JOC Article

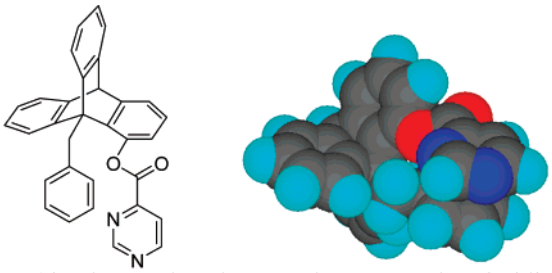
Stacking Interactions between Nitrogen-Containing Six-Membered Heterocyclic Aromatic Rings and Substituted Benzene: Studies in Solution and in the Solid State

Benjamin W. Gung,*[,†] Francis Wekesa,[†] and Charles L. Barnes[‡,§]

Department of Chemistry & Biochemistry, Miami University, Oxford, Ohio 45056, and Elmer O. Schlemper X-Ray Diffraction Center, University of Missouri−Columbia, Columbia, Missouri 65211

gungbw@muohio.edu; barnesch@missouri.edu

Received November 6, 2007



Stacking interactions between benzene and pyrimidine

The stacking interactions between an aromatic ring and a pyridine or a pyrimidine ring are studied by using a series of triptycene-derived scaffolds. The indicative ratios of the syn and anti conformers were determined by variable-temperature NMR spectroscopy. The syn conformer aligns the attached aromatic ring and the heterocycle in a parallel-displaced orientation while the anti conformer sets the two rings apart from each other. Comparing to the corresponding control compounds where a benzene ring is in the position of the heterocycle, higher attractive interactions are observed as indicated by the higher syn/anti ratios. In general, the attractive interactions are much less sensitive to the substituent effects than the corresponding nonheterocycles. The greatest attractive interactions were observed between a pyrimidine ring and a *N*,*N*-dimethylaminobenzene, consistent with a predominant donor−acceptor interaction. The interactions between a pyridine ring and a substituted benzene ring show that the pyridine is comparable to that of a NO_2- or a CN-substituted benzene ring except for the unpredictable substituent effects.

Introduction

Noncovalent interactions between aromatic molecules play a major role in the stability of biological systems.[1,2] In addition to the prominent role in DNA and RNA structures,[3] aromatic stacking interactions have been observed in the complexes of medicinal drugs and the targeted enzymes.[4] To understand aromatic stacking interactions, extensive theoretical studies of benzene dimers and substituted benzene dimers have been reported.[5−10] However, there have been few theoretical studies on the stacking interactions between a heterocyclic aromatic

[†] Miami University.
[‡] University of Missouri−Columbia.
[§] To whom questions regarding X-ray structure analysis should be addressed.

(1) Burley, S. K.; Petsko, G. A. Aromatic−Aromatic Interaction−a Mechanism of Protein-Structure Stabilization. *Science* **1985**, *229*, 23−28.
(2) Meyer, E. A.; Castellano, R. K.; Diederich, F. Interactions with aromatic rings in chemical and biological recognition. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210−1250.
(3) Guckian, K. M.; Schweitzer, B. A.; Ren, R. X. F.; Sheils, C. J.; Tahmassebi, D. C.; Kool, E. T. Factors contributing to aromatic stacking in water: Evaluation in the context of DNA. *J. Am. Chem. Soc.* **2000**, *122*, 2213−2222.
(4) Kryger, G.; Silman, I.; Sussman, J. L. Three-dimensional structure of a complex of E2020 with acetylcholinesterase from Torpedo californica. *J. Physiol.* (*Paris*) **1998**, *92*, 191−194.
(5) Jorgensen, W. L.; Severance, D. L. Aromatic Aromatic Interactions−Free-Energy Profiles for the Benzene Dimer in Water, Chloroform, and Liquid Benzene. *J. Am. Chem. Soc.* **1990**, *112*, 4768−4774.
(6) Jaffe, R. L.; Smith, G. D. A quantum chemistry study of benzene dimer. *J. Chem. Phys.* **1996**, *105*, 2780−2788.
(7) Hobza, P.; Selzle, H. L.; Schlag, E. W. Potential energy surface for the benzene dimer. Results of ab initio CCSD(T) calculations show two nearly isoenergetic structures: T-shaped and parallel-displaced. *J. Phys. Chem.* **1996**, *100*, 18790−18794.

