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A Threshold for Charge Transfer in Aromatic Interactions? A Quantitative Study of π-Stacking Interactions

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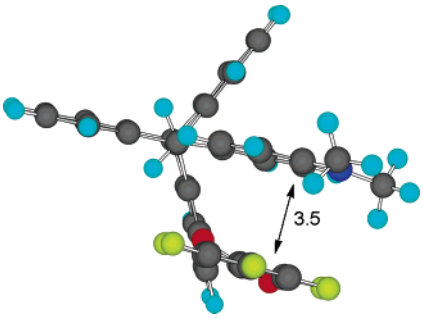

Attractive interactions between substituted arenes in the parallel displaced configuration have been quantitatively studied using triptycene-derived molecular conformational reporters. Charge-transfer bands are observed for models where the interactions are between strong donor and acceptors. Substituent effects on the strength of the aromatic interaction follow opposite trends for strongly electron-deficient arenes and mildly perturbed arenes. The free energy of interactions for models with strong electron donors and acceptors does not follow a linear correlation in the Hammett plot. Electrostatic models alone do not account for the nonlinearity of the free energy−substituents plot.

Introduction

Intermolecular interactions involving aromatic rings are important in both biological and chemical recognitions.[1−3] The majority of recent studies have demonstrated the importance of dispersion and electrostatic contributions, but not charge-transfer, to aromatic interactions.[4−16] It was shown, however, more than 5 decades ago that the mixing of aniline and dinitrobenzene produced an UV−visible spectrum that showed bands belonging to the two original compounds and also an additional broad band in the long-wavelength region, a charge-transfer (CT) band.[17] Many complexes of electron donors and electron acceptors have been found to have such absorption bands.[18] Many examples of π shielding have also been reported in the field of asymmetric synthesis,[19,20] yet there is still no unified picture whether charge-transfer interactions contribute to stereoselectivity. A charge-transfer complex was observed by Corey in a catalytic asymmetric Diels−Alder reaction that pro-

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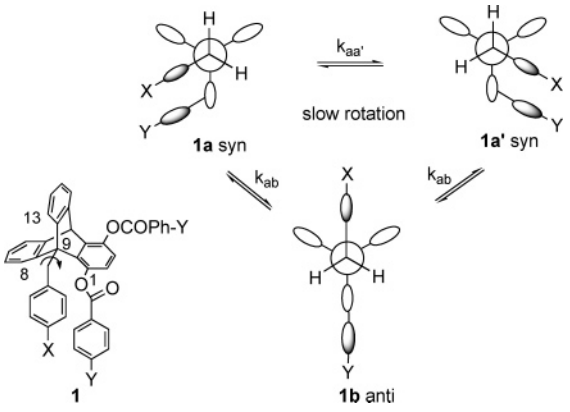


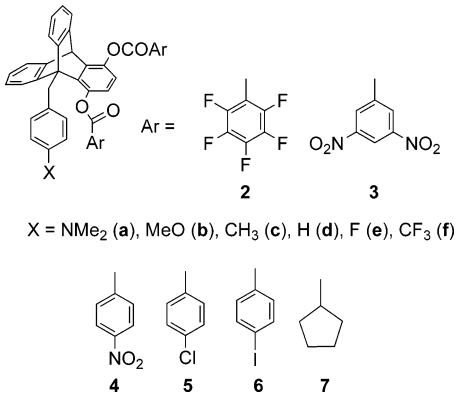
FIGURE 1. Sketches illustrating the *syn* and *anti* conformational isomers derived from 1,9-diaryl-substituted triptycene derivative, **1** (X = H, Me, F, CF_3, Y = NO_2, CN, F, Br, H, Me, MeO).[29]

duced a greater than 200:1 enantioselectivity.[21] In other studies of stereoselective reactions, only electrostatic effects were observed.[4] Despite the fact that charge-transfer complexes have been known for over half a century, it is still uncertain how charge-transfer interactions contribute to π-stacking of aromatic rings. Many chemical model systems have been designed to investigate the edge-to-face geometry of interacting aromatic rings.[22−26] However, few chemical model systems have employed aromatic rings that are strongly electronically perturbed in the parallel-displaced configuration.[11] Recently we employed the 1,9-disubstituted triptycene model system[27,28] in the determination of offset arene−arene stacking interactions, Figure 1.[29] Here we report our observation of charge-transfer effects in the interactions between perfluorophenyl group and a dimethylamino substituted phenyl group in the triptycene model system.

