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Guest-Accelerated Molecular Rotor

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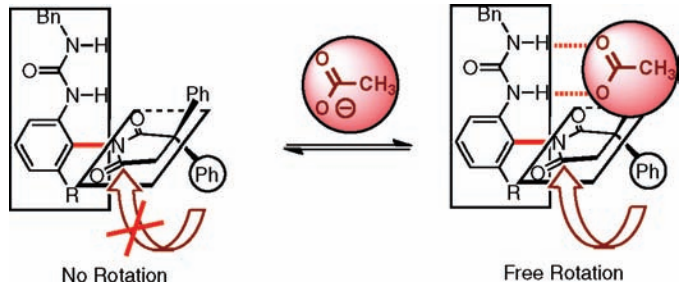
ABSTRACT



A molecular rotor was designed in which the rate of rotation is accelerated by guest complexation. The binding of an acetate guest to the urea groups lowers the barrier of the adjacent C_{aryl}−N_{imide} bond by 2 to 4 kcal/mol. This behavior is in contrast to most molecular rotors in which guest complexation slows rotation.

Molecular machines of increasing complexity have been developed over the last two decades with applications in electronics, catalysis, sensing, and nanotechnology.[1] One of the most common designs has been the molecular rotor.[2] The majority of molecular rotor devices have been molecular brakes in which bond rotation is slowed (ON to OFF) by the application of an external stimulus. Only a few examples have been reported of rotors that are accelerated (OFF to ON) by an external stimulus.[3] In this paper, we describe the development of molecular rotor **1** that is dramatically accelerated by the addition of a carboxylate guest (Figure 1).

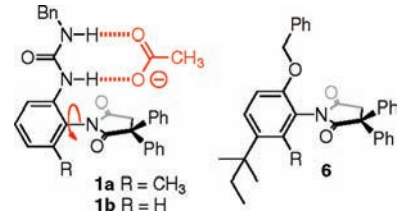


Figure 1. The proposed charge-assisted hydrogen bonded complex of urea **1a**,**b** with an acetate anion (left) and the structure of the control molecular rotor **6** (right), which cannot form hydrogen bonding interactions with an acetate guest.

Rotor **1** is based on the rigid *N*-arylsuccinimide framework, which is readily accessible and the rotational barrier can be

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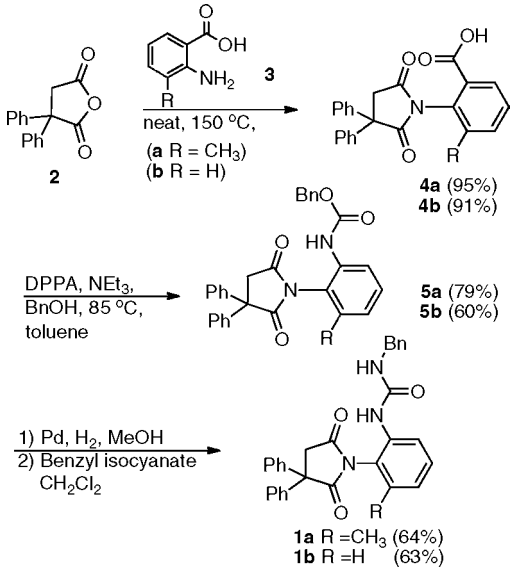
tuned by variation of the size and number of *o*-aryl substituents.[4] These attractive features have led to applications as a chiral synthetic intermediate,[5] molecular switch,[6] chiral switch,[7] and molecular torsional balance.[8] In these examples, the rates of the $C_{aryl}-N_{imide}$ bond rotation were controlled by raising or lowering the temperature. A key limitation of this approach is that elevated temperatures also disrupt the supramolecular interactions that are used to control the rotamer equilibrium. Thus, we began to explore other methods of attenuating the *N*-arylimide rotational barrier. In this paper, we report the unusual ability of carboxylate guests to catalyze bond rotations in *N*-arylsuccinimides containing urea recognition groups. The magnitude of the effect was characterized and possible mechanisms for the guest-accelerated bond rotation were explored.

N-Arylsuccinimides **1a** and **1b** containing urea recognition groups were synthesized by identical routes (Scheme 1). The

Scheme 1. Synthesis of Atropisomeric Ureas **1a** and **1b**



higher barrier **1a** had two *o*-aryl substituents (urea and methyl groups), whereas the lower barrier **1b** had only one *o*-aryl substituent (a urea group). The syntheses began with the thermal neat condensation of diphenyl succinic anhydride **2** with an anthranilic acid (**3a** or **3b**) to cleanly yield *N*-arylsuccinimide **4**.[9] The carboxylic acid in **4** was transformed into a urea group via a two-step process. A Curtis rearrangement using diphenylphosphoryl azide (DPPA) in the presence of benzyl alcohol yielded benzyl carbamate **5**. Deprotection of **5** gave an intermediate amine, which was directly converted to the desired atropisomeric ureas **1a** and **1b** via treatment with benzyl isocyanate.

