

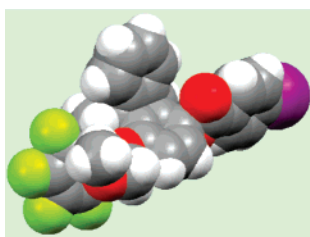
Quantitative Study of Interactions between Oxygen Lone Pair and Aromatic Rings: Substituent Effect and the Importance of Closeness of Contact

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Current models describe aromatic rings as polar groups based on the fact that benzene and hexafluorobenzene are known to have large and permanent quadrupole moments. This report describes a quantitative study of the interactions between oxygen lone pair and aromatic rings. We found that even electron-rich aromatic rings and oxygen lone pairs exhibit attractive interactions. Free energies of interactions are determined using the triptycene scaffold and the equilibrium constants were determined by low-temperature ¹H NMR spectroscopy. An X-ray structure analysis for one of the model compounds confirms the close proximity between the oxygen and the center of the aromatic ring. Theoretical calculations at the MP2/aug-cc-pVTZ level corroborate the experimental results. The origin of attractive interactions was explored by using aromatic rings with a wide range of substituents. The interactions between an oxygen lone pair and an aromatic ring are attractive at van der Waals' distance even with electron-donating substituents. Electron-withdrawing groups increase the strength of the attractive interactions. The results from this study can be only partly rationalized by using the current models of aromatic system. Electrostatic-based models are consistent with the fact that stronger electron-withdrawing groups lead to stronger attractions, but fail to predict or rationalize the fact that weak attractions even exist between electron-rich arenes and oxygen lone pairs. The conclusion from this study is that aromatic rings cannot be treated as a simple quadrupolar functional group at van der Waals' distance. Dispersion forces and local dipole should also be considered.

Introduction

In 1995, Egli and Gessner reported the intriguing observation that an attractive lone pair (lp)– π^* interaction stabilizes the Z-DNA structure, which explains the conformational stability of Z-DNA at high ionic strength despite poor base pair stacking.¹ More recently, a high-resolution X-ray structure analysis shows

a lp– π interaction between a H₂O molecule and a cytosine base in an RNA pseudoknot.² Very recently, Sankaramakrishnan and co-workers have systematically analyzed 500 high-resolution protein structures (resolution ≤ 1.8 Å) and identified 286 examples in which carbonyl oxygen atoms approach the aromatic centers within a distance of 3.5 Å.³ However, in spite of increasing recognition of the important role played by weak

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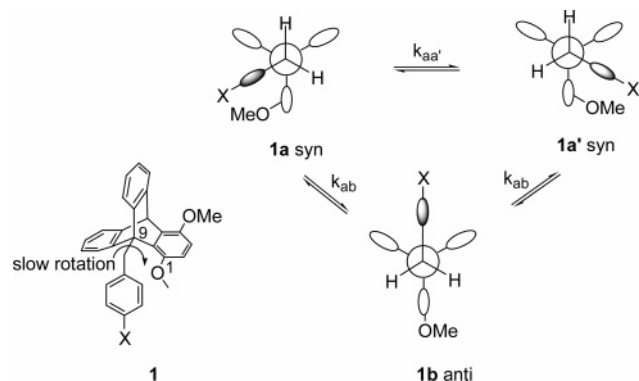


FIGURE 1. The equilibria among the syn and the anti conformational isomers of 1,9-disubstituted triptycene derivative **1** ($X = \text{H, Me, F, CF}_3$).

intermolecular interactions on macromolecular stability,^{4,5} quantitative study of $\text{lp}-\pi$ interactions is rare.^{6,7} Theoretical studies show that gas-phase $\text{lp}-\pi$ interaction is favorable with electron-deficient π -systems.^{8–14} Currently there is widespread interest in anion- π interactions since this area of research may lead to new designs of anion receptor and sensing devices. Experimental studies are also rapidly emerging.^{1,2,6,15–18} However, quantitative study is lacking for the interaction between oxygen lone pairs and aromatic rings that are not particularly electron-deficient. In the past few years, we have been studying weak molecular forces such as $\pi-\pi$ interactions using the triptycene scaffold, which is an excellent model system for studying interactions in the ± 1.5 kcal/mol range, Figure 1.^{19–21}

