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Off-Center Oxygen−Arene Interactions in Solution: A Quantitative Study

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

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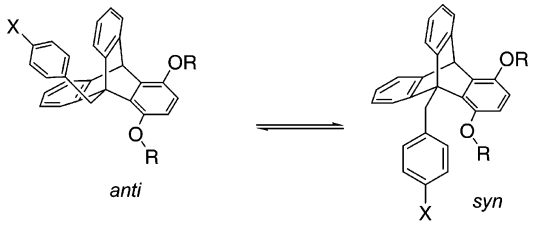

Ratio of *syn/anti* = 5.5 where X = CF_3, R = CH_3
syn/anti = 1.7 where X = H, R = $COCF_3$

Triptycenes with C(1)−MeO/RCOO (R = H, Me, Et, *i*-Pr, CF_3) and C(9)−$XC_6H_4CH_2$ (X = Me, H, F, CN, CF_3) have been prepared to determine lone pair−arene interactions in the off-center configuration. The ratios of the syn and anti conformers were determined by low-temperature NMR spectroscopy. The syn conformer allows the attached arene and the MeO/ester to interact with each other while the anti conformer does not. The free energies of interaction have been derived from the syn/anti ratios. Compound **7** in the ester series with X = H and R = CF_3 is the only compound that shows a slightly repulsive interaction (0.08 kcal/mol). Compound **2e** in the MeO series with X = CF_3 exhibits an attractive interaction (−0.47 ± 0.05 kcal mol). All other compounds show smaller attractive interactions.

Introduction

Noncovalent interactions involving aromatic rings are key processes in chemical and biological recognition.[1] These include $\pi-\pi$ interactions such as base pair stacking in DNA[2,3] and aromatic residue interactions in proteins[4−7] and cation−π and lone pair (lp)−π interactions.[8−13] While the concept of attractive lp−π interaction is counterintuitive, this type of attraction was observed as early as 1975.[14] More recently, crystallographic evidence has been provided for the stabilizing influence of sugar O4′ (lp)−π (nucleobase) intramolecular interactions and H_2O (lp)−π (cytosine) interaction in an RNA pseudoknot.[10,15−17] Recent ab initio studies indicate that lp−π interaction is favorable with electron-deficient π-systems.[8,9,18] Scheiner has shown that water prefers the lp−π approach instead of the OH−π interaction in the case of the

† Miami University.
‡ University of Wisconsin.

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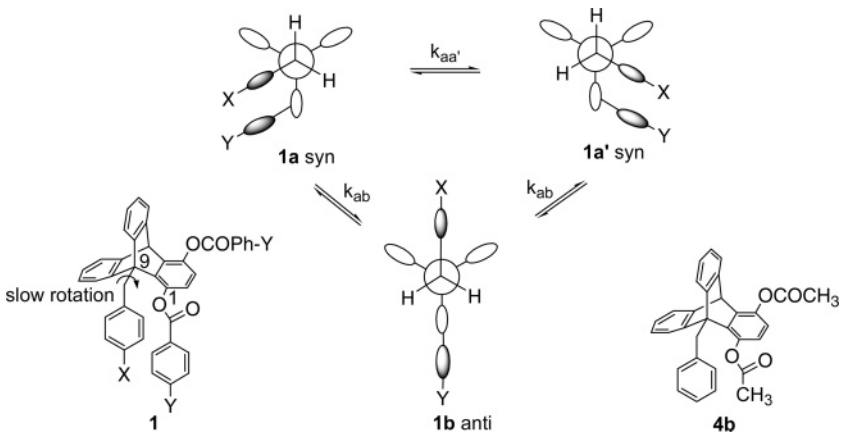
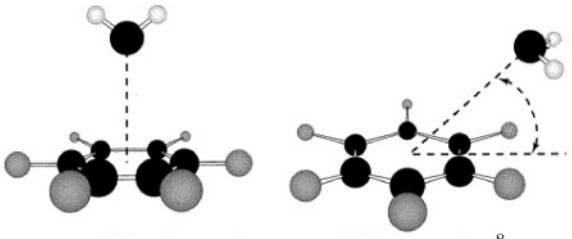


FIGURE 1. Equilibra among the syn and the anti conformational isomers of 1,9-disubstituted triptycene derivative, **1** (X = H, Me, F, CF_3; Y = NO_2, CN, F, Br, H, Me, MeO). (The sketch is a modified version of the drawing by Oki.)[20]

protonated imidazole.[9] The complex of hexafluorobenzene and H_2O was also found to prefer the lp−π approach.[8,18] Two structures of similar binding energy were located at the MP2/6-31G** level of theory, one of which has an off-axis H_2O molecule with the oxygen atom close to the edge of the π-system.[8]



