

Transition-State Stabilization by $n \rightarrow \pi^*$ Interactions Measured Using Molecular RotorsErik C. Vik,¹ Ping Li,² Perry J. Pellechia, and Ken D. Shimizu*

Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina 29208, United States

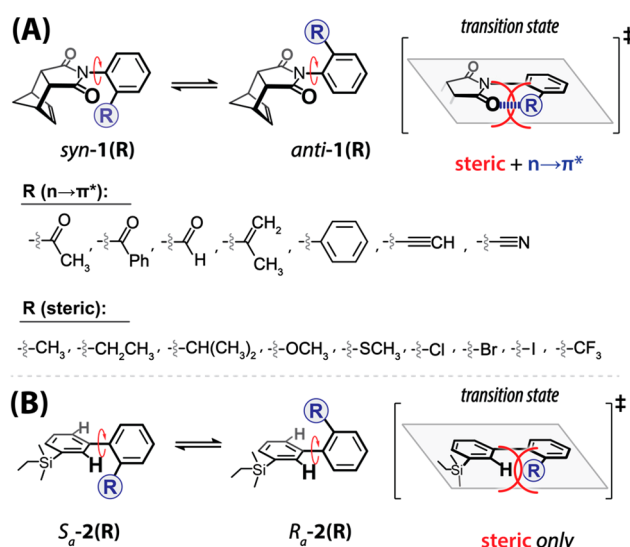
Supporting Information

ABSTRACT: A series of 16 molecular rotors were synthesized to investigate the ability of $n \rightarrow \pi^*$ interactions to stabilize transition states (TSs) of bond rotation. Steric contributions to the rotational barrier were isolated using control rotors, which could not form $n \rightarrow \pi^*$ interactions. Rotors with strong acceptor π^* orbitals, such as ketones and aldehydes, had greatly increased rates of rotation. The TS stabilization of up to ~ 10 kcal/mol was consistent with the formation of a strong $n \rightarrow \pi^*$ stabilization between the imide carbonyl oxygens and the *ortho* R group in the planar TS. Computational studies effectively modeled the TS stabilization and geometry, and NBO analysis confirmed the role of $n \rightarrow \pi^*$ interactions in stabilizing the TS.

The $n \rightarrow \pi^*$ interactions^{1–4} have been cited as playing a role in determining protein structures,^{4–7} molecular^{8,9} and polymer conformations,¹⁰ and fluorescent properties.^{11,12} However, studies of $n \rightarrow \pi^*$ interactions have primarily focused on thermodynamic measurements in the context of proteins and peptides.^{4,8,9,13–18} Despite their potential in catalysis, few researchers have examined their kinetic effects in reaction selectivity^{19–21} or enzymatic processes.²² Thus, in this study, we systematically examined the ability of $n \rightarrow \pi^*$ interactions to increase the rate of rotation of a molecular rotor (Scheme 1). Intramolecular $n \rightarrow \pi^*$ interactions in the planar transition state (TS) between the *ortho* R groups of the *N*-phenyl ring and the imide carbonyl oxygens dramatically lowered the barrier to rotation by up to ~ 10 kcal/mol. These results suggest that $n \rightarrow \pi^*$ interactions could be used to design new catalysts and could play a significant role in enzyme catalysis.^{19,20,22,23}

Studies of non-covalent interactions have been primarily measured in stable molecules and complexes.^{24–27} Few studies have quantified the effects of non-covalent interactions in unstable TSs and/or intermediates,^{28–30} despite the frequently cited role of these forces in catalysis and selectivity.^{31,32} The challenge lies in the isolation and measurement of non-covalent interactions within these high-energy and crowded structures.^{33,34} We were particularly interested in whether the strength and stability trend of $n \rightarrow \pi^*$ interactions in the TS were similar to those previously observed in ground-state (GS) systems. *N*-Phenylimide molecular rotors provide a simple model system to address these questions, as they have been successfully applied to measure the kinetic effects of non-covalent interactions such as intermolecular³⁵ and intramolecular hydrogen bonding^{36–38} and metal coordination.³⁹