Results and Discussion

The triptycene-derived model system allows the bridgehead (C9 in the triptycene name system) rotating arene to interact with a C1 group at near van der Waals' distance in the syn conformation, Figure 1. In the anti conformation, there is no

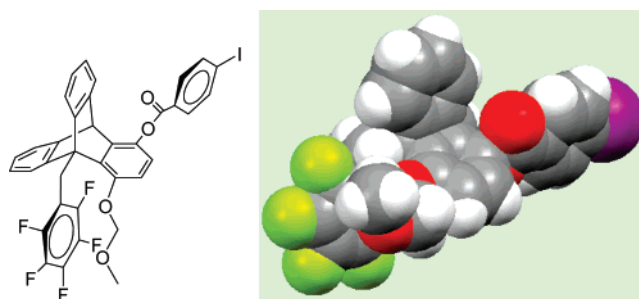


FIGURE 2. X-ray structure of compound **2** displayed as a space-filling model. The structure shows a syn conformation with the MOM group located in close proximity of the pentafluorophenyl ring. The distance from the methoxy oxygen to the center of the pentafluorophenyl ring is 3.48 Å.

contact between the C9 arene and the C1 oxygen atom.^{20,21} Since the triptycene scaffold provides an otherwise identical environment for the syn and the anti conformation, the syn:anti ratio represents the degree of preference for the interactions between the C1 and the C9 groups. Our previous study involved a C1 methoxy group, which was in contact with the edge of the rotating arene in the syn conformation.²¹ To model the $\text{lp}-\pi$ interaction more closely to that observed in the X-ray structures reported by Egli and by theoretical predictions,^{8,11,12} we needed a model system to place the oxygen lone pair directly above and near the center of the aromatic ring in the syn conformation. Through molecular modeling it was found that by replacing the C1 Me group in compound **1** with a MOM (methoxymethyl) group, the MeO oxygen lone pairs can be positioned directly at the center of the C9 arene in the syn conformation.

A single crystal was obtained for one of the new series of triptycene model compounds where the usual spectator 4-pivaloyl ester was replaced with a *p*-iodobenzoate group to increase crystallinity (**2**, Figure 2). Despite poor mean bond distances reported in the X-ray structure analysis for compound (**2**), the crystal structure confirms that the syn conformation is the preferred arrangement, where the methoxy oxygen atom of the MOM group is situated near the center of the pentafluorophenyl ring in the syn conformation (**2**). The distance from the methoxy oxygen to the center of the pentafluorophenyl ring is 3.481 Å. Caution should be exercised concerning the precision of the bond distances since the crystal was not the highest quality. This is a near van der Waals contact and consistent with most crystal structures.⁷ However, the oxygen-to-arene distance is significantly longer than the calculated equilibrium distance (3.0 Å) for the complex of dimethyl ether-hexafluorobenzene in the gas phase (see Figure 3), presumably due to the constraint of the scaffold. The torsional angles of the MOM group are trans (T) at the first dihedral angle (C1O-CH₂O) and gauche (G) at the second dihedral angle (CH₃O-CH₂O) in the crystal structure. Although the conformations of dimethoxymethane have been studied extensively,²² there appears to be no theoretical study of the conformations of phenyl methoxymethyl ether. At least two crystal structures containing the moiety of ArOCH₂OCH₃ have been reported and both show a gauche-gauche (G,G) conformation.^{23,24} The T,G conformation in structure **2**

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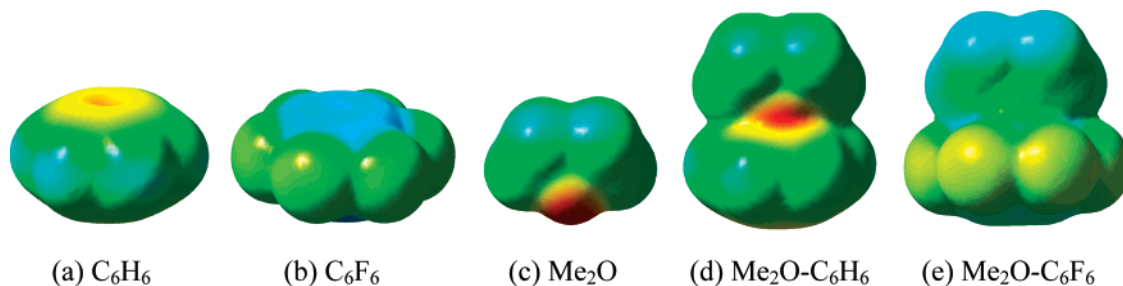
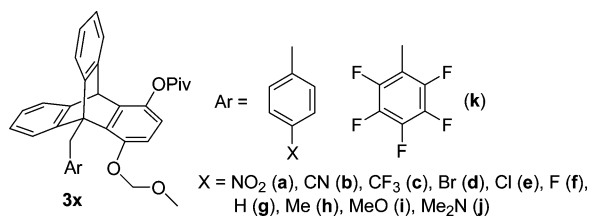