Results

As described in our recent report (Figure 1), the *syn* conformation in the triptycene model allows a stacking interaction between the two arene groups, whereas the *anti* conformation does not. Molecular modeling shows that the attached arenes in the triptycene model system assume the most stable parallel stacked conformation in the *syn* configuration. A statistical 2:1 *syn/anti* ratio is expected when there are no interactions between the C(1) and C(9) groups. A greater than 2:1 *syn/anti* ratio indicates an attractive interaction, while a smaller ratio is indicative of a repulsive interaction. In this study, the *syn/anti* isomeric ratios at −15 °C are determined in $CDCl_3$ and in BrC_6D_5 solutions (Table 1). To explore the rotational barrier around the C(9)−C(benzyl) bond, the rotational rate constants k_{ab} (see Figure 1) have also been determined by using line shape analysis at each temperature (see Supporting Information).[29−31] A barrier of 12.5 ± 0.5 kcal/mol separating the *anti* and the *syn* conformers was calculated using the Eyring equation based on the rotational rate constants for compound **7a**.

TABLE 1. Substituent Effect on Ratios of *syn/anti* Isomers and Free Energies (in parentheses) for Arene−Arene Interactions[a]



entry	compd	X	Ar	*syn*/*anti* ratio ($-\Delta G°_{anti\rightarrow syn}$) (−15 °C) in $CDCl_3$	in BrC_6D_5
1	**2a**	NMe_2	C_6F_5	21.7 (1.22 kcal/mol)	18.5 (1.14 kcal/mol)
2	**2b**	MeO	C_6F_5	16.8 (1.09)	13.9 (0.99)
3	**2c**	Me	C_6F_5	14.4 (1.01)	11.8 (0.91)
4	**2d**	H	C_6F_5	13.7 (0.99)	10.8 (0.86)
5	**2e**	F	C_6F_5	13.5 (0.98)	10.5 (0.85)
6	**2f**	CF_3	C_6F_5	13.5 (0.98)[b]	10.3 (0.84)
7	**3a**	NMe_2	$C_6H_3(NO_2)_2$	>50 (> 1.65)	>50 (> 1.65)
8	**3b**	MeO	$C_6H_3(NO_2)_2$	>50 (> 1.65)	>50 (> 1.65)
9	**3c**	CF_3	$C_6H_3(NO_2)_2$	>50 (> 1.65)	>50 (> 1.65)
10	**4a**	NMe_2	$C_6H_4NO_2$	5.2 (0.49)	5.2 (0.49)
11	**4b**	MeO	$C_6H_4NO_2$	6.0 (0.57)	5.9 (0.55)
12	**4c**	Me	$C_6H_4NO_2$	6.5 (0.6)	6.1 (0.57)
13	**4d**	H	$C_6H_4NO_2$	9.0 (0.77)	6.3 (0.59)
14	**4e**	F	$C_6H_4NO_2$	11.5 (0.90)	6.9 (0.63)
15	**4f**	CF_3	$C_6H_4NO_2$	12.7 (0.93)	7.4 (0.67)
16	**5a**	Me	C_6H_5Cl	2.6 (0.13)	
17	**5b**	H	C_6H_5Cl	3.15 (0.23)	
18	**5c**	F	C_6H_5Cl	3.8 (0.33)	
19	**5d**	CF_3	C_6H_5Cl	5.3 (0.50)	
20	**6a**	Me	C_6H_5I	2.8 (0.17)	
21	**6b**	H	C_6H_5I	3.3 (0.26)	
22	**6c**	F	C_6H_5I	4.0 (0.36)	
23	**6d**	CF_3	C_6H_5I	6.4 (0.59)	
24	**7a**	Me	(c-pentyl)	2.2 (0.05)	
25	**7b**	H	(c-pentyl)	2.5 (0.11)	
26	**7c**	F	(c-pentyl)	2.8 (0.17)	
27	**7d**	CF_3	(c-pentyl)	2.9 (0.19)	

[a] Errors are estimated at ± 0.05 kcal/mol (from an average of two runs). [b] The *syn*/*anti* ratio was 13.3 in CD_2Cl_2 and 10.5:1 in toluene-d_8.