Hexafluorobenzene-H_2O complex[8]

Although mounting evidence continues to accumulate, many unknowns remain concerning lp−π interactions. There are only a relatively small number of studies concerned with this topic compared to studies devoted to aromatic−aromatic interactions. The magnitudes of lp−arene interactions have been estimated by computational methods only. Experimental studies aimed at the strength of lp−arene interactions are practically unknown. The substituent effects have not been studied on either the aromatic ring or its interacting partner. In our recent study of Roush's allylation reaction, an attractive interaction between the ester oxygen lone pair and the boron-coordinated aldehyde carbonyl carbon was found to play a key role in controlling enantioselectivity.[19] In this report, we describe a quantitative study of an off-center arene−lone pair interaction using the triptycene model system.[20]

Results

Recently we have used the 1,9-disubstituted triptycene system[20,21] in the determination of arene−arene interactions, **1** (Figure 1).[22] As a control compound, **4b** was also studied, and a small attractive interaction was observed

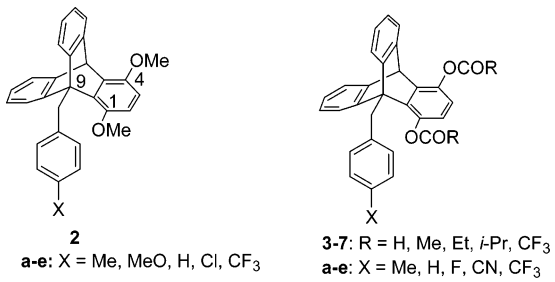


FIGURE 2. 1,9-Disubstituted triptycene derivatives used in this study.

between the acetate group and the phenyl ring. Possible origins of this attraction include CH−π interactions, dipole(C=O)−dipole/quadrupole (arene) interactions, and lp−π interactions. Compounds **2b**−**d** were reported by Oki in 1975, and small attractive interactions were observed.[14] An lp−π interaction was suggested but not confirmed. To understand the origin of the attractive interactions in **4b**, we have now investigated a series of triptycene compounds (**2**−**7**) that have a substituted arene at C(9) and a methoxy or an ester group at C(1) (Figure 2). The syn conformation of the triptycene system allows an attractive interaction between the C(1) and C(9) groups, while the anti conformation does not (Figure 1).

At around −40 °C, the rotation around the C(9)−benzyl carbon bond in **2**−**7** 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 (see SI for details). The benzyl CH_2 group serves as an effective *conformational equilibrium reporter*. A statistical 2:1 syn/anti ratio is expected when there is no interaction between the C(1) and C(9) groups. An increase in the syn/anti ratio can be interpreted as stabilization of the syn conformer and/or destabilization of the anti conformer, while a decrease in the syn/anti ratio is indicative of a repulsive interaction in the syn conformation and/or an attractive interaction in the anti conformation.

Compounds **2**−**7** were prepared as previously reported with minor modifications.[22] Variable temperature NMR

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TABLE 1. Substituent Effect on the Ratios of syn/anti Isomers and the Free Energies for Arene−Lone Pair Interactions[a]

entry	compd	R (C1 ester)	X (C9 arene)	ratio (syn/anti)	$-\Delta G°$ (-40 °C)$_{anti\rightarrow syn}$ (kcal/mol)
1	**2a**	(MeO)	Me	2.3	0.07 ± 0.05
2	**2b**	(MeO)	MeO	2.4[b]	0.08
3	**2c**	(MeO)	H	3.3	0.23
4	**2d**	(MeO)	Cl	3.5[b]	0.26
5	**2e**	(MeO)	CF_3	5.5	0.47
6	**3a**	H	Me	2.4	0.08
7	**3b**	H	H	2.9	0.17
8	**3c**	H	F	3.2	0.22
9	**4a**	Me	Me	2.9	0.17
10	**4b**	Me	H	3.2	0.22
11	**4c**	Me	F	3.7	0.28
12	**4d**	Me	CN	3.9	0.31
13	**4e**	Me	CF_3	3.5	0.26
14	**5a**	Et	Me	3.3	0.23
15	**5b**	Et	H	3.7	0.28
16	**5c**	Et	F	3.9	0.31
17	**5d**	Et	CN	4.2	0.34
18	**5e**	Et	CF_3	4.4	0.36
19	**6a**	*i*-Pr	Me	2.4	0.08
20	**6b**	*i*-Pr	H	2.7	0.14
21	**6c**	*i*-Pr	F	3.1	0.20
22	**6d**	*i*-Pr	CN	3.3	0.23
23	**6e**	*i*-Pr	CF_3	3.4	0.25
24	**7**	CF_3	H	1.7	−0.08