Scheme 1. (A) Conformational *Syn*–*Anti* Equilibrium of Molecular Rotor 1(R) Arising from Rotation of the *N*-Phenyl Ring, and Its Planar TS, and (B) Conformational *S_a*–*R_a* Equilibrium of Biphenyl Rotor 2(R) Used To Measure the Mazzanti's Steric Parameter *B*-Value of the R Groups, and Its Planar TS



Rotor 1(R) adopts distinct *syn*- and *anti*-conformers, which slowly interconvert via rotation around the $\text{C}_{\text{aryl}}-\text{N}_{\text{imide}}$ single bond (Scheme 1A). The *ortho* R groups are held in close proximity to the imide carbonyl oxygens in the planar TS, usually within the vdW radii. R groups that have an acceptor π^* orbital on an sp^2 or sp^1 carbon, such as ketones (COCH_3 , COPh), nitrile (CN), alkenes ($\text{C}(\text{CH}_2)\text{CH}_3$, Ph), and alkynes (CCH), have the potential to form stabilizing intramolecular $n \rightarrow \pi^*$ interactions with the lone-pair on the imide oxygen. On the other hand, rotors with *ortho* R groups that do not have an acceptor π^* orbital, such as CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , SCH_3 , Cl, Br, I, and CF_3 , cannot form $n \rightarrow \pi^*$ interactions and serve as controls for isolating the steric component in the TS interactions (*vide infra*).

The rotational barriers were measured using ^1H NMR exchange spectroscopy (EXSY).⁴⁰ All rotors were studied in the slow exchange regime (-60 to 130 °C) where the *syn*- and *anti*-conformers gave distinct sets of peaks.⁴¹ Eyring plots provided the enthalpy and entropy of the rotational barriers,

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and the free energies ($\Delta G_{\text{exp}}^\ddagger$) of rotation were recalculated for 25 °C. The $\Delta G_{\text{exp}}^\ddagger$ values ranged widely from 12.9 (R = COPh) to 24.0 kcal/mol (R = CF₃).

The ability of $n \rightarrow \pi^*$ interactions to stabilize the TS was initially assessed by comparing the rotational barriers ($\Delta G_{\text{exp}}^\ddagger$) of rotors **1**(R) with similarly sized R groups. This set of rotors had in their R group an sp² carbon as the first atom carrying an acceptor π^* orbital: **1**(COCH₃), **1**(COPh), **1**(CHO), **1**(C(CH₂)CH₃), and **1**(Ph). The steric sizes of these R groups are very similar as the atom type and hybridization of the first atom is the primary determinant for the steric term of the rotational barrier (*vide infra*).^{42,43} Yet, the barriers varied widely from 12.9 to 21.5 kcal/mol, suggesting the presence of additional important interactions in the TS. The variations correlated with the ability of the R groups to form $n \rightarrow \pi^*$ interactions.^{9,16} For example, rotors **1**(COPh), **1**(COCH₃), and **1**(CHO) contain polar carbonyl groups that are strong acceptors and had the lowest barriers (12.9, 13.9, and 15.2 kcal/mol). The through-bond (mesomeric) effects of these groups are relatively small and thus cannot explain the large reductions in rotational barriers.⁴⁴ By comparison, rotors **1**(C(CH₂)CH₃), and **1**(Ph) with nonpolar sp² carbons had high rotational barriers (19.5 and 21.5 kcal/mol) presumably due to weaker $n \rightarrow \pi^*$ interactions. Similar trends were observed for rotors **1**(CN) and **1**(CCH) with sp¹ carbons as the first atom. Again, the rotor **1**(CN) with the stronger acceptor *ortho*-cyano group had a lower barrier (15.4 kcal/mol) than the rotor **1**(CCH) with the weaker acceptor alkynyl group (18.8 kcal/mol).