FIGURE 3. Ab initio electron density (HF/aug-cc-pVTZ) isosurfaces color-mapped with electrostatic potential for C_6H_6 , C_6F_6 , dimethyl ether, and the complexes. The isosurface of the arenes shows a circular π system with a bowl-shaped center. In the complex, the oxygen is located at the center of the arene to achieve maximum contact area in spite of the unfavorable electrostatic interactions in the $Me_2O-C_6H_6$ complex.

suggests attractive interactions between the methoxy oxygen and the center aromatic ring because the preferred G,G conformation in **2** would have placed the methoxy group out of contact with the C9 aryl group. The crystal was grown between the interface of CH_2Cl_2 and hexane and the crystal cell contains a CH_2Cl_2 molecule (see the Supporting Information). One of the CH bonds of the CH_2Cl_2 may be considered to have a $CH-\pi$ interaction with one of the triptycene benzene rings.

The synthesis of the precursors to model compounds **3a–k** generally follows reported procedures and the installation of the MOM group gave the desired compounds.²¹ The preparation of the compound with $X = NO_2$ (**3a**) employs an alternate method (see the Supporting Information for details). The substituent X on the center arene varies from electron-withdrawing to electron-donating groups. Low-temperature NMR spectroscopy enabled us to study the population of the syn and anti conformations in chloroform solution. Distinct conformational isomers were observed at low temperatures by 1H NMR. The CH_2Ar protons become diastereotopic in the syn conformation and display an AB quartet while they are enantiomeric in the anti conformation and appear as a singlet. The CH_2 group between two oxygen atoms in the MOM group also displays the same distinct patterns in the syn and anti conformational isomers.



Integration of the relative peak area from the singlet and the AB quartet of the benzyl or MOM CH_2 protons provided the syn:anti isomer ratio for each compound. An average value from the integration of both CH_2 groups is recorded. The conformational freedom is rather limited for the rotating arene in either the anti or the syn isomers in the triptycene model system.²¹ The MOM group is free to rotate in the anti conformation, but its rotational freedom is limited in the syn conformation due to the $lp-\pi$ interaction. Thus the syn:anti ratio is effectively the equilibrium constant between the syn and the anti conformations. Since statistically two syn and one anti conformer are expected, the equilibrium constant, K_{eq} , equals a 1:2 syn:anti ratio. The experimentally determined syn:anti ratios in $CDCl_3$ and the free energies derived from these ratios are shown in Table 1.

All model compounds studied showed attractive interactions between the C9 substituted aromatic ring and the C1 MOM

group. The general trend for the interaction strength based on the data in Table 1 is consistent with electrostatic forces playing a dominant role, i.e., the more electron-deficient the aromatic ring is, the stronger the attraction. The strongest interaction is observed with the pentafluorophenyl group (entry 11, Table 1). For the monosubstituted aromatic rings, a Hammett plot did not give a good correlation between the substituent constants (σ_{para} or σ_{meta}) and the free energies obtained.²⁵ The Hammett σ parameters are known to not necessarily correlate with the π -electron density on the aromatic rings. This point has been discussed by both Dougherty and Sherrill.^{26,27} The reason for this has been attributed to how the Hammett parameters were determined. They were determined from the equilibrium constants for the dissociation of substituted benzoic acids, therefore, there is no reason to assume that they necessarily correlate with the π -electron density in the reactants for those dissociations.^{26,27}