Confirmation of the structure and restricted rotation of urea **1a** was provided by X-ray crystallographic and ^{1}H NMR analyses. Two different crystal polymorphs of **1a** were isolated from slow evaporation in ethyl acetate and recrystallization from hot acetonitrile (Figure 2).[10] Both X-ray

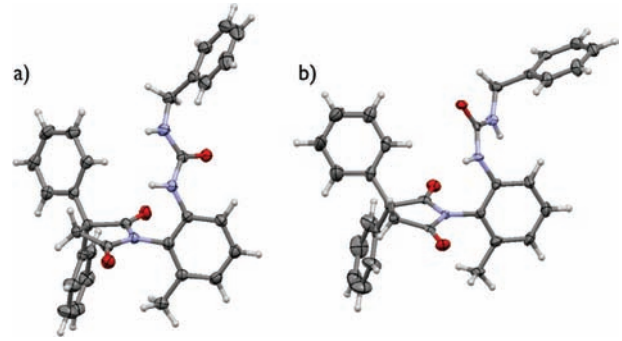


Figure 2. Selected molecular units from the two crystal polymorphs of urea **1a**. The polymorphs have three and two different molecular units, respectively. The conformations of the ureas in each crystal were very similar. Therefore, a single representative structure is shown for each X-ray structure.

structures confirmed the formation of the *N*-arylsuccinimide ring.

In addition, the steric hindrance about the $C_{aryl}-N_{imide}$ single bond was evident from the nonplanar conformation of the *N*-aryl and succinimide rings, which were twisted out of plane by 70° to 82°. The axial chirality generated by the nonplanar conformation was also evident from the ^{1}H NMR spectrum of **1a** and **1b**. The methylene protons of the succinimide ring are diastereotopic due to their proximity to the $C_{aryl}-N_{imide}$ chiral axis. The protons are well resolved at rt with geminal coupling of 18 Hz.

Restricted rotation about the $C_{aryl}-N_{imide}$ bond was characterized by measuring the rates of isomerization or the rates of interconversion of the rotamers (Table 1). In the case of the higher barrier **1a**, the enantiomeric rotamers were sufficiently stable at rt to allow separation by chiral HPLC (Chiralpak IC (250 × 4.6 mm) 1% v/v IPA:CH_2Cl_2). The rotational barriers were calculated from the measured rates of isomerization (k_{isom}) of enantiomerically enriched samples of **1a**. For example, in hot xylenes (130 °C), the measured k_{isom} of 9.9×10^{-5} s^{-1} corresponds to a rotational barrier ($\Delta G^{\ddagger}$) of 31.7 kcal/mol. In the case of the lower barrier **1b**, the rotational barriers were calculated from the rates of interconversion as measured by variable-temperature ^{1}H

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Table 1. Rotational Barrier Energies of Ureas **1a** and **1b** and Benzyl Ether **6**[a]

entry	atropisomer	equiv guest	rotational barrier (kcal/mol)	solvent
1	**1a**	0	31.7[a]	xylene
2	**1a**	2	27.1[a]	xylene
3	**1b**	0	24.9[b]	$CDCl_3$
4	**1b**	2	21.8[b]	$CDCl_3$
5	**1b**	0	24.4[b]	DMSO-d_6
6	**1b**	2	21.7[b]	DMSO-d_6
7	**6**	0	22.7[b]	TCE-d_2
8	**6**	2	22.2[b]	TCE-d_2

[a] The rotational barriers were calculated from the rates of isomerization of enantiomerically enriched samples heated in xylenes at 130 °C. [b] The rotational barriers were calculated from VT NMR line width analyses of the diastereotopic methylene protons of the succinimide ring.

