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Directly Probing the Racemization of Imidazolines by Vibrational Circular Dichroism: Kinetics and Mechanism

Shengli Ma, Carl A. Busacca, Keith R. Fandrick, Teresa Bartholomeyzik, Nizar Haddad, Sherry Shen, Heewon Lee, Anjan Saha, Nathan Yee, Chris Senanayake, and Nelu Grinberg*

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877

nelu.grinberg@boehringer-ingelheim.com

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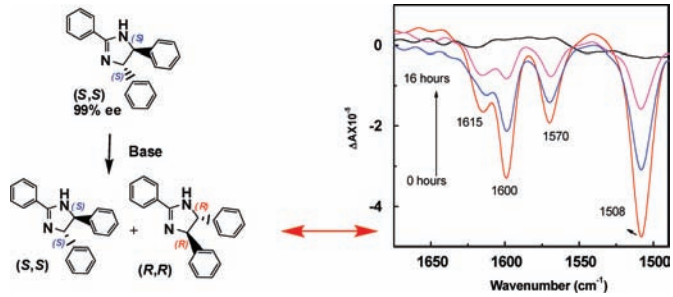
ABSTRACT



The first report of monitoring the kinetics of racemization in solution by online vibrational circular dichroism (VCD), chemometrics, and density functional theory (DFT) calculations is presented. The activation energy for the racemization of an imidazoline based on the experimental VCD was determined, and the detailed mechanism of the process utilizing DFT calculations was elucidated. This study demonstrates the utility of VCD for the determination of reaction mechanisms in asymmetric transformations.

Determination of the kinetics of asymmetric transformations is a very important task in establishing the mechanisms of such processes. Online monitoring of asymmetric reactions is challenging due to the limited number of techniques available for the direct observation of such reactions. Vibrational circular dichroism (VCD) is a demonstrated molecular level method that can provide stereochemical information on the behavior of specific functional groups linked to a chiral center. VCD is generally utilized for the determination of the absolute configuration of small chiral molecules[1,2] as well as the study of conformational changes of biomolecules.[3−6] Compared to other chiroptical methods such as electronic CD, VCD is based on vibrational transitions and thus is applicable to all types of chiral molecules, while UV-based CD is applicable only to chromophore-containing molecules.[7−11] To date, there are only a few reports on the application of VCD to kinetic studies of reactions involving chiral molecules. These studies pertain

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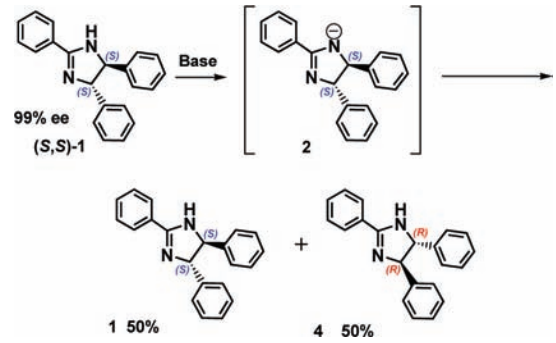
to reactions in the gas phase.[12−15] To the best of our knowledge, there are no reports on direct probing of online kinetic studies in solution. We report here the first online kinetic study of a racemization reaction of an imidazoline using online VCD measurements in solution.

Imidazolines are valuable chiral building blocks that have been used to construct libraries of chiral ligands including imidazoline−amines,[16] imidazoline−aminophenols,[17,18] imidazoline−pyrrolidines,[19] and imidazoline−phosphines.[20−24] Chiral imidazolines bearing the core of compound **1** are effective in a number of organic transformations,[25] including enantioselective hydrogenations,[20,26] asymmetric Henry reactions,[27] asymmetric Heck reactions,[28,29] and asymmetric Friedel−Crafts substitutions.[30] Imidazoline-containing drugs have been also used for the treatment of cancer, central nervous system (CNS) diseases, and hypertension.[31−33]

It was found that under strongly basic conditions (Scheme 1) imidazoline **1** in solution undergoes an unexpected racemization.[34] To understand this phenomenon, we present herein the first study of the racemization of chiral imidazoline **1** using online VCD measurements with the support of chemometrics and density functional theory (DFT) computations. This approach has provided a direct, stereochemical probe of the reaction and enabled the determination of both the reaction kinetics and the reaction mechanism.