However, if the substituents are broadly arranged into electron-withdrawing and electron-donating groups, the data in Table 1 are consistent with the expectations based on electrostatic interactions. The syn:anti ratios for the compounds with electron-withdrawing substituents (i.e., NO_2 , CN, and CF_3 , and the halogens) are greater than that of the standard compound (**3g**, $X = H$).²⁵ The syn:anti ratios for the compounds with electron-donating groups (CH_3 , CH_3O , and Me_2N) are smaller than that of **3g**. Interestingly, despite their known capacity to donate electrons to aromatic rings, weak interactions were observed even for the compounds with electron-donating groups (**3h**, **3i**, **3j**). Higher than statistical syn:anti ratios are observed for all three model compounds indicating the presence of attractive interactions (entries 8–10, Table 1). To probe alternative $CH-\pi$ interactions, we prepared three model compounds with a C(1) propyloxy group (entries 3, 7, and 8 in Table 1). Despite the C(9) arene in these three compounds bearing three different substituents (CF_3 , H, CH_3), all three exhibit weaker interactions than their corresponding C(1) MOM and MeO analogues. The propyloxy group and the MOM group are similar in steric bulk. However, the MOM derivatives exhibit higher than twice the syn:anti ratio as the propyloxy derivative. Furthermore, $CH-\pi$ interactions should prefer electron-rich C(9) aromatic rings. The opposite is observed. Therefore any $CH-\pi$ attraction may have been countered by steric interactions, which explains why the PrO is less favorable than the corresponding MeO derivatives in assuming the syn conformation. Taking the experimental evidence as a whole including the X-ray structure,

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TABLE 1. Substituent Effect for Lone Pair–Arene Interactions^a

| entry | compd | Ar | syn:anti ratio (−50 °C), | | | $\Delta G_{\text{anti-syn}}$ in CDCl ₃ for C1 MOMO, kcal/mol |
|-------|-----------|--|--------------------------|--------------------|------------------|---|
| | | | C1 MOMO | C1 MeO | C1 <i>n</i> -PrO | |
| 1 | 3a | C ₆ H ₄ NO ₂ | 8.4 | 7.2 ^c | | −0.64 ± 0.05 |
| 2 | 3b | C ₆ H ₄ CN | 9.4 | 8.5 ^b | | −0.69 |
| 3 | 3c | C ₆ H ₄ CF ₃ | 10.1 | 5.5 ^b | 4.1 ^c | −0.70 |
| 4 | 3d | C ₆ H ₄ Br | 7.8 | 4.7 ^c | | −0.59 |
| 5 | 3e | C ₆ H ₄ Cl | 7.1 | 3.5 ^b | | −0.57 |
| 6 | 3f | C ₆ H ₄ F | 7.5 | 3.9 ^c | | −0.59 |
| 7 | 3g | C ₆ H ₅ | 6.8 | 3.3 ^b | 2.5 ^c | −0.54 |
| 8 | 3h | C ₆ H ₄ Me | 4.8 | 2.3 ^b | 1.7 ^c | −0.40 |
| 9 | 3i | C ₆ H ₄ OMe | 5.2 | 2.4 ^b | | −0.38 |
| 10 | 3j | C ₆ H ₄ NMe ₂ | 3.1 | 2.0 ^c | | −0.19 |
| 11 | 3k | C ₆ F ₅ | >25:1 | >25:1 ^c | | <−1.2 |

^a The errors are estimated at ±0.05 kcal/mol from an average of two runs. ^b Reference 17.²¹ ^c This work.

¹H NMR data, and the results from the propoxy derivatives, the observed weak interactions between the bridgehead arene and the MOM group do indeed originate from lp– π interactions.

Several models have been developed, which depict aromatic rings as polar groups for studies related to π – π interactions, and cation– π interactions.^{26,28,29} The fact that benzene and hexafluorobenzene are known to have large and permanent quadrupole moments^{30,31} supports these descriptions. Other studies on the binding of cations and anions by aromatic rings with quadrupole moments of the same polarity indicate the importance of polarizability of the aromatic rings.^{32,33} Electrostatic potential surfaces of aromatic rings have also become a convenient tool to describe the polarity of the arenes.²⁶ The surface of hexafluorobenzene has positive potential and the surface of benzene has negative potential. The large attractive interaction between the pentafluorobenzyl group and the MOM group observed for compound **3k** (entry 11, Table 1) is consistent with the argument based on the polarity and the large positive quadrupole moment of hexafluorobenzene.