NMR line width analysis.[11] This analysis measured a rotational barrier (E_a) of 24.9 kcal/mol for **1b** (30 mM, $CDCl_3$). The rotational barriers for ureas **1a** and **1b** were both in line with previous measurements of *N*-arylsuccinimides having two and one ortho substituents, respectively.[4a]

In the course of studying the recognition abilities of the urea groups of **1**, we observed that hydrogen bonding guests appeared to dramatically lower the rotational barrier. This behavior is in contrast to most atropisomeric systems, which are relatively insensitive to changes in local environment.[4a,12] More interesting was the direction of the change in the barrier, as the guests appeared to accelerate the rate of rotation in **1**. Therefore, we decided to examine this unusual phenomena more carefully using tetrabutylammonium acetate (TBAA) as a typical hydrogen bonding guest. The addition of TBAA (2.0 equiv) decreased the rotational barriers of **1a** by 4.6 kcal/mol and **1b** by 3.1 kcal/mol (Table 1, entries 3 and 4), which corresponded to a dramatic change in the rates of rotation about $C_{aryl}-N_{imide}$ bonds in **1a**,**b**. For example, in the absence of guest, enantiomerically pure (−)-**1a** was very stable at 80 °C showing less than 1% isomerization after 3 h in xylenes (Figure 3). However, in the presence of 2.0 equiv of TBAA, (−)-**1a** rapidly isomerized and was almost completely racemic within 3 h.

The ability of TBAA to lower the rotational barrier appeared to be directly related to its ability to complex to the urea recognition groups of **1a** and **1b**. The formation of

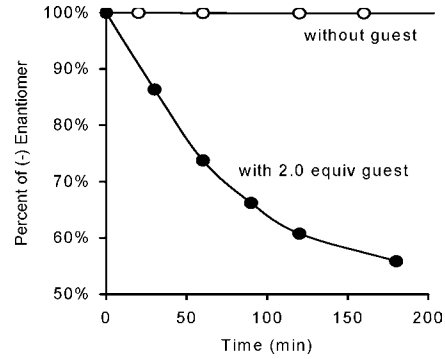

Figure 3. Racemization of (−)-**1a** (80 °C, xylenes) in the absence (open circles) and presence (filled circles) of 2.0 equiv of TBAA guest as monitored by chiral HPLC.

charge enhanced hydrogen bonded complexes between carboxylates and ureas is well established.[13] Even in polar solvent DMSO, ^{1}H NMR titration experiments confirmed the formation of strong hydrogen bonded complexes between TBAA and **1a** (K_a = 475 M^{-1}) and **1b** (K_a = 1060 M^{-1}). Indeed, similar effects were observed on the addition of 2 equiv of TBAA to **1b** in DMSO, which led to a lowering of the rotational barrier by 2.7 kcal/mol (Table 1, entries 5 and 6). The importance of urea−acetate complexation was also evident from measurements of the rotational barriers in the presence of varying equivalents of TBAA guest (Figure 4).

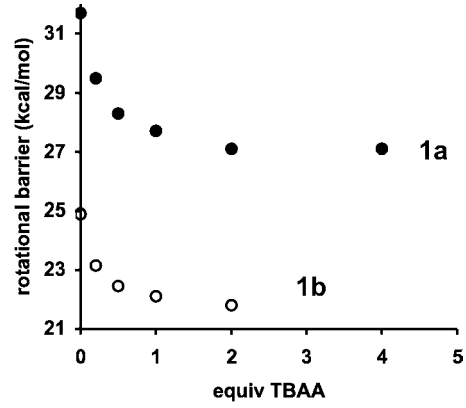

Figure 4. The rotational barriers of ureas **1a** (in xylene) and **1b** (in $CDCl_3$) measured in the presence of varying equivalents of TBAA.

For both **1a** and **1b**, the rotational barriers initially rapidly decreased with increasing TBAA concentration and then plateaued with >1 equiv of TBAA. This saturation behavior is consistent with effects on the rotational barriers being due to the formation of a carboxylate−urea complex.

The importance of the formation of a urea−carboxylate complex was also tested by studying a control atropisomer

(10) The major difference between the two polymorphs was in the configuration of the urea groups. In the first crystal (Figure 2a), the urea groups were in the more stable trans−trans configuration. In the second crystal (Figure 2b), the urea groups were in the more unusual cis−trans configuration. See: Semetey, V.; Hemmerlin, C.; Didierjean, C.; Schaffner, A. P.; Giner, A. G.; Aubry, A.; Briand, J. P.; Marraud, M.; Guichard, G. *Org. Lett.* **2001**, *3*, 3843–3846.

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6 (Figure 1), which cannot form a hydrogen bond complex with TBAA. *N*-Arylsuccinimide **6** contains the same atropisomeric $C_{aryl}-N_{imide}$ framework as ureas **1a**,**b** but has an *o*-benzyl ether group in place of the urea recognition group.