Quantification of the TS $n \rightarrow \pi^*$ stabilizations required separating the steric and $n \rightarrow \pi^*$ components of the rotational barriers.¹⁶ The steric component is the major determinant of the rotational barrier, which is evident by the observed barriers tracking the steric trend of the R groups. The steric component of the barriers in rotors **1**(R) was assessed using Mazzanti's steric *B*-value parameter.^{43,45–48} *B*-values are well-suited to this study because they are measured from the rotational barriers of biphenyl rotors **2**(R) with varying *ortho* R groups (Scheme 1B).⁴⁹ The R groups in rotor **2**(R) cannot form $n \rightarrow \pi^*$ interactions due to the absence of lone-pair donors on the hydrogens on the opposing phenyl ring.

The rotors were divided into *two* groups based on whether their R groups contained acceptor orbitals. The first group of rotors had R groups without acceptor π^* orbitals (R = CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, SCH₃, Cl, Br, I, CF₃) and thus cannot form $n \rightarrow \pi^*$ interactions. Hence, their barriers are primarily due to steric interactions as evidenced by the correlation ($R^2 = 0.87$) of $\Delta G_{\text{exp}}^\ddagger$ with the *B*-values of the R groups (Figure 1, black circles).⁵⁰ This steric trendline also provided an estimate of the steric component in the rotational barriers for the rotors that formed $n \rightarrow \pi^*$ interactions.

Rotors with acceptor orbitals that could form $n \rightarrow \pi^*$ interactions (R = COPh, COCH₃, CHO, CN, C(CH₂)CH₃, CCH, Ph) generally deviated from the steric trendline (Figure 1A, blue circles). Most $n \rightarrow \pi^*$ rotors had barriers noticeably below the steric trendline, suggesting that the additional TS interactions were stabilizing. Thus, a measure of the $n \rightarrow \pi^*$ interaction is provided by the deviation of the barrier from the steric trendline on the *y*-axis. The magnitude of the $n \rightarrow \pi^*$ stabilizations varied widely from −0.3 kcal/mol for **1**(Ph) to −9.7 kcal/mol for **1**(COPh). The R groups with strong acceptor abilities (COPh, COCH₃, and CHO), due to the presence of electronegative oxygens, had the strongest $n \rightarrow \pi^*$