However, an aromatic ring similar to benzene should have negative potential and show repulsive interactions with an oxygen lone pair. In contrast, the current study shows that a phenyl ring and a MOM group exhibit considerable attractive interaction (syn:anti ratio: 6.8, entry 7, Table 1). Electron-donating groups should increase the electron density of the aromatic ring and therefore cause the arene surface to have a higher negative potential than benzene. Although compounds **3h–j** (where X = Me, MeO, and NMe₂) did exhibit smaller attractive interactions, they still showed greater than statistical syn:anti ratios, indicating weak *attractive* interactions.

The data in the Table lead to the conclusion that any repulsive interactions are outweighed by attractive ones when aromatic rings and oxygen lone pairs are placed into close contact at their van der Waals distance. Although electron-deficient arenes interact with oxygen lone pairs more strongly, electron-rich arenes also show weak attractive interactions. The observation of the attractive interactions with the electron-rich arenes cannot be rationalized by considering either the quadrupole moments

or the electrostatic potential surface of the arenes. The attractive interactions with a MOM group are universally greater than that with a methoxy group for the model compounds studied. With a MOM group a lone pair of the outer (or second) oxygen is located at the center of the arene (model series **3**) while with a MeO group the oxygen lone pair is located at the edge of the arene (model series **1**). The data in Table 1 clearly indicate that the center approach of oxygen-to-arene is more favorable. Based either on the quadrupole moment of the arenes or on examination of the color-coded electrostatic potential surface of the arenes,^{26,34} one would not be able to predict these observations because the edges of the aromatic rings should have more positive potential and the center of the arene should have more negative potential.^{28,34} Hence the edge of the arenes should be more attractive toward an oxygen lone pair and the center of the arenes should be repulsive toward an oxygen lone pair. The data in Table 1 show that all interactions with a MOM group are about twice as large as that with a MeO group except for the arenes with a strong EWG (NO₂ and CN), and the pentafluorophenyl group. This appears to indicate that the interactions between arenes with EDG and less strong EWG and an oxygen atom may originate less from electrostatic forces and more from dispersion forces. However, no correlation was found between the free energy of interaction and the polarizability of the substituted benzyl groups.³⁵

To understand the nature of the lp– π interaction, we have carried out molecular orbital calculations for benzene–dimethyl ether, and hexafluorobenzene–dimethyl ether complexes, Figure 3. At the MP2/aug-cc-pVTZ level of theory, the complex formation energy is −1.09 kcal/mol for C₆H₆–OMe₂ and −4.59 kcal/mol for C₆F₆–OMe₂ with optimized oxygen-to-arene plane distances of 3.2 and 3.0 Å, respectively. The corresponding calculations were also carried out at the Hartree–Fock level of theory. The C₆H₆–OMe₂ dimer has no energy minimum at the Hartree–Fock level. If the intermolecular distance between benzene and dimethyl ether is fixed at 3.2 Å, the interaction energy is repulsive (~3 kcal/mol). The C₆F₆–OMe₂ has a complex formation energy of −1.2 kcal/mol at the Hartree–Fock level. Since the difference between calculations at the Hartree–Fock level and at the MP2 level is correlation energy, which is primarily made up of the dispersion energy, our computational results indicate that electrostatic forces are attractive in the complex of C₆F₆–OMe₂, but are repulsive in

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the complex of $C_6H_6-OMe_2$. Thus the attractive interactions observed in the dimers with electron-rich aromatic rings must be due to dispersion forces.

The calculated complex formation energies for these two complexes corroborate our experimental measurements although a solvent effect has not been considered. The ab initio electron density (HF/aug-cc-pVTZ) isosurfaces color-mapped with electrostatic potential for C_6H_6 , C_6F_6 , dimethyl ether, and the complexes are displayed in Figure 3. As we pointed out recently,³⁶ the total electron density isosurfaces reveal that the aromatic π system has a doughnut-shaped surface with the center depressed. The preferred center-approach of the oxygen lone pair toward an aromatic ring may be explained by considering the shape-sensitive close-contact hypothesis.³⁶ The oxygen of dimethyl ether fits into the depressed center area of the arene to achieve maximum overlap. The fact that the electron clouds interpenetrate, and the electrostatic penetration term is usually attractive provide a rationale for the favorable center-approach of the lone pair- π interaction.²⁷