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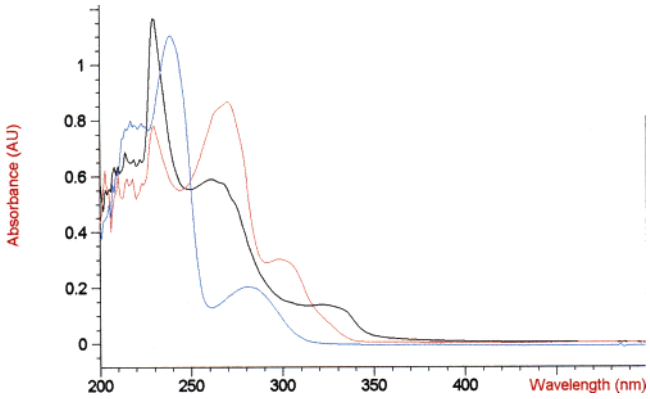


FIGURE 2. Absorption spectra of compound **2a** (black), **8a** (red), and **9** (blue) in CH_2Cl_2. The absorption at 321 nm remains unchanged for compound **2a** at various concentrations from 0.06 to 0.56 mM. Concentration as shown: 0.09 mM.

Our recent study shows that stronger attractive interactions occur between the substituted arenes (**1**, Figure 1) when both X and Y are electron-withdrawing groups (EWGs, for example, X = CF_3 and Y = NO_2).[29] The interactions between arenes bearing electron-donating groups (EDG) are either negligible or slightly repulsive in the triptycene model system (e.g., X = Y = Me), whereas those compounds bearing one arene with an EDG and one with an EWG gave intermediate binding energy.[29] No CT bands were observed for any of the monosubstituted arenes (such as compounds **4**−**7**) studied.[29] Our results obtained using the triptycene model system were consistent with the electrostatic models.[3,6]

Different results are obtained in this study based on quantitative investigations of a series of triptycene compounds (**2**−**7**) bearing a wide range of electron acceptors and donors, including the strong acceptors **2a**−**f** and **3a**−**c** with C(1) pentafluorobenzoate and dinitrobenzoate. As shown in Table 1 (entries 7−9), the strongest attractions (>50:1 *syn/anti* ratio) are observed for compounds **3a**−**c** in $CDCl_3$ as well as in BrC_6D_5. The *anti* isomer was not detectable using 500 MHz ^{1}H NMR.

As a result of competition from interactions with the solvent, the *syn/anti* ratios are smaller in bromobenzene-d_5 than in chloroform. As shown in Table 1, the strongest attractions are exhibited by compounds **2a** and **3a**, where the substituent on the C(9) arene is an *N*,*N*-dimethylamino group. Compound **2f**, where the corresponding substituent is CF_3, displayed the smallest attraction in this series (10.3 *syn/anti* ratio). In contrast to our recent observation,[29] the free energy of interaction increases according to the X-substituent on the C(9) arene in the following order: CF_3 < F < H < Me < MeO < NMe_2.

To gain a better understanding of the structure of the model system, we proceeded to examine the electronic effects of aromatic interactions with a study of electronic absorption spectra. The solution of compound **2a** in CH_2Cl_2 has a yellow color. A charge-transfer band at 321 nm is observed for compound **2a** in CH_2Cl_2, Figure 2. This UV absorption band is absent in the solutions of the

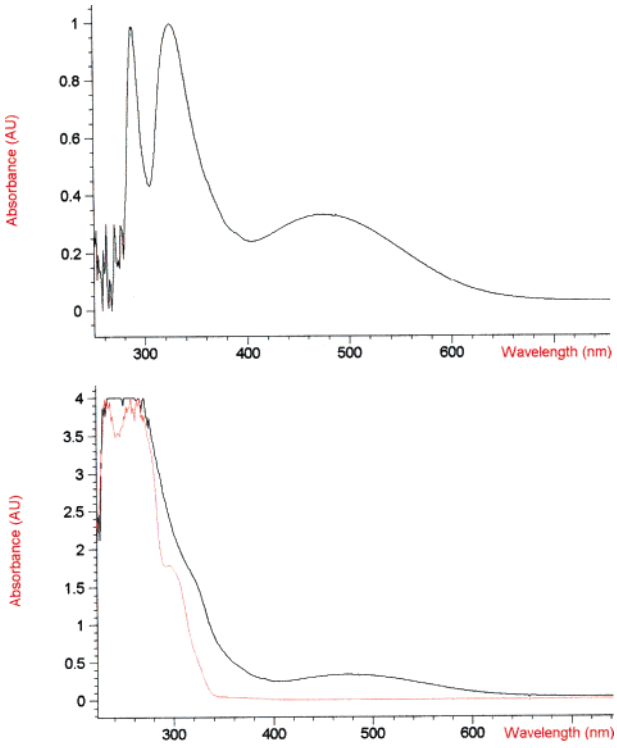
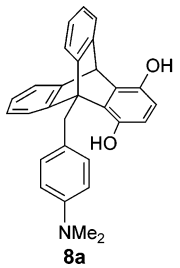
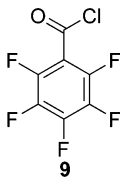