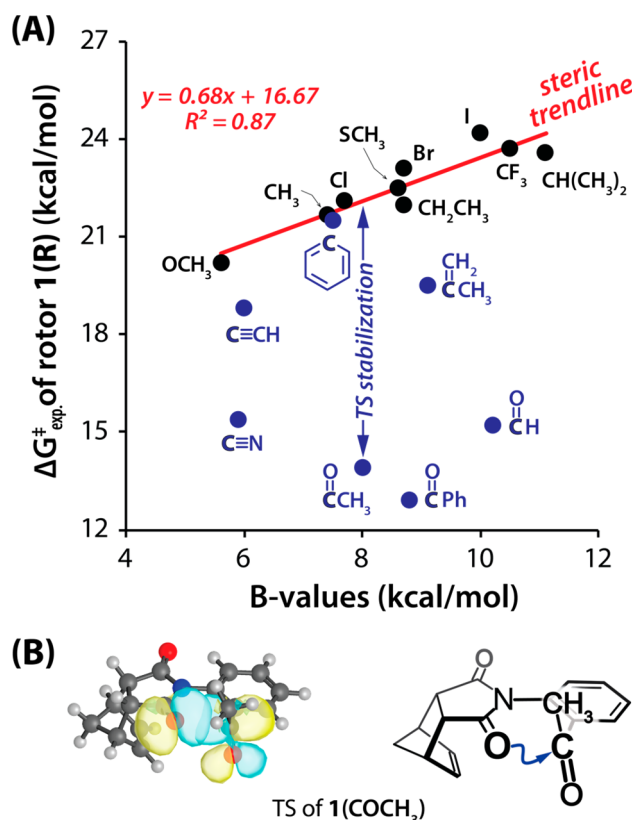


Figure 1. (A) Correlation plot of the experimentally measured rotational barriers for rotor **1**(R) versus the steric *B*-values of the R groups. The steric trendline is drawn through the rotors that have *ortho* R groups without a π^* orbital (black circles) and thus lack $n \rightarrow \pi^*$ interactions. The blue circles correspond to the rotors that can form $n \rightarrow \pi^*$ interactions. (B) Overlap of *n* and π^* orbitals in the calculated TS (B3LYP-D3/6-311G*) of **1**(COCH₃) in the three-dimensional orbital rendering and the ChemDraw presentation of TS highlighting the intramolecular $n \rightarrow \pi^*$ interaction (blue arrow).

stabilizations of −8.4 to −9.7 kcal/mol. The R group with moderate acceptor ability (CN) was moderately stabilizing (−5.2 kcal/mol). Finally, R groups with weak acceptor abilities (C(CH₂)CH₃, Ph, and CCH) due to the lack of electronegative atoms yielded the least stabilizing $n \rightarrow \pi^*$ stabilizations of −0.3 to −2.7 kcal/mol. Interestingly, the acceptor abilities of these *ortho* R groups appeared to follow the NBO atomic charges of their first atoms (Supporting Information (SI), Figure S1).⁵¹

Computational modeling was conducted to establish the role of $n \rightarrow \pi^*$ interactions in stabilizing the TS of **1**(R). DFT calculations of rotors **1**(R) with the 16 R groups (B3LYP-D3/6-311G*) were able to reproduce the experimental barriers ($\Delta G_{\text{exp}}^\ddagger$) with an accuracy of ± 1.2 kcal/mol (SI, Figure S29). The calculated TS and GS geometries were thus deemed accurate and adopted for further analysis on TS $n \rightarrow \pi^*$ stabilization.

Pyramidalization or bending of the acceptor atoms of the R groups provided the structural evidence for the formation of TS $n \rightarrow \pi^*$ interactions.^{4,9,52} The $n \rightarrow \pi^*$ orbital–orbital interaction is known to alter the geometry of the acceptor atom.⁹ Trigonal planar sp² acceptor atoms become pyramidalized and linear sp¹ acceptor atoms become bent when forming $n \rightarrow \pi^*$ interactions. The geometry change is quantified by the parameter Θ (Figure 2), which measures the angle of

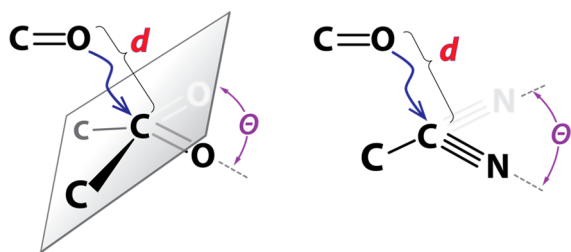


Figure 2. Definitions of the parameter Θ measuring the pyramidalization of sp^2 and bending of sp^1 acceptor carbons in $n \rightarrow \pi^*$ interactions and the distance parameter d measuring the O...C distance.

deviation from planarity or linearity. R groups with good acceptors displayed significant TS pyramidalization or bending. For example, the sp^2 acceptor carbons of the ketone (**1**(COCH₃) and **1**(COPh)) and aldehyde (**1**(CHO)) rotors displayed the highest degree of pyramidalization ($\Theta = 13.0^\circ$, 11.3° , and 11.0° respectively). These Θ values are significantly larger than the $n \rightarrow \pi^*$ interactions in protein and peptide crystal structures ($\sim 2^\circ$ – 7°), and are consistent with the observed stronger TS $n \rightarrow \pi^*$ interactions.⁵³ Similarly, the sp^1 -hybridized CN group of **1**(CN) displayed significant bending ($\Theta = 15.4^\circ$) in the TS. Interestingly, this is also one of the few examples of an $n \rightarrow \pi^*$ interaction involving an sp^1 -hybridized acceptor.