Scheme 1. Racemization Process



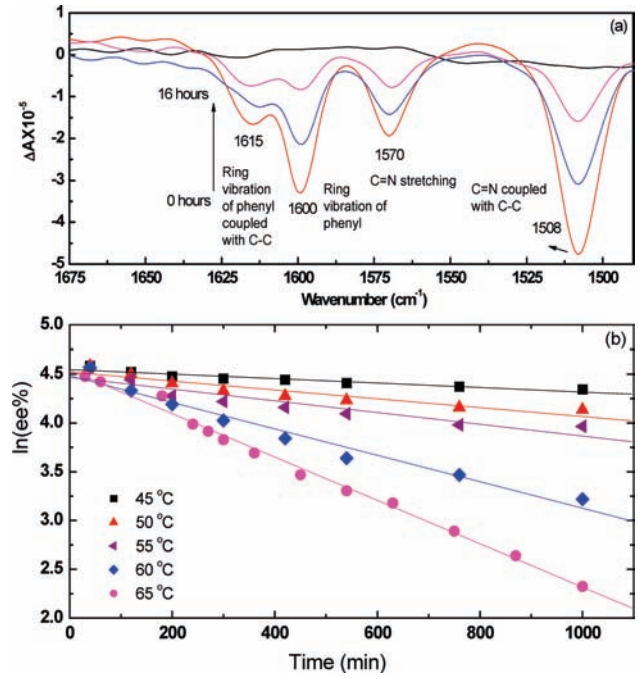


Figure 1. (a) VCD spectra of (*S*,*S*)-imidazoline **1** at different reaction times during racemization in DMSO solution at 60 °C. (b) Relationship of ln (ee %) versus time at different temperatures.

Figure 1a presents the VCD spectra measured at different time intervals during the racemization of (*S*,*S*)-imidazoline **1** at 60 °C. The reaction mixtures were continuously pumped through a spectrophotometric flow cell, and the spectra were automatically recorded with a FT-VCD instrument during the entire course of the reaction. Due to the absorbance interference from the solvent and reagents, we focused on the region from 1650 to 1480 cm^{-1}, where four distinct VCD bands at 1615, 1600, 1570, and 1508 cm^{-1} can be observed.

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The band assignment is presented in Figure 1a as well as in the Supporting Information. The decrease in intensity as a function of reaction time of all four bands clearly indicates that the imidazoline **1** undergoes racemization at 60 °C in a DMSO-d_6 solution. The VCD measurements performed at different temperatures showed significant spectral changes during the reaction. To determine the enantiomeric excess we utilized chemometric calculations on the spectra region between 1650 and 1480 cm^{-1}. The prediction of the enantiomeric excess (ee %) at different time intervals during the racemization reaction at different temperatures is shown in the Supporting Information..

A plot of the ln(ee %) versus time produced straight lines at all temperatures examined (Figure 1b), and the activation energy obtained from the corresponding Arrhenius plot is ~24 kcal/mol, which corresponds approximately to a near doubling of the rate constant with a 10 °C temperature increase, consistent with a first-order kinetics.[35,36]

