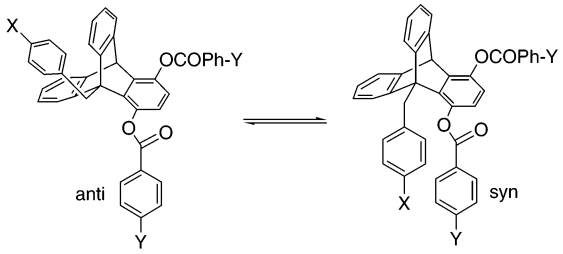
The Strength of Parallel-Displaced Arene−Arene Interactions in Chloroform

Benjamin W. Gung,*,† Xiaowen Xue,† and Hans J. Reich‡

Department of Chemistry & Biochemistry, Miami University, Oxford, Ohio 45056, and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

gungbw@muohio.edu

Received January 10, 2005



Ratio of syn/anti = 16.9 where X = CF_3, Y = NO_2
syn/anti = 1.3 where X = Y = Me

Triptycene-derived compounds have been prepared to serve as conformational equilibrium reporters for direct measurements of arene−arene interactions in the parallel-displaced orientation. A series of such compounds bearing arenes with different substituents were synthesized, and the ratios of the *syn* and *anti* conformers were determined by variable-temperature NMR spectroscopy. The *syn* conformer allows attached arenes to interact with each other while the *anti* conformer does not. The free energies derived from the *syn*/*anti* ratios in chloroform range from slightly positive (0.2 kcal/mol) to considerably negative (−0.98 kcal mol) values. The interactions between the arenes bearing electron-donating groups (EDG) are either negligible or slightly repulsive, while the interactions between arenes bearing electron-withdrawing groups (EWG) are attractive. Intermediate free energy values are obtained for those compounds bearing arenes with one EDG and one EWG.

Introduction

Nonbonded interactions between aromatic molecules contribute significantly to the stability of biological systems.[1] Aromatic stacking interactions are abundant between aromatic amino acid side chains in proteins and have been observed in the complexes of medicinal drugs and the targeted enzymes.[2] Both the edge-to-face and the parallel-displaced orientations were found.[1,3] The biological significance and the progress in the study of arene−arene interactions have been reviewed.[4−6] For synthetic organic chemists, the aromatic ring has long been suggested to play a significant role in enhancing stereoselectivity. In the pioneering work on asymmetric induction, Corey showed the importance of the phenyl ring in his 8-phenylmenthol chiral auxiliary.[7] Subsequently, aromatic rings have been suggested to selectively shield diastereofaces in many reactions.[8,9] Evans was able to provide compelling evidence that π facial differentiation, although controlled largely by steric effects, is enhanced by $\pi-\pi$ interactions.[8]

Results and Discussion

Despite the important role played by aromatic stacking interactions, the magnitude of individual arene−arene interactions has been addressed mainly by computational

---

† Miami University.

‡ University of Wisconsin. E-mail: (H.J.R.) reich@chem.wisc.edu.

(1) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23−28.

(2) Kryger, G.; Silman, I.; Sussman, J. L. *J. Physiol.−Paris* **1998**, *92*, 191−194.

(3) McGaughey, G. B.; Gagne, M.; Rappe, A. K. *J. Biol. Chem.* **1998**, *273*, 15458−15463.

(4) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651−669.

(5) Waters, M. L. *Curr. Opin. Chem. Biol.* **2002**, *6*, 736−741.

(6) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210−1250.

(7) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908−9.

(8) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

(9) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999−8016.

10.1021/jo050049t CCC: $30.25

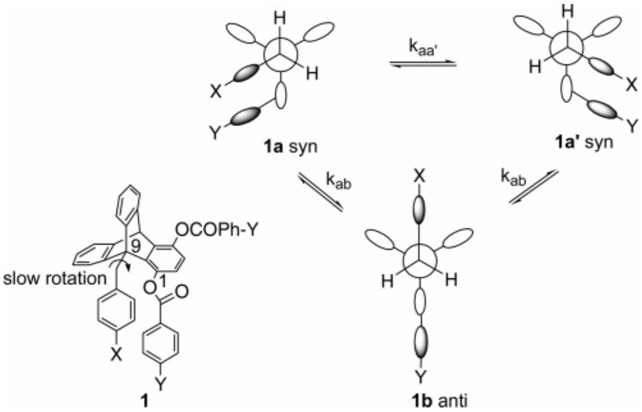
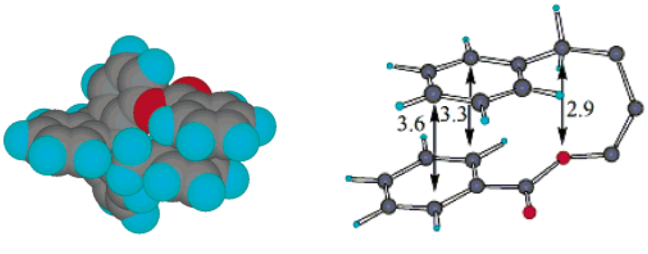