FIGURE 3. Absorption spectra of **3a** in CH_2Cl_2: (top) difference spectrum (0.08 mM) and (bottom) **3a** and its precursor (0.15 mM).

precursors hydroquinone (**8a**) or pentafluorobenzoyl chloride (**9**). Previously, hexafluorobenzene and aromatic



8a



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amines have been reported to form 1:1 complexes, which also exhibit the characteristic UV absorption bands.[32] The assignment of the 321 nm absorption as a CT band was based on a comparison to the previous report for the intermolecular complex between hexafluorobenzene and *N*,*N*-dimethylaminobenzene, which exhibited a CT band at 316 nm.[33]

The CH_2Cl_2 solution of the model compound **3a** has a red color. An overlay of the electronic absorption spectra of **3a** and its precursor (Figure 3, bottom) indicates a new band centered around 475 nm. The extinction coefficient is low, and the band is broad. The presence of the CT band becomes more apparent in the difference spectrum (Figure 3, top). Further evidence supporting the assignment of the 475 nm absorption as a CT band was ascertained by a comparison to a previous report for the intermolecular complex between *s*-trinitrobenzene and

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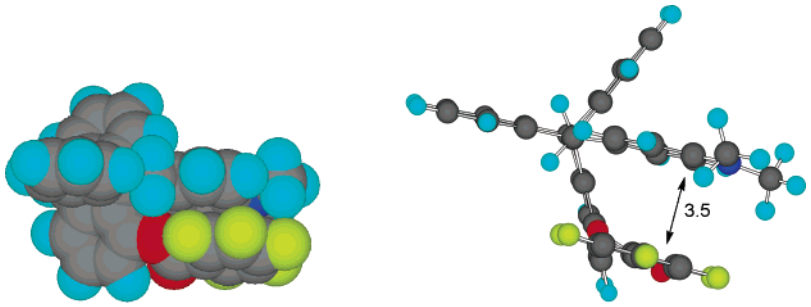

FIGURE 4. Minimum energy conformation of compound **2a** (X = NMe_2) found by MacroModel using MM2 force field:[36] (a) space-filling model and (b) ball-and-stick model. The distance between the arenes is labeled in angstroms.

N,*N*-dimethylaniline. A CT band for the complex was reported to be centered around 487 nm.[18] Compounds **2a** and **3a** are the only models that show charge-transfer bands in our study to date.

Compounds **4a**−**f**, **5a**−**d**, and **6a**−**d** (entries 10−23, Table 1), which have a single arene substituent, exhibit the "normal" substituent effects, i.e., a stronger EWG leads to a higher population of the *syn* conformation. The population of the *syn* isomer for these compounds increases according to the X-substituent in the following order: CF_3 > F > H > Me > MeO > NMe_2. Compounds **4a**−**f** (entries 10−15) have a nitrobenzoate group at C(1). The highest *syn*/*anti* ratio (12.7) was observed for **4f**, where X = CF_3, and the lowest was for **4a** (5.2, X = NMe_2) in $CDCl_3$. Compounds **5a**−**d** and **6a**−**d** exhibit a similar trend. The *syn*/*anti* ratios range from slightly over 2.5 to 6.4 when X changes from a Me group to a CF_3 group (entries 16−23, Table 1).

Compounds **7a**−**d** serve as control as the C(1) benzoate group is replaced with a cyclopentane-carboxylate group. The preference for the *syn* conformation is much less pronounced when the X-substituent changes to CF_3. This is expected because there is no arene stacking interactions in these compounds. The relative weak preference for the *syn* isomer is largely due to a lone pair−π* interaction between the phenolic oxygen and the C(1) arene.[34]