[a] Errors are estimated at ± 0.05 kcal/mol. Experiments were conducted in $CDCl_3$. [b] Reference 14.

experiments were performed from −55 to 25 °C in chloroform. As shown in Table 1, all compounds except **7** (R = CF_3) prefer the syn conformation to some extent despite the fact that the anti conformation is less crowded. The highest syn/anti ratio (5.5:1) was found for compound **2e**, where the interactions are between a *p*-$CF_3C_6H_4$ at C(9) and a MeO group at C(1). Within this series (**2a**−**e**, entries 1−5, Table 1), **2a** with a $CH_3C_6H_4$ at C(9) shows the smallest syn/anti ratio (2.3:1). The trend is apparent, that is, electron-withdrawing groups lead to a higher syn/anti ratio. The same trend is also observed when the MeO group at C(1) is replaced with an ester group (entries 6−23, Table 1). The syn/anti ratio increases as a function of the aryl substituent X according to the following order: Me < H < F < CN ≈ CF_3. The slope of the trend line is greater when the C(1) substituent is a MeO group than when it is an ester group (Figure 3). For example, the syn/anti ratio increases 139% from 2.3 to 5.5 (corresponding to a free energy change from 0.07 to 0.47 ± 0.05 kcal/mol) when the arene substituent X in **2** changes from a methyl group to a CF_3 group. The syn/anti ratio increase is 33% from 3.3 to 4.4 (corresponding to a free energy change from 0.23 to 0.36 ± 0.05 kcal/mol) for the same change in X in **5**. In other words, the syn/anti ratio in the ester series is not as sensitive to the aryl substituent X as in the MeO series (see Figure 3).

In the ester series (**3a**−**7**), the α group R is also varied to study the origin of the attractive interactions. There are small but clear differences in syn/anti ratios with the same aryl X substituent but a different alkyl R group attached to the carbonyl. For example, when X = H (**3b**, **4b**, **5b**, **6b**, and **7**, entries 7, 10, 15, 20, and 24, Table 1), the syn/anti ratio increases as a function of the group R

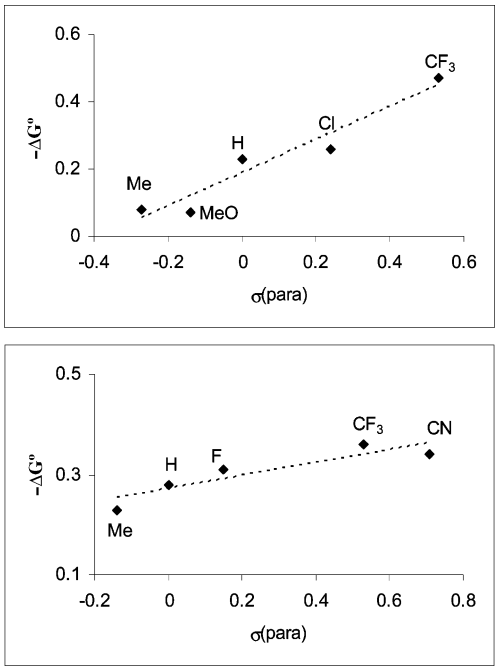


FIGURE 3. Plot of free energy of attraction ($-\Delta G°$, kcal/mol) vs σ_{para} for compounds **2** (top) and **5** (bottom). The slope of the trend line is greater when the C(1) substituent is a MeO group (top) than when it is an ester group (bottom). Experiments were conducted in $CDCl_3$.