In the absence of guest, **6** has a similar rotational barrier (22.7 kcal/mol) to urea **1b**, as both have a single ortho substituent. However, this rotational barrier does not change appreciably in the presence of 2.0 equiv of TBAA (Table 1, entry 8).

Next, a series of different mechanisms for the guest-accelerated rotation of ureas **1a**,**b** were tested. The first possibilty is that binding of the guest raises the ground state (GS), bringing it closer to the TS (Figure 5, a → b). This

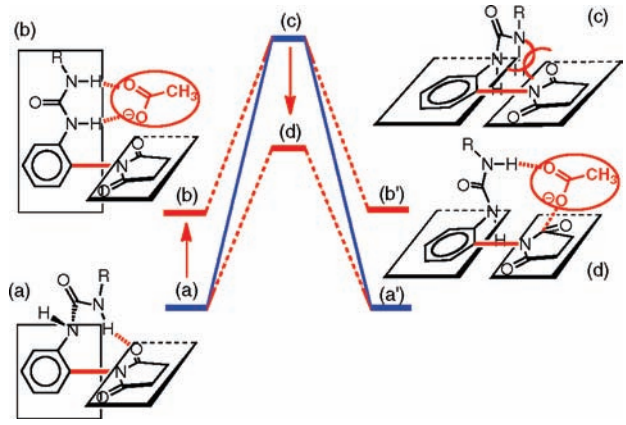

Figure 5. The energy pathway for $C_{aryl}-N_{imide}$ bond rotation in the absence of guest (blue line), and two possible energy pathways for the guest accelerated rotation (red lines). The carboxylate guest can either destabilize the GS (a → b) or stabilize the TS (c → d). Possible structures of the corresponding species are also shown.

could occur if the GS was stabilized by intra- or intermolecular hydrogen bonding interactions. Then the binding of the carboxylate guest would disrupt this interaction. This intramolecular hydrogen bonded GS mechanism was proposed by Luis et al. to explain the solvent-accelerated rotation of a macrocyclic rotor.[3] However, our data rule out the presence of an intra- of intermolecular hydrogen bond in the GS. If inter- and intramolecular hydrogen bonds were attenuating the rotational barrier, then the rotational barrier should be different in nonpolar and polar solvents. However, very little solvent effect was observed, as the barrier of **1b** was 24.9 kcal/mol in $CDCl_3$ and 24.4 kcal/mol in DMSO-d_6. The crystal structures of **1a** also showed no evidence of intramolecular hydrogen bonding of the urea recognition groups. The ureas did form intermolecular hydrogen bonds in the crystal structures, but dilution experiments showed that these interactions were too weak in solution to account for the magnitude of the changes in the rotation barrier.

The second possible mechanism is that the guest lowers the energy of the TS (Figure 5, c → d). Raines et al. has recently shown that the electrostatic n → π^* interaction of lone pairs with C=O carbons are important stabilizing interactions in peptidic structures.[14] We propose that similar stabilizing interactions between the acetate anion and the imide carbonyl carbon are possible in the TS. This interaction lowers the rotational barrier by partially pyramidalizing the imide carbonyl carbon thus relieving steric strain in the planar TS. Computational Monte Carlo experiments (AM1) of the interactions of the planar TS of **1** and a carboxylate guest predict that the carboxylate can form partial bonding interactions with the carbon of the opposing imide carbonyl. Further refinement of these bridged structures at higher levels of theory (HF/6-311+G**) verified that these structures are minima on the energy surface. Verification of this mechanism, however, will require additional studies.

In conclusion, a molecular rotor was designed with restricted rotation about a $C_{aryl}-N_{imide}$ bond and an adjacent urea recognition group. Binding of carboxylate guest lowered the rotational barrier by up to 4 kcal/mol, providing a simple way of controlling the rotational barrier under mild conditions. The guest-induced lowering of the rotational barrier is superior to molecular brakes that raise the barrier because the rotor is stable under "normal" conditions and only rotates in the presence of the external stimuli. The possibility that guest binding was destabilizing the GS by twisting the urea group out of the plane of the *N*-aryl ring thus breaking conjugation was initially discounted due to modeling that showed the urea could bind the acetate guest while maintaining planarity. This was confirmed by the crystal structure of the trans−trans configuration, which forms hydrogen bonds to the urea N−H's while still maintaining planarity.[15] Mechanistic studies appear to rule out the destabilization of the GS by the guest, suggesting that the guest lowers the energy of the TS.

Acknowledgment. This work was supported by the National Science Foundation (CHE 0911616).

Supporting Information Available: Full experimental details, ^1H and ^{13}C NMR spectra, and X-ray data for compounds **1a**,**b** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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