DFT calculations on the reaction were performed to obtain further insight into the reaction. From a series of conformational searches and reaction pathway calculations a reaction coordinate diagram for the racemization process was constructed (Figure 2). The calculated transition state energy for the 6π ring opening is 20.7 kcal/mol, which is in close agreement with the experimental VCD determined activation energy of 24 kcal/mol. The calculation also revealed that prior to the transition state a charge dissymmetry occurs throughout the imidazoline ring and the aromatic moieties connected to the two chiral centers (see the Supporting Information). Thus, the reaction may be initiated by the mutual charge-transfer interaction between the π and the σ bond to be broken. This interaction will take place between the HOMO (bonding) and the LUMO (antibonding) of each bonding region. The charge transfer from the bonding HOMO to the antibonding LUMO[37] will cause the weakening and accordingly the stretching of both bonds (Figure 2b). An increase in bond length will cause a lowering of the LUMO level and an elevation of the HOMO energy, so that the charge transfer is further facilitated. Such interactions may be assisted by vibrational motions.[37,38] A conformation search (B3LYP 6-31*) of the ring-opened product produces three sets of enantiomers. The lowest energy of these is intermediate **2**, the direct product of the 6π ring disrotatory ring-opening of the substrate which is 8.0 kcal/mol higher in energy than the starting material **1**. Due to the nonbonding interactions of the *cis*-imine phenyl ring with the neighboring *trans*-imine, the *cis*-imine fragment is twisted 35.4° (dihedral angle) out of plane and thus imparts chirality to the structure (Figure 3a). However, due to the chiral nature of the intermediate (**2**), a conformational change has to take place in order to produce the opposite enantiomer of **1** (**1′**). The ring system will otherwise close to produce the same enantiomer as the original starting material (**1**).

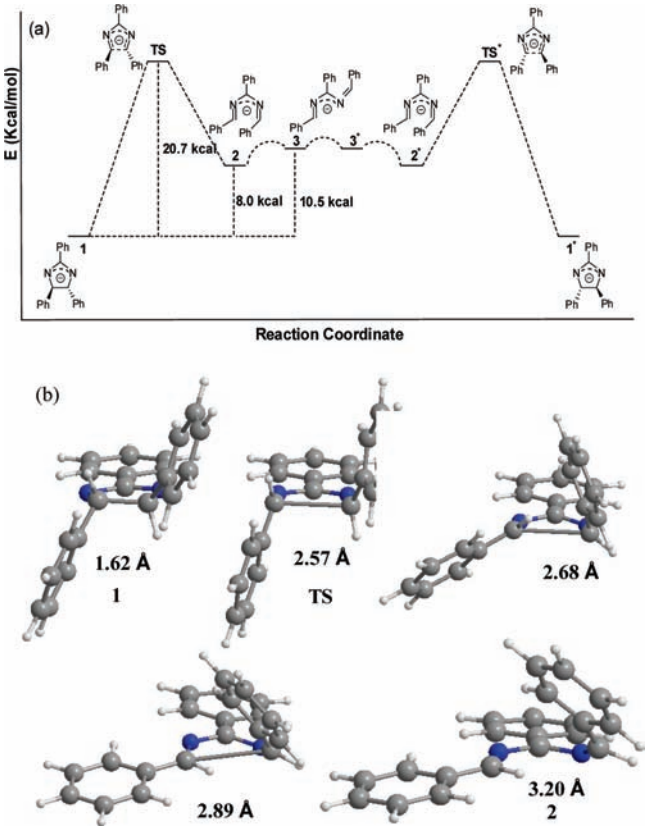

Figure 2. (a) Energy diagram of the racemization process of **1**. (b) Reaction path simulation of the racemization: structure and changes of the C−C bond length of ground, transition, and intermediate states.

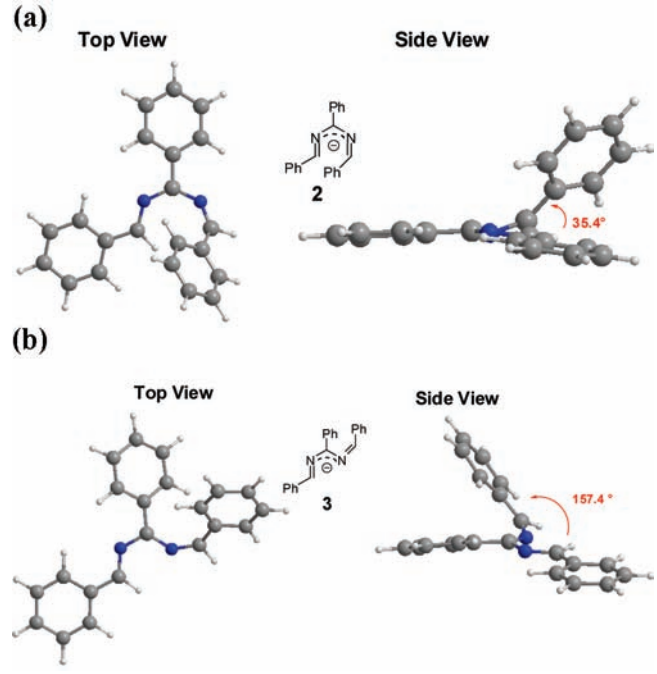

Figure 3. (a) Calculated lowest energy conformation of intermediate **2**. (b) Calculated lowest energy conformation of intermediate **3**.