TABLE 2. Observed Chemical Shifts for the Alkyl Groups at C1 and C4 in Compounds 3b−6c

		chemical shifts (δ, ppm)		
			−OCOR at C1 (ppm, shielded)	
compd	R	−OCOR at C4 (ppm)	23°	−40°
3b	H	8.44 (s)	4.64 (s)	4.71 (s)
4b	CH_3	2.50 (s)	1.67 (b)	1.44 (s)
5b	CH_2CH_3	CH_2: 2.78 (q)	2.0 (b)	1.87, 1.47 (AB_m)
		CH_3: 1.44 (t)	0.97 (b)	0.74 (t)
6b	$CH(CH_3)_2$	CH: 3.0 (m)	2.20 (b)	1.73 (m)
		CH_3: 1.51 (d)	1.07 (b)	1.0 (3H, d), 0.60 (3H, d)
3c	H	8.44 (s)	4.52 (s)	4.88 (overlap)
4c	CH_3	2.48 (s)	1.73 (b)	1.53 (s)
5c	CH_2CH_3	CH_2: 2.78 (q)	2.05 (b)	1.94, 1.54 (AB_m)
		CH_3: 1.43 (t)	0.98 (b)	0.78 (t)
6c	$CH(CH_3)_2$	CH: 3.03 (m)	2.20 (b)	1.81 (m)
		CH_3: 1.52 (d)	1.14 (b)	1.0 (3H, d), 0.67 (3H, d)

(see structures **3**−**6**, Figure 2) according to the following order: CF_3 < *i*-Pr < H < Me < Et.

In addition to the splitting pattern changes of the C(9) benzyl CH_2 (see SI for details), the chemical shifts of the α R group in compounds **3**−**7** also change during VT NMR experiments. A comparison of the chemical shift changes for the R groups located at C(1) and at C(4) is shown in Table 2. The chemical shifts for the R group at C(4) remained constant, while the NMR peaks for the R group at C(1) moved increasingly upfield as the probe temperature was decreased for compounds **4**−**6**. Compounds **3b**,**c** have the most dramatic differences (nearly 4 ppm) in the chemical shifts of the formyl protons. The chemical shifts of the C(1) formyl proton in **3b**,**c** do not change with temperature, indicating little change in conformation. The CH_2 protons of the ethyl group in compounds **5b**,**c** (Table 2) become nonequivalent at −40

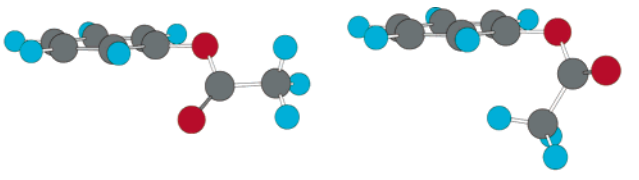
°C, and the isopropyl group in **6b**,**c** also exhibits two sets of diastereotopic CH_3 peaks, indicating dynamic conformational behavior of the ethyl and isopropyl groups. The NMR data indicate that the R group at C(1) is located in the cone area of the C(9) aromatic ring, thus providing additional support for the syn conformation. As discussed later, the dramatic differences in chemical shifts between C(1) and C(4) R groups are due to the shielding effect from the C(9) arene and the limited conformational freedom for the syn conformer. The R group is located near the center of the C(9) arene in the syn conformer. The next isomeric syn conformation, which moves the R group away from the C(9) arene, is ∼4.5 kcal/mol higher in energy.[23]

Discussion

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_{sp3}(benzylic)−C_{sp2}(phenyl) bond. However, the phenyl rotation is hindered by the triptycene scaffold hydrogen atoms at C(8) and at C(11) 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 the C(9) phenyl group is fit snugly between the triptycene blades but has no forced contact. This conformation also puts the para-substituent X away from contacts with the triptycene skeleton.

According to MacroModel (MM2) calculations, the distance between C(1′) of the phenyl group and the triptycene skeletal hydrogen atoms at C(8) and at C(11) is 2.7 Å in the anti conformation. This contact is shortened to 2.65 Å in the syn conformation because the C(1) oxygen atom pushes the phenyl ring slightly toward C(8) or C(11). The distance between C(1) oxygen atom and C(1′) of the phenyl group is ∼2.8 Å. Thus, sterically the anti conformation is less crowded. Furthermore, the C(8) and the C(11) hydrogen atoms are near the edge of the C(9) phenyl ring in the anti conformation. Thus, the CH−π type of interactions are not important here considering the quadrupole moment of benzene places the π-clouds in the center of the aromatic ring.[24] Therefore, we conclude that a greater than 2:1 syn/anti ratio is indicative of attractive interactions in the syn conformation, not repulsive interactions in the anti conformation.

With respect to the C(1) ester conformation in the triptycene system, a recent computational study of phenyl acetate provides some useful information.[23] Two conformational minima, *s*-cis and *s*-trans, were found for phenyl acetate.