Discussion

As shown in Figure 1, the rotation of the benzyl group at C(9) around the C_{sp3}−C_{sp3} bond gives rise to three rotational minima, one *anti* and two *syn* conformations. In each of these three conformations, the phenyl ring of the benzyl group should be able to rotate around the C_{sp2}-(phenyl)−C_{sp3}(benzylic) bond. However, the phenyl rotation is hindered by the triptycene scaffold hydrogen atoms at C(8) and at C(13) (triptycene numbering) and the oxygen atom at C(1). Thus with regard to the benzyl group at C(9), both the *anti* and the *syn* isomer have only one minimum conformation in which the phenyl group bisects the two blades of the triptycene skeleton. This leads to a symmetrical *anti* conformation in which, although there is no forced contact, the C(9) phenyl group is fit snugly between the triptycene blades. In the *syn* isomer, the stable conformation of the ester function places the pentafluorobenzoate ring parallel to the C(9) benzyl group.[34,35] For a closer look, the global minimum conformation of compound **2a** found by Macromodel is shown in Figure 4.[36] The pentafluorobenzoate ring and the *N*,*N*-dimethylaminobenzyl ring assume the parallel stacked configuration. The interplanar distance is about 3.5 Å.

The Macromodel calculated conformations indicate that the two arenes lie parallel to each other in a stable conformation allowing potential electronic interactions. To study the electronic effects involved in these aromatic interactions, one has to employ ab initio electronic structure calculations on an appropriate model. The Macromodel structures, however, allow one to visualize the interacting aromatic rings and to have a better understanding of the model system. The rigid structure of the triptycene skeleton should leave little room for structure errors even with simple molecular mechanics calculations.

The data in Table 1 demonstrate opposite trends in substituent effects for compounds with pentafluorobenzoate at C(1) (**2a**−**f**) and for compounds with a mononitrobenzoate (**4a**−**f**) or with other singly substituted benzoate groups (**5a**−**d** or **6a**−**d**). We assume that the preference for the *syn* conformation arises from attractive interactions between the two attached arenes because the *anti* conformation is free from steric repulsion. Thus the *syn*/*anti* ratios are related to the free energy of attractive interactions by the following relationship: $\Delta G° = \Delta H° - T\Delta S° = -RT \ln K_{eq} = -RT \ln(1/2 \cdot syn/anti)$. Free energies of arene−arene interactions ($\Delta G°$, T = 258 K) are obtained for compounds **2**−**7**. The free energies of attraction versus σ_{para} are plotted for two series of compounds in Table 1 (**2a**−**f** and **4a**−**f**) to contrast the opposite trends and the nonlinearity in substituent effects for compounds **2a**−**f** (Figure 5). Compound **2a** with a dimethylaminobenzyl group at C(9) has an "abnormally" higher free energy of attraction than the Hammett plot would predict.

The opposite trends shown in Figure 5 may be rationalized by the electrostatic model proposed by Hunter and Sanders.[3,11] Namely, the C(1) pentafluorobenzoate group in **2a** has a positive potential surface that interacts

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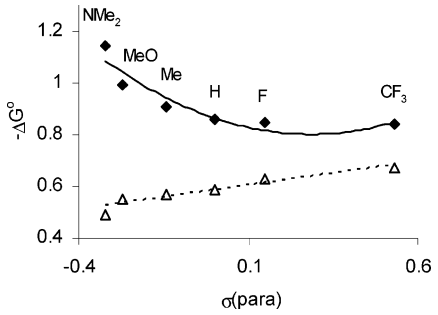

FIGURE 5. Plot of free energy of attraction ($-\Delta G°$) versus σ_{para} for compounds **2a**−**f** (♦) and **4a**−**f** (△). Nonlinearity in substituent effects was observed for compounds **2a**−**f**. Experiments were conducted in BrC_6D_5.

attractively with electron-rich aromatics, and the monosubstituted C(1) benzoate groups in **4a**−**f** has a slightly negative potential surface that interacts attractively with electron-deficient aromatics. However, the nonlinearity in the Hammett plot cannot be explained by a simple electrostatic effect. In a recent theoretical study of aromatic interactions, Sherrill pointed out that electrostatics alone are insufficient to predict the correct trends in binding energy.[37] We propose that charge-transfer interactions contribute significantly to the arene interaction energy exhibited by compounds **2a** and **3a**, which have strongly electronically perturbed aromatic groups. In contrast, charge-transfer effects are negligibly small in other compounds with a monosubstituted benzoate group. Organic charge-transfer complexes are defined as structures involving a usually small contribution from a covalent dative structure in which one electron has been transferred from the donor to the acceptor component of the complex.[18] In compounds **2a** and **3a**, this small contribution from the covalent dative structure appears to operate and to produce an attractive interaction that is in addition to or greater than a simple electrostatic interaction. It seems reasonable to suggest that there is a threshold for charge-transfer effects to occur in aromatic interactions. To reach this threshold, the aromatic system must be strongly perturbed with substituents of opposite polarity on each interacting arene. Thus model compounds **2a** and **3a** have met the requirement for charge-transfer interactions, whereas the rest of the model compounds do not reach the threshold. Most of the previous studies reported in the literature did not employ strongly perturbed aromatic systems. Therefore no charge-transfer interactions have been observed in these studies.

