

Conformational Preferences of a Polar Biaryl: A Phase- and Enantiomeric Purity-Dependent Molecular Hinge

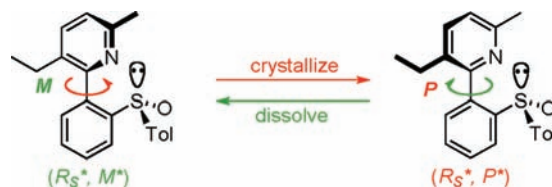
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Received March 31, 2009

ABSTRACT



The favored (R_S^*, M^*) diastereoisomer of 2-aryl-pyridine 1 in the solution state results from intramolecular dipole–dipole interactions. In the crystalline state, intermolecular interactions dominate, and the conformation switches reversibly to (R_S^*, P^*). Only racemic 1 exhibits this switching property: enantiomerically pure 1 exists as the (R_S^*, M^*) diastereoisomer in both the solution and crystalline state.

Control of mechanical motion at the molecular level is an area of great contemporary interest.¹ A wide variety of molecular devices including ratchets, switches, shuttles, and rotors have been developed.² This work has revealed that while achieving restricted motion at the molecular level is not difficult, designing molecular devices that *control motion* is much more challenging.

Structures that are shown to move in a unidirectional sense are of special interest, as it may be possible to harness work from these machines.^{2a,3} Mechanisms of unidirectional control include photochemical isomerization,⁴ redox events,⁵ chelation or dative bonding to a transition metal,⁶ and selective hydrogen bonding or pH driven processes.⁷

Devices that control motion in a unidirectional rotary sense are rarer: Feringa has developed a series of light driven molecular motors,⁸ and also reported chemically driven 360° rotation by combining a series of four 90° events.⁹ Leigh has described complex [3]catenane-based motors that achieve rotation through a sequence of chemical, thermal and photochemical events.¹⁰ Kelly achieved nonreversible 120° bond rotation in a modified molecular ratchet using phosgene as the chemical fuel,¹¹ and Haberhauer recently reported a

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hinge that opens and closes ($\sim 180^\circ$) unidirectionally based on addition or removal of Cu(II) to a chiral bipyridine unit.¹²

Here we report a synthetic structure which undergoes unidirectional bond rotation when either opening or closing, in the sense of a molecular hinge. Controlled motion is driven by a combination of steric restrictions and the thermodynamic preferences resulting from dipole interactions in two different states. Simply dissolving or crystallizing the material serves to change the shape of the potential energy surface of the system, effecting rotation exclusively in one direction or the other.

We have shown that dipole–dipole interactions can exert thermodynamic control over the stereochemistry of atropisomeric amides,¹³ diaryl ethers,¹⁴ and 2-aryl-pyridines.¹⁵ Screening of “conformational auxiliaries” adjacent to atropisomeric, or near-atropisomeric, axes has shown that the most effective control is obtained with those having the greatest dipoles, with sulfoxides being particularly effective.¹³ In the case of sterically hindered conformers or atropisomers, interconversion of the stereoisomers may be monitored by ^1H NMR or circular dichroism spectroscopy at low, ambient, or elevated temperatures as appropriate. In many cases, extremely high levels of conformational control (up to 200:1) can be achieved. While we have thus far aimed to demonstrate the utility of this “dynamic thermodynamic resolution”^{13a,14,15} in the synthesis of atropisomerically pure compounds we were aware that this process could also be used to power a molecular device.

As part of a study of the asymmetric synthesis of QUINAP-like arylisouquinolines,¹⁵ we recently synthesized the 2-arylpyridine **1**. Owing to the presence of the chiral sulfinyl substituent, **1** can exist in either of two axially diastereoisomeric conformations, shown in Figure 1 as **1a**

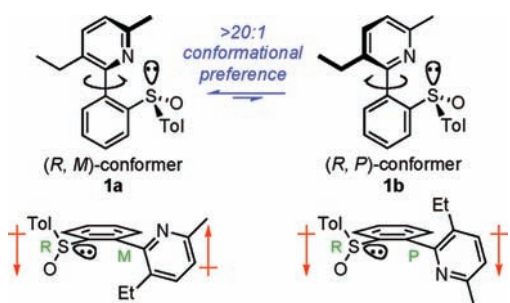


Figure 1. Conformational preference in 2-aryl-pyridine **1**.

and **1b**. Slow interconversion between these conformers on the NMR time scale at achievable temperatures allowed NMR spectroscopy to show that the compound favors largely one diastereoisomeric conformation. Circular dichroism

spectroscopy showed that **1** adopts, in solution, the *M* conformation, which allows the dipole repulsion between the aryl C–N and the sulfoxide S–O bonds to be minimized. Density functional theory (DFT) calculations (Figure 2)