Phenyl acetate: *s*-trans (0.0) *s*-cis (4.49 kcal/mol)

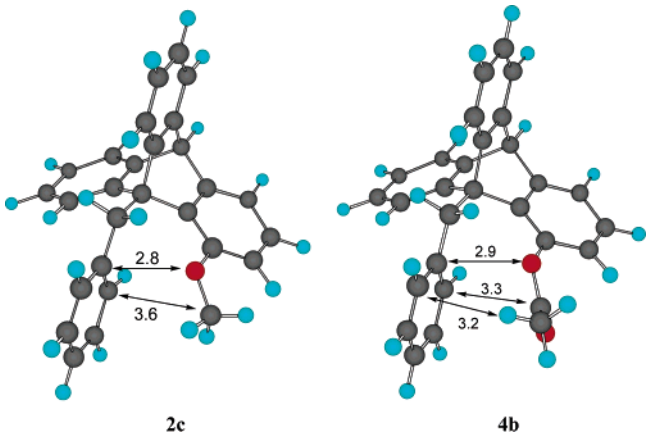


FIGURE 4. Computer-generated minimum conformation for compounds **2c** (X = H) and **4b** (X = H, R = Me) using MacroModel(MM2).[25] The distance between the oxygen atom and the carbons is labeled in angstroms.

The *s*-trans conformer is the one in which the carbonyl group (C=O) is anti to the lone pair electrons of the phenolic oxygen, and it is more stable than the *s*-cis isomer by 4.5 kcal/mol at the B3LYP/6-3111*//B3LYP/6-31G* level of theory. Furthermore, the acetyl group assumes a near-perpendicular arrangement with regard to the phenyl ring. This is consistent with the minimum conformation found by MacroModel in this study. Namely, the ester function is near-perpendicular to the triptycene skeleton ring and parallel to the C(9) phenyl group. Thus, both the anti and the syn conformations in the triptycene system employed in this study have one conformation that is considerably (∼4.5 kcal/mol) more stable than other conformational isomers. This reduces the complexity for the interpretation of the results. We may concentrate on the low-energy conformers calculated by MacroModel shown in Figure 4.

From the substituent effects shown by data collected in Table 1, the syn/anti ratio is proportional to the degree of electron deficiency of the C(9) aromatic ring and to the electron density of the C(1) oxygen atom (entry 5, Table 1). This indicates that the dominant interaction is between the partial negative charge (or lp) on oxygen and the positive potential of the aromatic ring. In the triptycene model, the C(1) oxygen atom is constrained to be near the edge of the C(9) arene in the syn conformation (Figure 4). The distance between the oxygen atom and the nearest carbons in the arene is shorter than the sum of van der Waals radii of 3.27 Å (O = 1.52 Å and C = 1.75 Å).[26]

Dougherty has located two structures of similar binding energy for the complex of hexafluorobenzene and H_2O.[8] One of them has the H_2O molecule off the axis of the hexafluorobenzene with the oxygen atom close to the edge of the π-system.[8] This structure places the oxygen atom in a similar juxtaposition to the syn conformation shown in Figure 4 and has a calculated gas-phase binding

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energy of 3.77 kcal/mol at the MP2/6-31G** level of theory.[8] Our study was carried out in chloroform solution. The strongest binding energy was determined for **2e** (X = CF_3) at 0.47 ± 0.05 kcal/mol. It is expected that the attraction is much smaller since the aromatic ring in **2e** is not nearly as electron-deficient as hexafluorobenzene. Furthermore, the solvent chloroform is expected to attenuate the lp−arene interaction by competitively forming weak CH−O hydrogen bonds to the oxygen in discussion.[27]

There was no charge-transfer band in the UV spectrum of compound **2e**. Therefore, the origin of the attraction appears to be electrostatic interactions. Previous studies have shown that for arene−lp interactions to be attractive, the aromatic π-system must be electron-deficient.[8,9] However, compounds **2a** and **2b**, which bear an electron-donating group on the C(9) arene, prefer the syn conformation although only to a small degree (entries 1 and 2, Table 1). Considering the short distance between the MeO oxygen and the C(9) aromatic ring, it is counterintuitive that the interaction is not repulsive in the syn conformation of **2a** and **2b** (syn/anti ratio: 2.3−2.4:1). The answer may come from considering the structure of benzene. Benzene has a large, permanent quadrupole moment,[24] such that there is substantial negative electrostatic potential above and below the plane of the ring and a belt of positive potential around the edge. Therefore, an oxygen lone pair should be attracted to the positive potential of the edge by electrostatic interactions. Since the syn/anti ratios are only slightly higher than the statistical 2:1 ratio for **2a** and **2b**, van der Waals interactions between the MeO group and the aromatic ring and CH−π interactions may play a more prominent role in the preference for the syn conformation. However, CH−π interactions cannot be the dominant force after examining the entire data in Table 1. CH−π interactions would prefer an electron-rich arene while the lp−π interactions prefer an electron-deficient arene.