10.1021/jo702354x CCC: $40.75
Published on Web 02/12/2008

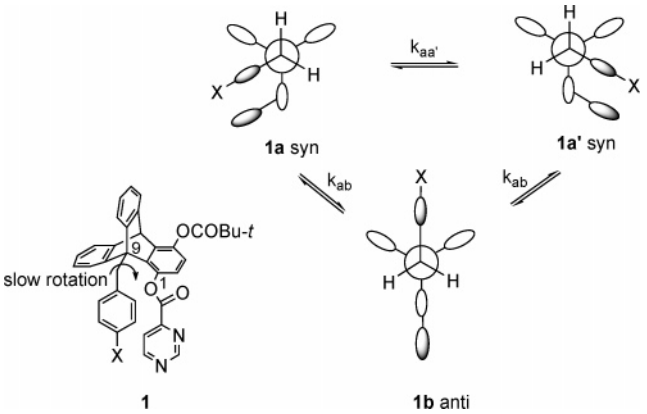


FIGURE 1. Equilibrium between syn and anti conformations in the triptycene-derived scaffold. The C9-benzyl bond has hindered rotation. At low temperature, the two conformations can be observed by ^{1}H NMR spectroscopy.

ring and a benzene ring.[11,12] To our knowledge, no solution experimental studies have been reported on the relative strength of stacking interactions between a heterocycle and a benzene ring. Recently we reported experimental studies of arene−arene interactions in organic solvents using the triptycene-derived scaffold.[13,14] This report details our study of the interactions between a pyrimidine or a pyridine ring and a substituted benzene. We found that these 6-membered nitrogen-containing heterocycles when arranged in a parallel-displaced configuration with a benzene ring in general exhibit higher attractive interactions than the corresponding normal arene−arene interactions. Furthermore, we found that the attractive interactions are much less sensitive to substituent effects than the corresponding arene−arene interactions.

Results

The triptycene-derived model system allows the two aromatic rings, one attached to the bridgehead (C9 in the triptycene name system) and the other to C1, to assume a near, but not perfect, parallel displaced conformation in the syn conformation, Figure 1. The stacking contact between the C9 arene and the C1 heterocycle is at near van der Waals' distance in the syn conformation, but not possible in the anti conformation.[15,16] 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 recent studies on aromatic interactions using the triptycene-derived model system allowed quantitative studies of the magnitude of noncovalent interactions. Our previous study involved the normal arene−arene interactions, and we have now expanded our study to the interactions between a six-membered nitrogen-containing heterocycle and a benzene ring.

Molecular modeling with MacroModel with MMFFs force field shows that the replacement of the C1-benzoate with a pyridine or pyrimidine carboxylate does not change the stacking conformation. The global minimum conformation is the syn conformation with the pyrimidine ring and the benzyl group assuming a parallel-displaced conformation. We are aware of the limitations of the molecular mechanics model in the calculations of the stacking interactions. Any serious inclusion of London dispersion forces should consider using a high level of theory in computations.[17] The only purpose of the molecular mechanics calculations is to examine the three-dimensional structure of the model compounds. The results show that the replacement of the C1 benzoate with a 6-membered heterocycle does not change the parallel displaced conformation in the syn isomer.

The synthesis of the desired heterocyclic (**6a**−**7g**) started with 9-substituted benzyltriptycene-1,4-diol, which have been reported by us recently, Scheme 1.[13,15,16] The hydroxyl group at the C4 position is protected as a pivalate ester. The precursors (**5a**−**g**) to model compounds (**6a**−**7g**) were then treated with the corresponding aryl acyl chloride in the presence of a base to yield the desired target products. Pyridine-4-acyl chloride is commercially available. Pyrimidine-4-acyl chloride was prepared from 4-methylpyrimidine via SeO_2 oxidation followed by treatment of oxalyl chloride.[18] The resulting acyl chloride was used in situ to prepare the target esters (**6a**−**7g**).

A variable-temperature NMR study was carried out in chloroform with these model compounds. Two conformational isomers, the syn and the anti, were observed at low temperatures as usual. This is due to the slow rotation of the bridgehead CH_2 group in these compounds on the NMR time scale, which allows the integration of the peak area for each conformation and the determination of the syn/anti isomer ratio for each compound (Figure 2).

The primary solution NMR data are shown in Table 1. The syn conformation is preferred for all heterocyclic model compounds (**6a**−**7f**), in contrast to the control compounds (**8a**−**f**). The observed syn/anti ratios range from below the statistical value of 2 for control compounds (**8a**−**d**) to an almost exclusive syn conformation at −50 °C for the pyrimidine−dimethylaminobenzyl pair (**6a**).