FIGURE 1. Sketches illustrating the *syn* and *anti* conformational isomers derived from 1,9-diaryl-substituted triptycene derivative **1** (the sketch is a modified version of the drawing by Oki).[10]



(a) (b)

FIGURE 2. Computer-generated minimum conformation for compound **1** ($X = Y = H$) using MacroModel:[12] (a) space-filling model and (b) cylindrical bonds model with the triptycene skeleton omitted for clarity.

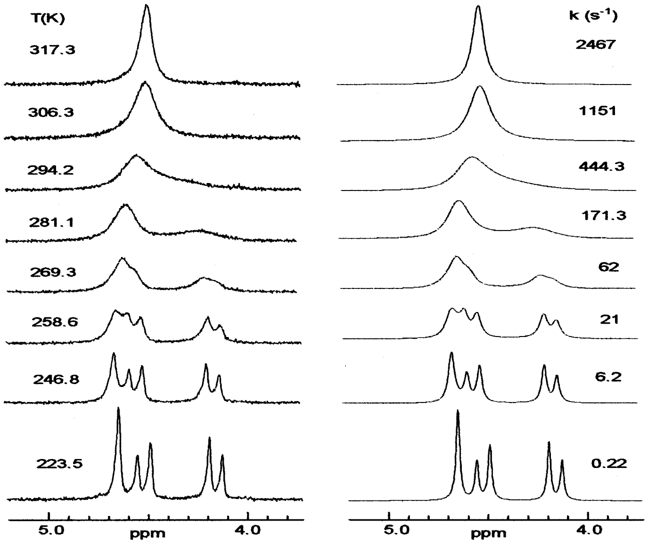


FIGURE 3. Experimental (left column) and simulated (right column) ^{1}H NMR spectra for the benzylic CH$_2$ protons of compound **9f** at different temperatures. Simulation was done using WINDNMR[14] to give rate constants k_{ab} at the corresponding temperature. From the rate constants k_{ab}, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were extracted by plotting $\ln(k/T)$ vs $(1/T)$. For compound **9f**, $\Delta H^{\ddagger} = 13.3 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -1.1 \pm 0.5$ cal mol^{-1} K^{-1}.

studies.[6] To our knowledge, there are no specific experimental methods to directly determine the magnitude of parallel displaced arene−arene interactions thus far. We have found, through molecular modeling and experimental studies, that modified triptycene-derived compounds can be used to directly measure the strength of arene−arene interactions in the parallel-displaced configuration in organic solvents. Oki and co-workers pioneered the use of the triptycene molecular system in the study of weak molecular interactions.[10,11] No work related to π-stacking, however, has been reported using this system. The conformational equilibrium between the symmetrical *anti* form and the chiral *syn* forms in the triptycene molecular system (**1**, Figure 1) can be measured by low-temperature NMR spectroscopy by taking advantage of the slow rotation of the C9-benzyl carbon−carbon bond in compound **1**.

At around −30 °C, the rotation around the C(9)-benzyl carbon bond becomes sufficiently slow that the signals for the *syn* and *anti* conformations decoalesce, with the former becoming an *AB* quartet and the latter a singlet, Figure 3. Therefore the benzyl CH$_2$ group serves as a *conformational equilibrium reporter* for the triptycene molecular models. In a pure statistical state, a *syn*/*anti* ratio of 2:1 should be observed when there is no interactions between the arenes at C(1) and C(9). The attractive interactions should lead to a higher than 2:1 *syn*/*anti* ratio while the repulsive interactions lead to a smaller than 2:1 *syn*/*anti* ratio. Thus, the *syn*/*anti* ratio determined at low temperature provides a measure of the interactions between the two attached aryl groups, Figure 2. This model system probes the interaction of two attached arenes in the parallel displaced, rather than the edge-to-face orientation according to molecular modeling studies using MacroModel.[12] The global minimum for compound **1** with $X = Y = H$ is shown in Figure 2. The alternative T-shape orientation is prohibited by the triptycene skeleton. Due to the constraint from the tether, the two interacting arenes are not perfectly parallel as indicated in Figure 2b. However, the minimum conformation is similar to the benzene dimer configuration predicted by computational studies with an interplanar distance of 3.3−3.6 Å and a displacement of 1.6−1.8 Å.