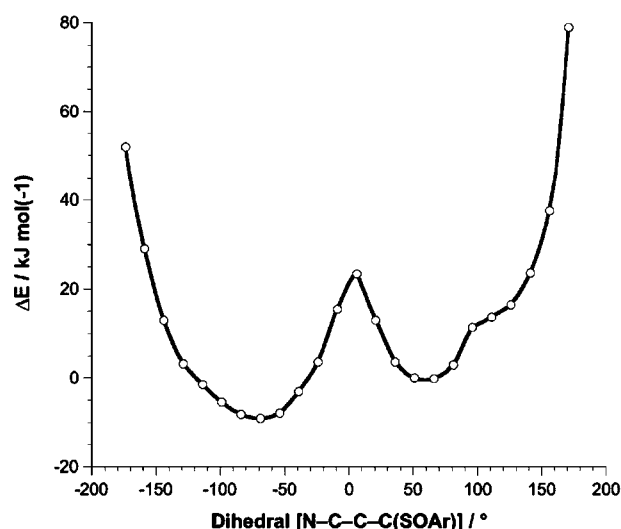


Figure 2. Fully optimized potential energy scan (B3LYP/6-31G**) along the dihedral [N–C–C–C(SOAr)] coordinate of **1** using **1b** as a starting point (0 kJ/mol).

furthermore indicated that conformer **1a** is 9 kJ mol^{-1} lower in energy than conformer **1b** in the gas phase.

We have now uncovered conditions in which the opposite conformation (**1b**) is exclusively observed. While investigating the conformation **1** we were initially unable to obtain crystals from enantiomerically pure material, but the racemate crystallized readily. In the solid state (\pm)-**1** exists exclusively as diastereoisomer **1b**, with opposite relative stereochemistry to that observed in solution (Figure 3). Assignment of the solid state conformation is based on single crystal X-ray analysis of (\pm)-**1**, with the same crystal form obtained reproducibly from both DCM/hexane and ether/hexane.

In 2-arylpyridines **1** conformational restraints imposed by nonbonding interactions between the alkyl group of the pyridine ring and the sulfinyl group force the conversion of atropisomers **1a** to **1b** to occur through rotation in one direction, and conversion of **1b** to **1a** to occur exclusively in the opposite direction. Rotation is driven by thermodynamically controlled conformational preferences in the solution phase (favoring **1a**) or the solid state (favoring **1b** in the racemate). The shape of the potential energy surface is changed through adding or removing solvent from the system¹⁶ forcing the biaryl axis to rotate only in one direction in moving from the solid phase to the solution phase, and only in the opposite direction in moving from the solution phase the solid phase.

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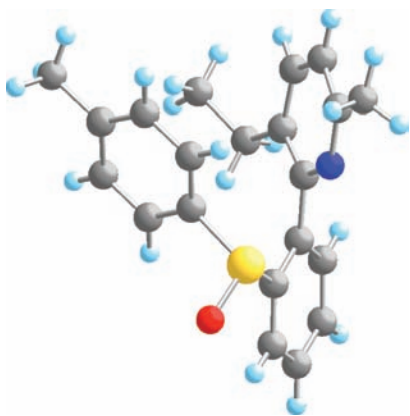


Figure 3. X-ray crystal structure of (±)-**1** showing the (R_S^*, P^*) diastereoisomer. Dihedral angle [N–C–C–C(SOAr)] = +51.4°.

The ability of the dipole-driven rotor to invert the thermodynamically favored conformation incorporates reversibility into the system, allowing it to act in the sense of a rotary switch or hinge. While controlled motion is here driven specifically by changing phases, the results suggest that controlling motion by altering the thermodynamic landscape of a rotary system by other methods is feasible. Conditions which may be more applicable to designing functional molecular devices,^{2–7} such as changing solvents, using additives, or even applying an electric field¹⁷ may also work.

The conformation adopted by **1b** in crystals of the racemate approximates closely to the calculated higher energy local minimum (Figure 2)—for example, calculated dihedral angle [N–C–C–C(SOAr)] = –51.1°; actual value = –51.4°. The reason why crystalline (±)-**1** adopts what is in the gas phase an inherently unfavorable (by 9 kJ mol^{–1}) conformation is not clear. Inspection of the crystal packing suggests that the conformation of (±)-**1** may be stabilized by stacking interactions between the pyridine alkyl substituents and the tolyl groups, along with close contact between the electron-rich oxygen of the sulfoxide and a nearby relatively acidic (*ortho* to pyridyl) arene hydrogen atom.¹⁸

While (±)-**1** is a crystalline solid, (+)-**1** exists as an oil which would not crystallize in a closed vessel. However we found that (+)-**1** solidified on extended exposure to air. Single crystals of (+)-**1**·½H₂O were then obtained from dichloromethane/hexane. Remarkably, in the crystalline state, (+)-**1**·½H₂O was found solely as the (R_S, M) conformation (**1a**). Two conformations were found in the unit cell, with dihedral angles about the biaryl C–C bond of –85.6 and –62.1°.