The orbital–orbital interaction energies were estimated via a natural bond order (NBO) analysis of the TS geometries of rotors **1**(R). NBO calculations (ω B97M-V/6-311G*) were performed on the calculated TS geometries of rotors **1**(R) (SI, Tables S4–S33).^{54,55} The orbital–orbital interaction energies (E_{NBO}) between the imide oxygen (n) and the R group acceptor carbon (π^*) showed an excellent linear correlation ($R^2 = 0.94$) with the measured TS stabilizations ($\Delta\Delta G_{\text{exp}}^\ddagger$) (Figure 3A). The strong correlation and similar magnitudes suggest that the majority of the TS stabilization can be attributed to the orbital–orbital $n \rightarrow \pi^*$ interaction. Note that the NBO analysis systematically overestimated the strength of $n \rightarrow \pi^*$ interaction as the slope of the correlation plot is 0.55, presumably due to discounting the effects of solvent on experimental models.

Finally, the origins of the strong TS-stabilizing $n \rightarrow \pi^*$ effects (5.3–9.7 kcal/mol) were investigated especially in comparison with the much weaker GS $n \rightarrow \pi^*$ interactions in peptides and proteins (~ 0.3 – 0.7 kcal/mol).⁴ The discrepancy cannot be attributed to the donor and acceptor properties of the interacting groups in rotors **1**(R), as they are very similar to those of the amide oxygen and amide carbon of peptide and protein systems.^{15,22,56} A portion of the difference can be attributed to the choice of the control rotors that selectively removed the repulsive component of the compactly positioned atoms in the TS interactions. However, the attractive component of the interactions appeared to be significantly enhanced by the compact nature of the TS. The O...C distances (d , Figure 2) in the TSs of **1**(COCH₃), **1**(COPh), and **1**(CHO) were all significantly shorter (2.35, 2.37, and 2.37 Å) than the sum of the vdW radii (3.22 Å). By comparison, proline-containing α -helices have some of the shortest $n \rightarrow \pi^*$ O...C distances which are only slightly shorter than the vdW radii (2.89 ± 0.10 Å).⁶ Confirmation of the short, strong $n \rightarrow \pi^*$ interactions in **1**(R) was provided by an analysis of the measured TS stabilization energies ($\Delta\Delta G_{\text{exp}}^\ddagger$) versus the