A group of such *conformational equilibrium reporters* have been prepared (**7a**−**10d**, Scheme 1). Four series of the substituted 1,9-diaryltriptycene were studied in which the X-substituents are H, Me, F, and CF$_3$ for compound series **7**, **8**, **9**, and **10**, respectively. By using variable-temperature NMR, we have determined the *syn*/*anti* isomeric ratios at −40 °C (Table 1) in CDCl$_3$ solutions. The rate constants k_{ab} (see Figure 1) have been determined by using line shape analysis at each temperature.[13,14] The simulation involves two independent rate constants (Figure 1), the conversion of the *syn* isomers to the *anti*, k_{ab}, and the interconversion between the two enantiomeric syn conformers ($k_{aa'}$). Excellent simulations

---

[10] Oki, M. *Acc. Chem. Res.* **1990**, *23*, 351−356.

[11] Oki, M.; Nishino, M.; Kaieda, K.; Nakashima, T.; Toyota, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 357−361.

[12] Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

[13] Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, U.K., 1982.

[14] Reich, H. J. In *WinDNMR: Dynamic NMR Spectra for Windows*; *J. Chem. Educ.* Software, 1996−2003; p 3D2. For an updated version see: http://www.chem.wisc.edu/areas/reich/plt/winplt.htm.

SCHEME 1

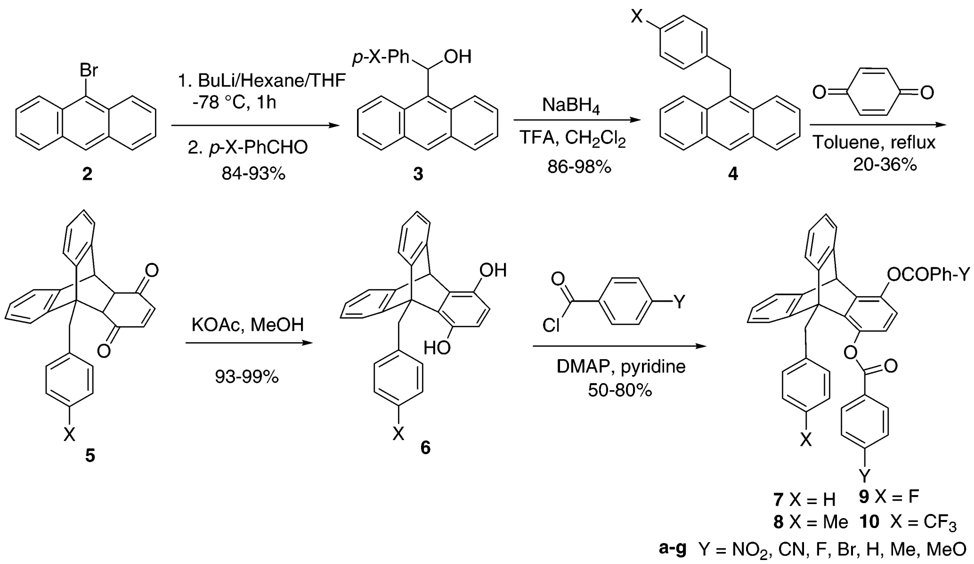
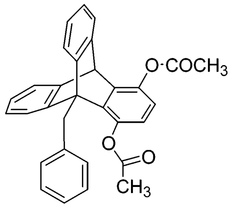