Summary

The electrostatic model traditionally used to describe aromatic interactions is not sufficient for cases where multiple strong donors and acceptors are involved or when charge-transfer interactions are identified for the complexes. We have shown that two groups of compounds behave differently with regard to aromatic interactions in the parallel stacked configuration. One group with monocyclic arenes (such as compounds **4**−**7**) shows a good correlation between the free energy of attraction and Hammett σ_{para} parameters. The other group, in which the aromatic rings are strongly perturbed by multiple substituents, however, has exceptions to this correlation. Charge-transfer interactions are proposed to be the dominant force in the "abnormally behaved" compounds. In theory, the intensity of charge-transfer interactions is inversely proportional to the difference between the ionization potential (IP) of the donor and the electron affinity (EA) of the acceptor.[38] It is therefore not surprising that only the model compounds with a C(1) pentafluorobenzoate (**2a**) and dinitrobenzoate (**3a**) and C(9) dimethylaminobenzyl group exhibit the charge-transfer bands, because these electron-acceptors have relatively high EA (the EA of hexafluorobenzene and some dinitrobenzenes have been reported).[39−42] An additional requirement for charge-transfer interactions to occur is the need for the two arenes to be in a parallel stacked configuration. Any deviation from this configuration may prevent the HOMO−LUMO interactions between the arenes. Recently, Hunter and colleagues reported a study of aromatic interactions involving similarly substituted arenes and charge-transfer effects were not reported.[11] However, as noted by the authors, the geometric constraints of the model system probably prevent the aromatic groups from reaching the minimum energy arrangement. Therefore in order for charge-transfer interactions to occur, the two interacting arenes must be able to adopt a nearly perfect parallel stacked arrangement in addition to being strong electron acceptors and donors. This study does not include aromatic systems with multiple rings or with heteroatoms. Studies on these systems are currently underway in our laboratories.

Experimental Section

Representative Procedure for the Preparation of the Model Compounds. 9-(4′-Dimethylaminobenzyl)-1,4-di-(pentafluorobenzoyl)triptycene (2a). Pentafluorobenzoyl chloride **9** (0.06 mL, 0.4 mmol) was added to a solution of 9-(4′-dimethylaminobenzyl)-1,4-dihydroxytriptycene **8a** (71 mg, 0.2 mmol) in dichloromethane (3 mL) and pyridine (1.5 mL) at 0 °C. The mixture was allowed to stir at 0 °C for 10 min and at room temperature for 6 h, and then 20 mL of water was added to quench the reaction. The precipitate was collected by filtration and washed with water. The crude product was then dissolved in a minimum amount of dichloromethane and precipitated with hexanes to afford the pure product **2a** as a yellow solid (68 mg, 50%): mp 270−271 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (6 H, s), 4.43 (2 H, m), 5.61 (1 H, s), 6.35 (2 H, br), 6.70−7.59 (12 H, br); ^{19}F NMR (188 MHz, $CDCl_3$) δ −136.38 (2 F, br), −138.41 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), −148.13 (1 F, tt, J = 5.6, 20.7 Hz), −149.09 (1 F, br), −160.33 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), −162.66 (2 F, br); HRMS calcd for $C_{43}H_{23}F_{10}NO_4$ + H 808.1545, found 808.1549.

Variable Temperature NMR Procedure. The ^{1}H NMR spectra were recorded on a Bruker 500 MHz instrument with a variable temperature probe. A 0.05 M solution of the sample in a deuterated solvent such as bromobenzene or chloroform was placed in a high quality NMR tube. All samples were

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degassed by passing a stream of nitrogen through the sample for ~1 min. The NMR tube was then capped and sealed with Parafilm. The sample tube was placed into the NMR probe and the airline to the probe was replaced with liquid nitrogen transfer line. The desired temperature was set on the variable temperature unit, and the sample was allowed to equilibrate for ~15 min at each set temperature. Then the ^{1}H NMR spectrum at each temperature was recorded. The *syn/anti* ratios of the conformations were obtained through the integrations of selected peaks.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2a**−**7d** and details of line shape analysis by computer simulation. This material is available free of charge via the Internet at http://pubs.acs.org.

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