For compounds **3**−**7**, the interactions are between an ester group at C(1) and the arene at C(9). The carbonyl group of the ester reduces the electron density on the oxygen atom leading to a reduced lp−arene interaction. Such is the case when the arene is substituted with the electron-withdrawing group CF_3. Compound **2e** with a C(1) methoxy group has a higher population of the syn conformation (syn/anti ratio: 5.5:1) than compounds **4e**, **5e**, and **6e** (syn/anti ratio: 3.4−4.4:1), all of which have a C(1) ester group. This is consistent with MeO being a better donor than an OCOR group and also consistent with the electrostatic argument.

A small reversal was observed when the C(9) arene has an electron-donating group (**2**−**6a**, X = Me): compounds **3a**, **4a**, **5a**, and **6a** with a C(1) acetate group have a slightly higher syn conformation than **2a** (syn/anti ratio: 2.4−3.3:1 versus 2.3:1). This suggests that there is a secondary interaction in addition to the electrostatic force between the phenolic oxygen and the arene. When the primary electrostatic interactions are diminished due to increased arene electron density in the case of **2a**−**6a**, the secondary interactions become more important. It is reasonable to suggest that the secondary interactions are from van der Waals forces between the COR group and the C(9) aromatic ring, which increase when the contacting area between the two components is increased. Thus, the syn/anti ratio increases as a function of the group on C(1) oxygen among **2a**−**5a** according to the following order: Me < CHO < COMe < COEt. When R = *i*-Pr, the syn conformation is favored, but the preference is smaller than when R = Et. We attribute this to the size of the isopropyl group, which causes some steric repulsion in the syn conformation. Steric effects are assumed to be absent for R = CHO, COMe, and COEt groups. The fact that a higher syn/anti ratio was observed in the order of Me < CHO < COMe < COEt supports the argument that van der Waals contact area determines the order of attractive interactions among the electron-rich **2a**−**5a**.

There is a repulsive interaction in the syn conformation of **7** when R = CF_3 (entry 24, Table 1), and the anti conformation is preferred. This result excludes the argument that the preference for the syn conformation is due to arene−carbonyl dipole interactions. The CF_3CO group should have the largest dipole moment among the compounds in Table 1. This repulsive interaction also cannot be explained by steric effects. According to MacroModel calculations, the syn conformer of **7** is more stable than the anti conformer by ~1 kcal/mol in contrast to the experimental results. A CF_3 group is definitely smaller than an isopropyl group and probably smaller than an ethyl group.[28] Molecular mechanics is best to detect steric repulsions, but not equipped to detect various types of electronic repulsions. The observed repulsive interactions in the syn conformation of **7** can be rationalized by the fact that the CF_3 group in the syn conformation is positioned in the cone area of the C(9) arene where substantial negative electrostatic potential is centered. Repulsive interactions are expected between the π-cloud and the fluorine atoms of the CF_3 group. Through this study we have demonstrated that one can improve the performance of molecular mechanics by taking into account the electron density locations on aromatic rings.

Summary

Quantitative experimental determination of lp−π interactions with the oxygen atom approaching the edge of an aromatic ring is reported. The dominant attractive interactions in compounds **2**−**7** are electrostatic in nature as shown by the substituent effect on both the C(9) arene and the C(1) oxygen atom in **2**−**7**. Compounds **2a**−**e** with a MeO group at C(1) are more responsive to the nature of the substituent X on the C(9) arene than compounds **3**−**7** in terms of syn/anti ratios. The interactions between an electron-rich arene (X = Me or MeO) and MeO are weakly attractive with the methoxy oxygen located near the edge of the aromatic ring. For the C(1) ester series of compounds (**3**−**7**), the R group is positioned in the cone area of the C(9) arene in the syn conformation. As such,

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a repulsive interaction was observed when R = CF_3, and some steric interactions were associated with the *i*-Pr group. Van der Waals forces play a role in the weaker interactions between the ester group and the aromatic ring. Our current models do not include strongly electron-deficient arenes, such as a pentafluorobenbenzyl group at C(9) or oxygen approaching the center of the arene. Studies toward these goals are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**−**7**. Variable temperature NMR procedures and computer simulation procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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