TABLE 1. Substituent Effect on the Ratios of *Syn/Anti* Isomers and the Free Energies for Arene–Arene Interactions in $CDCl_3$[a]

entry	compd	X	Y	ratio (syn/anti)	$\Delta G°$ (-40 °C)$_{anti\rightarrow syn}$ (kcal/mol)
1	**7a**	H	NO_2	9.1	-0.69 ± 0.05
2	**7b**	H	CN	6.4	-0.55
3	**7c**	H	F	2.9	-0.17
4	**7d**	H	Br	3.3	-0.24
5	**7e**	H	H	1.9	0.02
6	**7f**	H	Me	1.5	0.14
7	**7g**	H	MeO	1.7	0.07
8	**8a**	Me	NO_2	6.7	-0.55
9	**8b**	Me	CN	4.4	-0.36
10	**8c**	Me	F	2.5	-0.10
11	**8d**	Me	Br	3.0	-0.19
12	**8e**	Me	H	1.6	0.10
13	**8f**	Me	Me	1.3	0.20
14	**8g**	Me	MeO	1.4	0.17
15	**9a**	F	NO_2	11.9	-0.84
16	**9b**	F	CN	8.4	-0.67
17	**9c**	F	F	3.3	-0.24
18	**9d**	F	Br	3.8	-0.29
19	**9e**	F	H	2.5	-0.10
20	**9f**	F	Me	2.1	-0.02
21	**9g**	F	MeO	2.3	-0.07
22	**10a**	CF_3	NO_2	16.9	-0.98
23	**10b**	CF_3	F	7.4	-0.60
24	**10c**	CF_3	Me	3.1	-0.22
25	**10d**	CF_3	MeO	3.7	-0.29
26	**11**	H	n/a	3.3	-0.24



11

[a] The errors are estimated at ±0.05 kcal/mol.

can be achieved with $k_{aa'}$ set to zero (see Figure 3), so we conclude that this process is negligibly slow in this system. This is reasonable, since this process requires the two large groups to pass each other. The barrier separating the *anti* and the *syn* conformers has been calculated using the Eyring equation based on the rotational rate constants.

The *anti* conformation is less congested sterically. Therefore the preference for the *syn* conformation must arise from attractive interactions between the two attached groups. The *anti* conformer does not allow interactions between the two attached groups. In this study, the population of the *syn* isomer is dependent on both the X- and the Y-substituents and decreases in the following order in terms of the Y-substituent, NO_2 > CN > Br > F > H > MeO > Me, and in the following order based on the X-substituent: CF_3 > F > H > Me.

Negligible temperature dependence of the *syn/anti* ratios was observed for the majority of the compounds in Table 1 and an increase in the population of the *syn* conformation at lower temperatures was only observed for the compounds with large *syn/anti* ratios (e.g., **10a**). By using the equation: $\Delta G = \Delta H - T\Delta S = -RT \ln K_{eq} = -RT \ln(^1/_2 syn/anti)$, free energies ($\Delta G$, $T = 233$ °K) are obtained for compounds **7a**–**11**, Table 1. In general, the interactions between the two arenes are attractive when both X and Y are electron-withdrawing groups (EWG) and repulsive when both X and Y are electron-donating groups (EDG). The magnitude of the arene-arene interactions observed in this study is smaller than the reported computational values for benzene dimers in the gas phase (~ -2 kcal/mol).[15,16] However, they are in line with the limited a few experimental observations.[17–19] The difference between the current study and a previous study using a "torsional balance" is the arene orientation and the substituent effects. In the previous studies with an edge-to-face model,[20] no difference in the strength of

---

(15) Sinnokrot, M. O.; Valeev, E. F.; Sherrill, C. D. *J. Am. Chem. Soc.* **2002**, *124*, 10887–10893.

(16) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104–112.

(17) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498.

(18) Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res.* **2001**, *34*, 885–894.

(19) McKay, S. L.; Haptonstall, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 1244–1245.

(20) Kim, E.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193.

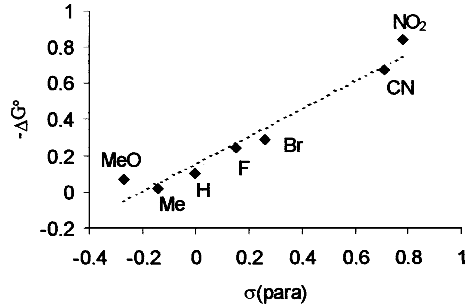


FIGURE 4. Plot of free energy of attraction ($-\Delta G°$) vs σ_{para} for compounds **9a**−**g**. Experiments were conducted in $CDCl_3$.

aromatic interactions was observed as a function of arene substitution. The current study documents a greater attractive force in the parallel-displaced orientation and a significant difference in strength of interactions as a function of substitution (see Figure 4).