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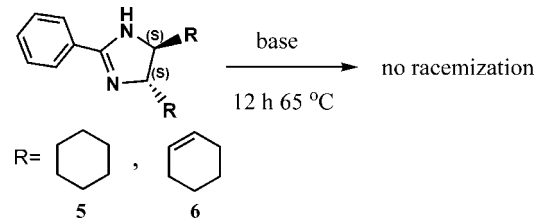
The next lowest energy conformer of the intermediates is **3** (Figure 3b) which is 10.5 kcal/mol higher in energy than the starting compound **1** (as shown in Figure 2a). Intermediate **3** is a rotamer of **2**, in which the *cis*-imine is twisted 157.4° out of plane with the *trans*-imine fragment. The difference between **2** and **3** is that the *cis*-imine in **3** is twisted an additional 122° out of plane relative to the opposite *trans*-imine fragment. This twisting to form **3** from **2** would render the *cis*-imine orthogonal to the conjugated anion (central carbon) and thus lose the stabilization that arises from conjugation of the anion. As the corresponding π systems of the phenyl rings of compounds **2** and **3** are not orthogonal to the central anion, there will still be some delocalization (conjugation) of the central anion, and these structures would represent the best compromise between the benefits of conjugation and the reduction of nonbonding interactions of the neighboring phenyl substituents.

As it would be more sterically demanding to interconvert **2** to **2*** directly (via twisting the *cis*-imine through the *trans*-imine, Figure 3a), the best process for the racemization would be for the intermediate **2** to twist to intermediate **3** where intermediate **3** could more easily access its enantiomer **3*** (Figure 3b). This process then would constitute the racemization mechanism of the substrate through the rotation of the *cis*-imine. It should be noted that a similar process can occur with the *trans*-imine, but the *trans*-imine rotamer similar to **3** is 1.5 kcal/mol higher in energy than **3** described here. These results are in concert with a disrotatory pericyclic ring-opening/closing racemization mechanism.

A key finding is thus the important role played by the aromatic moiety linked to the chiral center of **1** in the racemization process. To further explore these observations we synthesized two chiral imidazolines in which the phenyl groups were replaced by cyclohexyl (**5**) and cyclohexenyl (**6**) substituents, respectively (Scheme 2). Racemization experiments were conducted under the same conditions used for **1**. No racemization was observed for either compound **5** or **6** during the 12 h reaction at 65 °C. This result has both practical and conceptual importance. Asymmetric transformations using chiral imidazoline ligands bearing alkyl and alkenyl substituents can thus be safely carried out under strongly basic conditions without fear of racemization. In addition, the presence of unsaturation alone (**6**) is not sufficient to induce racemization, supporting the idea that the aryl substituent induces the imidazoline racemization process.

Scheme 2. Attempted Racemization of **5** and **6**



In summary, we have described here the first online kinetic and mechanistic study of a racemization reaction in solution phase using VCD spectroscopy. With the aide of chemometrics and DFT computations, the spectral properties, transition state, and activation energy of the reaction were elucidated and showed good agreement with experimental data, allowing detailed mechanistic information to be obtained. It was found that the aromatic substituents linked to the chiral centers play a crucial role in the racemization of these imidazolines, due to the charge asymmetry generated by the substituents. The racemization occurs through a disrotatory pericyclic ring-opening and closing process facilitated by the charge transfer between LUMO and HOMO orbitals. This observation was further confirmed by the stereochemical stability of chiral imidazolines lacking these arene substituents. The combined methodologies of online VCD, chemometrics, and DFT thus provide a powerful tool for studying critical asymmetric transformations.

Supporting Information Available: Experimental procedures, DFT calculations, and details of VCD experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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