformational isomerization (SACI), as observed in meta substituted phenol derivatives^{65,66} or in the imidazole hydrate,⁶⁷ and involving

formation of transient complexes in the collision zone.⁶⁸ The mechanism we propose here combines the intramolecular (conformational isomerization of THIQM) and intermolecular versions (displacement of the solvent) of SACI. We postulate that the first step of the complex formation consists of direct sticking of the most stable forms of THIQM and ML , namely THIQM_{I} or THIQM_{II} and ML_{syn} , which have all been evidenced in the gas phase. This is what is expected from a purely statistical point of view. This leads to hot transient collisional complexes like an *Addition of NH_{THIQM} to OH_{ML}* complex formed between THIQM_{I} or THIQM_{II} and ML_{syn} . Like in SACI, the internal energy of the hot complex, the upper limit of which is its binding energy, can flow into the intramolecular and intermolecular modes of the complex and induce isomerization. Whereas $\text{THIQM}_{\text{I}} \leftrightarrow \text{THIQM}_{\text{II}}$ isomerization is prohibited because none of the complex displays binding energy larger than the corresponding isomerization barriers; it is possible to induce isomerization from THIQM or ML to their metastable counterpart in which the intramolecular hydrogen bond is disrupted through an addition–elimination mechanism in which the incoming ML molecule displaces the bonded one to lead to a complex with higher binding energy. It is therefore possible to induce $\text{ML}_{\text{syn}} \leftrightarrow \text{ML}_{\text{G}}$ transformation within the complex. For this mechanism to operate, the internal energy, i.e., the binding energy of the addition complex, has to be larger than the sum of the barriers to formation of the final complex. The dissociation energy of *Addition of NH_{THIQM} to OH_{ML}* is not large enough (4.1 kcal/mol) to overcome the sum of the deformation energies (5.6 kcal/mol) and make the interconversion to *Insertion of ML* possible or to induce the $\text{ML}_{\text{syn}} \leftrightarrow \text{ML}_{\text{G}}$ or $\text{ML}_{\text{syn}} \leftrightarrow \text{ML}_{\text{G}}$ conversion. *Addition of*

NH_{THIQM} to OH_{ML} is therefore simply cooled in the supersonic expansion, which explains that it is one of the experimentally observed complexes (band B). In contrast, in the case of $THIQM_{II}$ and ML_{syn} (Figure 4b), the binding energy of NH_{THIQM} to OH_{ML} is large enough (almost 6 kcal/mol) to overcome the barrier to *Head to head* formation (sum of deformation energies = 4.8 kcal/mol) or to make the $ML_{syn} \leftrightarrow ML_G$ conversion possible. The formation of the most stable complexes formed between $THIQM_{II}$ and the different conformers of ML are therefore expected to be formed, namely *Head to head* involving $THIQM_{II}$ and ML_{syn} , *Head to head* involving $THIQM_{II}$ and ML_G , or *Cycle* involving $THIQM_{II}$ and ML_G . It must be noted that the deformation energies only give an estimation of the barriers, that the rate for IVR also plays a role, and that only part of the binding energy of the intermediate complex may be used for inducing SACI. The values given here above are only an estimation. This, together with the fact that the very red-shifted frequencies are usually not well reproduced in the calculation does not allow definite assignment of the complex responsible for band A to *Head to head* involving $THIQM_{II}$ – ML_{syn} or *Cycle* involving $THIQM_{II}$ and ML_G .

As already mentioned, the results obtained for the SS complexes parallel those obtained for SR. In other word, band B is assigned to an *Addition* complex formed from the most stable conformers, i.e., $THIQM_I$ and ML_{syn} . Band A observed experimentally is assigned to the *Head to head* complex containing $THIQM_{II}$ and ML_{syn} or to the *Cycle* made from $THIQM_{II}$ and ML_G . Last, band C is assigned to the *Head to head* complex built from $THIQM_{II}$ and ML_G .

Chiral Recognition. At first sight, chiral recognition is not spectacular in this system. Similar structures are formed for the two diastereomer complexes, in contrast with previously studied complexes, in which the binding pattern observed in the homochiral complex completely differs from that observed in its heterochiral counterpart. This can be explained in terms of the rigidity of the structures. In the *Head-to-head* or *Cycle* complexes, the chiral centers are kept far apart and do not see each other. The same phenomenon has been observed in a rigid structure like the complexes of (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol and methyl lactate.³¹ In the *Addition* structure, there is only one interaction point which is not enough to achieve chiral recognition.⁶⁹ Other interactions points, like dispersion and $OH \cdots \pi$ or $CH \cdots \pi$ interactions, which would increase chiral recognition,^{15,24} are not possible due to the structure of the complex that keeps the molecular frame of ML far from $THIQM$. However, there is a difference in the relative abundance of the *Addition* and the *Head-to-head/Cycle* complexes for the two diastereomers, as can be inferred from the relative intensities of bands A and B. It is not possible to rationalize this ratio on the basis of theoretical considerations as it is influenced by too many energetic and kinetic factors. We can only conclude that the *S* enantiomer of ML seems to have a preference for (S) $THIQM_{II}$ whereas (R) ML seems to preferentially bind to (S) $THIQM_I$.

CONCLUSION

The jet-cooled complexes between the two enantiomers of Methyl-lactate (ML) and (S) 1,2,3,4-tetrahydro-3-isoquinoline methanol ($THIQM$) have been studied by double resonance spectroscopy combined with *ab initio* calculations. The observed complexes contain one of the stable forms of $THIQM$, which are both observed as isolated species in our

experimental conditions. However, the complexes containing $THIQM_I$ or $THIQM_{II}$ show very different structures. In the first case, the most stable form of the chromophore, $THIQM_I$, directly sticks to the most stable form of the solvent, ML_{syn} , with no reorganization of the subunits. This leads to an *Addition* complex. The energy content of this complex is not large enough to induce isomerization of the subunit and it is simply cooled down in the supersonic expansion. In the second case, $THIQM_{II}$ also sticks to the most stable form of the solvent, ML_{syn} in the early stage of the expansion. However, the internal energy is large enough to induce opening of the internal hydrogen bonds or isomerization of ML, leading to the most stable complexes containing $THIQM_{II}$, which involve strong reorganization of the subunits. It is striking that $THIQM_I$ and $THIQM_{II}$ differ not only by their hydrogen bond direction ($OH \cdots N$ for $THIQM_I$ and $NH \cdots O$ for $THIQM_{II}$) but also by their mechanism of complex formation. This is probably related to the weaker hydrogen bond in $THIQM_{II}$ which makes it easier to rearrange.³⁸

ASSOCIATED CONTENT

Supporting Information

Figure of the most stable calculated structures of the SS complex. Table of the most stable calculated structure for each family of the SS complex. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ahmed.mahjoub@latmos.ipsl.fr. Phone: +33180285270. Fax: +33145171564. Present address: LAT-MOS-UVSQ-CNRS 11 Bd d'Alembert F-78280 Guyancourt France.

Notes

The authors declare no competing financial interest.

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