Polar/π (dipole−dipole, dipole−multipole, and van der Waals) forces, not charge-transfer (CT), have been suggested to be responsible for aromatic stacking interactions.[8,21−23] The current study supports these conclusions. No forced contact exists in either the *syn* or the *anti* isomers in the current study. Therefore, the preference for the *syn* conformation is entirely due to attractive interactions. The arenes that show the strongest attractive interactions are X = CF_3 and Y = NO_2 ($\Delta G = -0.98 \pm 0.05$ kcal/mol, entry 22, Table 1). Compounds **7a**−**g** with X = H (entries 1−7, Table 1) should be a reasonable model for the amino acid side chain of phenylalanine (Phe). Our results show attractive interaction between the two arenes if the other arene is substituted with an EWG and repulsive interaction with EDG (entries 1−7, Table 1). This indicates that in the parallel displaced orientation a favorable arene-arene interaction should occur with the side chain of Phe if the other arene is electron poor, such as a protonated arene. The control compound **11** shows a small preference for the *syn* conformation indicating there is a small attractive interaction between the acetyl group and the benzene ring ($\Delta G = -0.24 \pm 0.05$ kcal/mol, entry 26, Table 1). This weak interaction is most likely due to a lone pair−π^* attraction between the phenolic oxygen and the benzyl aromatic ring. For compounds **7**−**10**, this lone pair-π^* interaction is prohibited by the parallel arrangement of the two attached arenes. Another possibility involves a CH−π interaction, which has not been ruled out. More studies are being conducted to identify the origin of this weak attraction.

Conclusions

This study has shown that the current system works well in directly determining individual attractive interactions between arenes in the offset-stacked orientation. The current results can be used in conjunction with computational studies to evaluate the magnitude of arene−arene interactions in solution. With a better knowledge of the magnitude of arene−arene interactions, it is possible to achieve a better understanding of the contributions from arene−arene interactions in molecular recognition involving biological macromolecular systems. The current results are consistent with several recent studies that polar/π forces are responsible for aromatic stacking interactions. However the current study does not rule out the possibility of charge-transfer interactions if the aromatic systems are strongly different in electron density. Extension of this system to the study of π−π interactions with strongly electron-deficient and -rich arenes is currently under way in our laboratories.

Experimental Section

A. Preparation of the Triptycene Derivatives. The triptycene derivatives were prepared as shown in Scheme 1 following previously published procedures for similar compounds.[24−28] For general preparations and NMR spectroscopic data, see the Supporting Information.

B. Variable-Temperature NMR Procedures. 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 deuterated chloroform was placed in a high quality NMR tube. All samples were degassed by passing nitrogen through the sample for ~1 min. The NMR tube was then capped and sealed with Parafilm. The temperature of the NMR probe was calibrated using a ^{13}C internal thermometer.[29] The process involves recording the ^{13}C NMR spectrum of tris(trimethylsilyl)methane ($(TMS)_3CH$) immediately before or after a ^1H NMR spectrum was recorded.[29] Actual sample temperature was determined from the calibration equation for $CDCl_3$: T (°C) = 84.711 ($\Delta\delta$) − 36.5, in which $\Delta\delta$ is the ^{13}C chemical shift difference in ppm between the methyl and the methine carbons of $(TMS)_3CH$.[29]

Acknowledgment is made to the donors of the Petroleum Research Fund (PRF #36841-AC4) administered by the American Chemical Society.

Supporting Information Available: Experimental procedures for the preparation of compounds **5a**−**10d** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050049T

---

[21] Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729−5733.

[22] Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330−5331.

[23] Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem.* **2003**, *1*, 157−162.

[24] Effenberger, F.; Niesert, C. P. *Synthesis—Stuttgart* **1992**, 1137−1144.

[25] Ogata, F.; Takagi, M.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1981**, *103*, 1145−1153.

[26] Oki, M.; Izumi, G.; Yamamoto, G.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 159−166.

[27] Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762−3768.

[28] Cunningham, B. D. M.; Lowe, P. R.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1275−1283.

[29] Sikorski, W. H.; Sanders, A. W.; Reich, H. J. *Magn. Reson. Chem.* **1998**, *36*, S118−S124.