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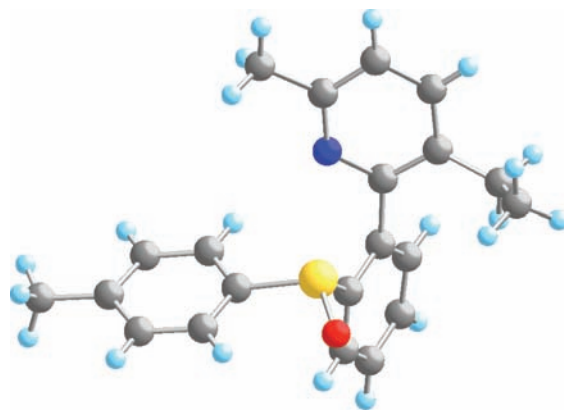


Figure 4. X-ray crystal structure of (+)-**1**·½H₂O showing the (R_S, M) diastereoisomer (water molecule omitted for clarity). Dihedral angle [N–C–C–C(SOAr)] = –85.7°.

The greater stability of the crystalline racemate, despite the molecules' adoption of a substantially less favorable conformation, is suggested by the properties of the two crystal forms. The density of the racemic crystals was found to be 1294 kg m^{–3}, while optically pure material was an oil and (+)-**1**·½H₂O has a density of 1282 kg m^{–3}. Comparison of the melting points of the racemate and optically pure solids (102–104 and 46–47 °C, respectively) also suggest the racemic crystals are more stable. Molecules in both crystal structures adopt conformations which maximize the intramolecular electrostatic interaction between the pyridine nitrogen and the S–O dipole.¹⁸

Compound **1** is thus a rare example of a compound that may exist as a different diastereoisomer in the solid state according to whether it is racemic or enantiomerically pure. Enantiomeric composition is well-known to affect crystal packing forms¹⁹ and differences in conformational preference²⁰ have also been observed. In most cases of conformational polymorphism²¹ the less favorable conformation is stabilized through hydrogen bonding or close packing interactions.²² It is however rare for a conformer lying more than 4.2 kJ mol^{–1} above the gas phase minimum to be

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avored in the crystalline state.²³ Exceptions to this occur when high-energy conformations are stabilized by enhanced intermolecular interactions,²⁴ stabilizations which are not obvious from inspection of the crystal structures of **1**. The fact that (+)-**1** crystallizes in a hydrated form makes direct comparison difficult.

Preferential formation of either hetero- or homomultimers very often explains differences in the behavior of racemic and enantiopure material.^{25,26} However, no such interactions are evident in the crystal structures of (±)-**1** or (+)-**1**· $\frac{1}{2}$ H₂O. Here, racemic **1** crystallized in the centrosymmetric space group $P2_1/n$, while (+)-**1** is an oil and (+)-**1**· $\frac{1}{2}$ H₂O crystallizes in the chiral space group $P3(1)$. As enantiopure samples of chiral molecules necessarily crystallize in noncentrosym-

metric space groups it limits the availability of packing modes (65 out of 230 space groups).^{19a} These differences in packing ability likely dictate the geometry of the racemic and optically pure crystals and help explain the apparent discrepancy of racemic material forming more stable crystals yet a less stable conformation. Further, the additional possibilities for favorable packing arrangements available in achiral space groups, the same symmetry argument used to explain Wallach's rule^{19b} by Dunitz,^{19c} may make conformational polymorphism between racemic and enantiomerically pure compounds fairly common, although this does not appear to have been explicitly explored in the literature.

The difference in the crystal forms of (±)-**1** and (+)-**1**· $\frac{1}{2}$ H₂O creates an unusual situation where the racemic material acts as a switchable molecular hinge, while the optically pure material is inactive as a machine. The ability to use a phase change to modify a potential energy landscape and achieve reversible unidirectional molecular rotation of a rotor driven by dipole–dipole interactions represents a new and powerful way to control the movement of synthetic molecular devices and suggests that other molecular machines may also be designed based on this principle.

Acknowledgment. We are grateful to the EPSRC for support of this work.

Supporting Information Available: Characterization and crystallographic data for **1a** and **1b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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