Thus, in spite of the negative potentials of both the oxygen atom and the benzene ring, the preferred contact point is such that the closeness of contact and maximum overlap are achieved. It appears that at the van der Waals contact distance, the criteria of closeness of contact override the polarity consideration for aromatic rings. As pointed out by both Reisse and Dougherty, the representation of the electronic distribution of a molecule as a multipole expansion is valid only at large interaction distances.^{34,37} Because of the distance requirement, cation- π interaction cannot be quantitatively modeled as just an ion-quadrupole interaction when van der Waals contact distance is involved.³⁴ For the same reason, it is improper to view the arene-oxygen interaction as just a quadrupole-dipole interaction at the van der Waals distance especially when the arenes are not symmetric. The additional polarizability of the aromatic ring makes it a special functional group.^{32,33} Although it is convenient to describe aromatic rings as quadrupolar groups, this study has shown the circumstances where this is not entirely accurate. Other forces such as dispersion and local dipole should come into play at the van der Waals distance. It has been recognized that dispersion forces play an important role in π - π interactions.^{5,27} It is reasonable to consider the attractive interactions between the electron-rich arenes and oxygen lone pair are mainly due to London dispersion forces. Consideration of dispersion forces allows the understanding of both the weak interactions between electron-rich arenes and oxygen lone pairs and the center-approach of the oxygen toward arenes. In addition, the fact that substituents with strong inductive electron-withdrawing ability, such as CF_3 and MeO groups, produced higher than expected syn:anti ratios indicates that local dipoles

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from the C–X bond in the aromatic rings might play a role as well. The substituent constants normally used for constructing the Hammett plot become inadequate when London dispersion forces become a dominant factor. To gain further insight on lp- π interactions, an additional systematic computational study and a study involving heterocyclic arenes are underway in our laboratories.

Experimental Section

Representative Procedure for the Preparation of the Model Compounds: 9-(4-Nitrobenzyl)-1-(methoxymethoxy)-4-pivaloyloxytritycene (3a). 9-(4-Nitrobenzyl)-1-hydroxy-4-pivaloyloxytritycene (**5**) (0.25mmol) was dissolved in 2 mL of dry CH_2Cl_2 at 0 °C. DIPEA (0.44 mL, 2.5 mmol) and chloromethyl methyl ether (0.095 mL, 1.25 mmol) were added dropwise at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h, then 10 mL of CH_2Cl_2 was added to dilute the reaction mixture, which was washed with 1 N HCl three times, followed by water. The organic layer was dried over $MgSO_4$. Solvent was removed and the residue was purified by column chromatography to afford 9-(4-nitrobenzyl)-1-(methoxymethoxy)-4-pivaloyloxytritycene (**3a**). Yellow solid; mp 238–239 °C; 1H NMR (300 MHz, $CDCl_3$) δ 8.06 (2H, br), 7.92–7.31 (4H, br), 7.24–6.89 (6H, m), 6.80–6.70 (2H, q), 5.43 (1H, s), 5.42–3.80 (4H, br), 3.07 (3H, s), 1.52 (9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 151.8, 148.8, 145.7, 140.5, 140.2, 130.1, 125.4, 124.8, 123.8, 122.7, 120.4, 113.7, 85.5, 55.8, 52.2, 48.7, 39.4, 35.3, 27.5; HRMS calcd for $C_{34}H_{31}NO_6 + Na$ 572.2049, found 572.2051.

Variable-Temperature NMR Experimental Procedure The 1H NMR spectra were recorded on a 300 MHz instrument with a variable-temperature probe. A 0.05 M solution of the sample in a deuterated solvent such as chloroform was placed in a high-quality NMR tube. All samples were degassed using a needle-to-bubble nitrogen through the sample for ~1 min. The NMR tube was then capped with a cap and sealed with Parafilm. The sample tube was placed into the NMR probe and the air line to the probe was replaced with a liquid nitrogen transfer line. The desired temperature was set on the variable-temperature unit and the sample was allowed to equilibrate for 10–15 min at each set temperature. Then the 1H NMR spectrum at each temperature was recorded. The ratios of rotamers were obtained through the integrations of selected peaks.

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Supporting Information Available: Experimental procedures including low-temperature NMR spectroscopy, X-ray structure analysis, and computational details including the absolute energies and optimized geometries. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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