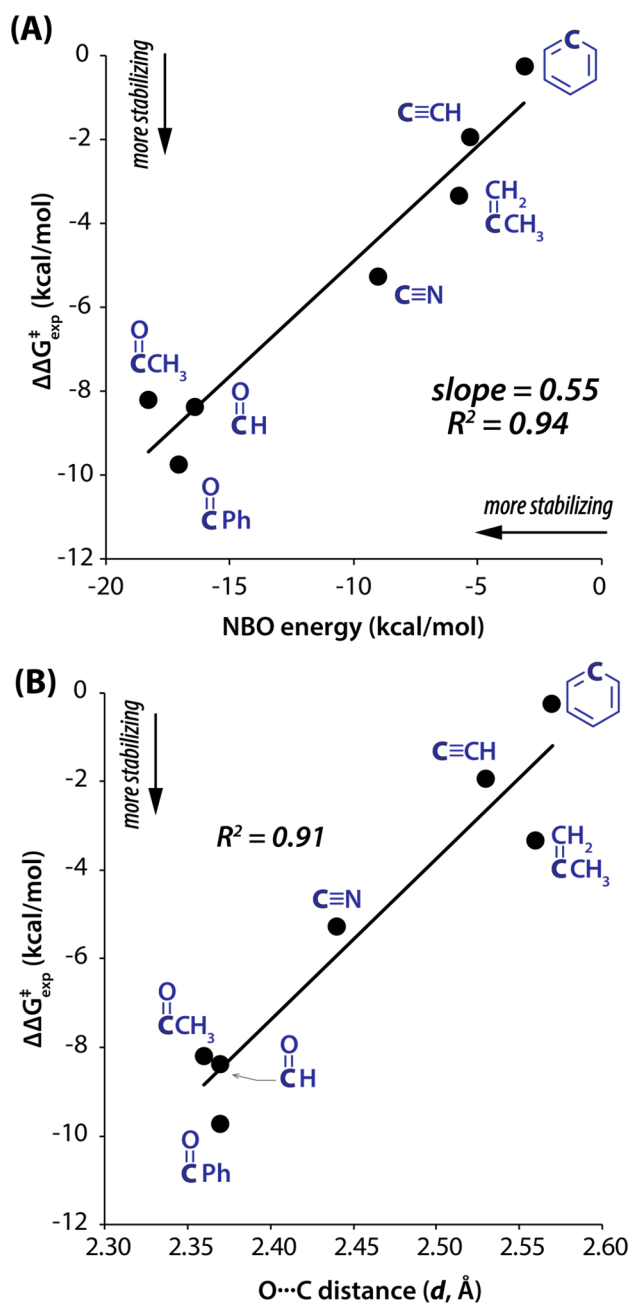


Figure 3. (A) Correlation plot of the measured TS stabilization ($\Delta\Delta G_{\text{exp}}^\ddagger$) and the calculated natural bond order (NBO) energies for the TS $n \rightarrow \pi^*$ interaction in **1**(R). (B) Correlation plot of the measured TS stabilization ($\Delta\Delta G_{\text{exp}}^\ddagger$) and the calculated donor-to-acceptor distance (d) in the TS of **1**(R).

calculated TS O...C distances (Figure 3B).⁴ For R groups that can form $n \rightarrow \pi^*$ interactions, a strong linear correlation ($R^2 = 0.95$) was observed with shorter atom distances corresponding to stronger interactions.^{9,57} The trend-line had a steep slope showing that the magnitude of the TS stabilization increased rapidly as the O...C distance decreased.

Molecular rotor **1** was successfully employed to measure the kinetic and TS-stabilizing effects of $n \rightarrow \pi^*$ interactions. Rotors that form an intramolecular $n \rightarrow \pi^*$ interaction in the TS between the imide oxygen and the *ortho* R group had significantly lower rotational barriers. The $n \rightarrow \pi^*$ interactions stabilized the TS of rotors **1**(R) by up to 9.7 kcal/mol,

significantly exceeding the stabilizations (~ 0.3 – 0.7 kcal/mol) imparted by the similar $n \rightarrow \pi^*$ interactions in peptides and proteins. The steric component of the rotational barriers was measured using the steric parameter B -value, allowing the isolation of the attractive component, and thus the stabilizing effect, of the $n \rightarrow \pi^*$ interactions. The presence of $n \rightarrow \pi^*$ interactions was confirmed by the pyramidalization or bending of the acceptor carbon and the strong correlation between the experimentally quantified TS stabilizations and the calculated NBO energies. The large TS stabilizing effects of $n \rightarrow \pi^*$ interactions were found to be closely associated with the short donor-to-acceptor ($O \cdots C$) distance in the compact TS. The results of this work provide support for the potential applications of $n \rightarrow \pi^*$ interactions in reaction kinetics and chemical catalysis.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08542.

Additional tables and figures, synthesis and characterization of the molecular rotors, measurements of rotational barriers, calculations of the rotational barriers and transition- and ground-state geometries, NBO energies, and ^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*li246@mailbox.sc.edu

*shimizu@mail.chem.sc.edu

ORCID

Erik C. Vik: 0000-0003-1334-0293

Ping Li: 0000-0001-9339-3111

Ken D. Shimizu: 0000-0002-0229-6541

Notes

The authors declare no competing financial interest.

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