A single crystal was obtained for one of the pyrimidine-containing model compounds where X = Br on the C9-benzyl

(8) Sinnokrot, M. O.; Valeev, E. F.; Sherrill, C. D. Estimates of the ab initio limit for $\pi-\pi$ interactions: The benzene dimer. *J. Am. Chem. Soc.* **2002**, *124*, 10887−10893.

(9) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. Origin of attraction and directionality of the x/x interaction: Model chemistry calculations of benzene dimer interaction. *J. Am. Chem. Soc.* **2002**, *124*, 104−112.

(10) Sinnokrot, M. O.; Sherrill, C. D. Substituent effects in $\pi-\pi$ interactions: Sandwich and T-shaped configurations. *J. Am. Chem. Soc.* **2004**, *126*, 7690−7697.

(11) Mignon, P.; Loverix, S.; De Proft, F.; Geerlings, P. Influence of stacking on hydrogen bonding: Quantum chemical study on pyridine−benzene model complexes. *J. Phys. Chem. A* **2004**, *108*, 6038−6044.

(12) Waller, M. P.; Robertazzi, A.; Platts, J. A.; Hibbs, D. E.; Williams, P. A. Hybrid density functional theory for π-stacking interactions: Application to benzenes, pyridines, and DNA bases. *J. Comput. Chem.* **2006**, *27*, 491−504.

(13) Gung, B. W.; Xue, X. W.; Reich, H. J. The strength of parallel-displaced arene−arene interactions in chloroform. *J. Org. Chem.* **2005**, *70*, 3641−3644.

(14) Oki, M. 1,9-Disubstituted Triptycenes—an Excellent Probe for Weak Molecular-Interactions. *Acc. Chem. Res.* **1990**, *23*, 351−356.

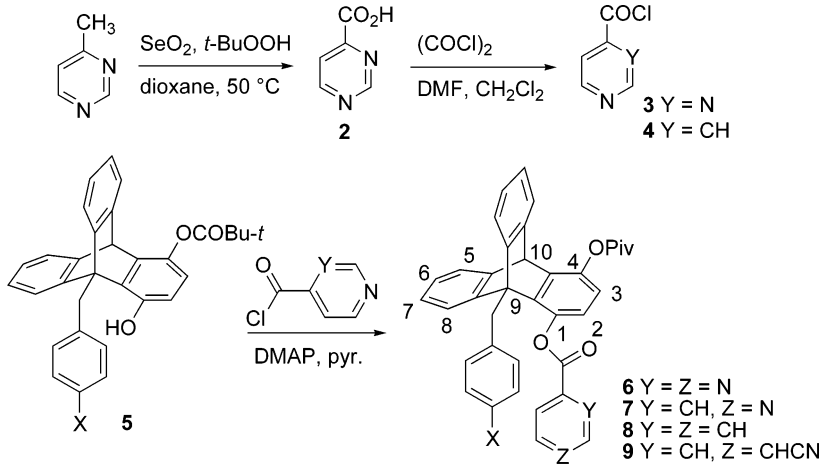
(15) Gung, B. W.; Patel, M.; Xue, X. W. A threshold for charge transfer in aromatic interactions? A quantitative study of π-stacking interactions. *J. Org. Chem.* **2005**, *70*, 10532−10537.

(16) Gung, B. W.; Xue, X. W.; Reich, H. J. Off-center oxygen−arene interactions in solution: A quantitative study. *J. Org. Chem.* **2005**, *70*, 7232−7237.

(17) Grimme, S.; Antony, J.; Schwabe, T.; Muck-Lichtenfeld, C. Density functional theory with dispersion corrections for supramolecular structures, aggregates, and complexes of (bio)organic molecules. *Org. Biomol. Chem.* **2007**, *5*, 741−758.

(18) Tagawa, Y.; Yamashita, K.; Higuchi, Y.; Goto, Y. Improved oxidation of active methyl group of N-heteroaromatic compounds by selenium dioxide in the presence of *tert*-butyl hydroperoxide. *Heterocycles* **2003**, *60*, 953−957.

SCHEME 1. Preparation of the Model Compounds



X = NMe_2(**a**), OMe(**b**), Me(**c**), H(**d**), F(**e**), Br(**f**), NO_2(**g**)

ring (**6f**, Figure 3). Surprisingly the anti conformation is shown, in contrast to its solution structure based on ^{1}H NMR data, which shows overwhelming syn conformation (**6f**, Table 1).

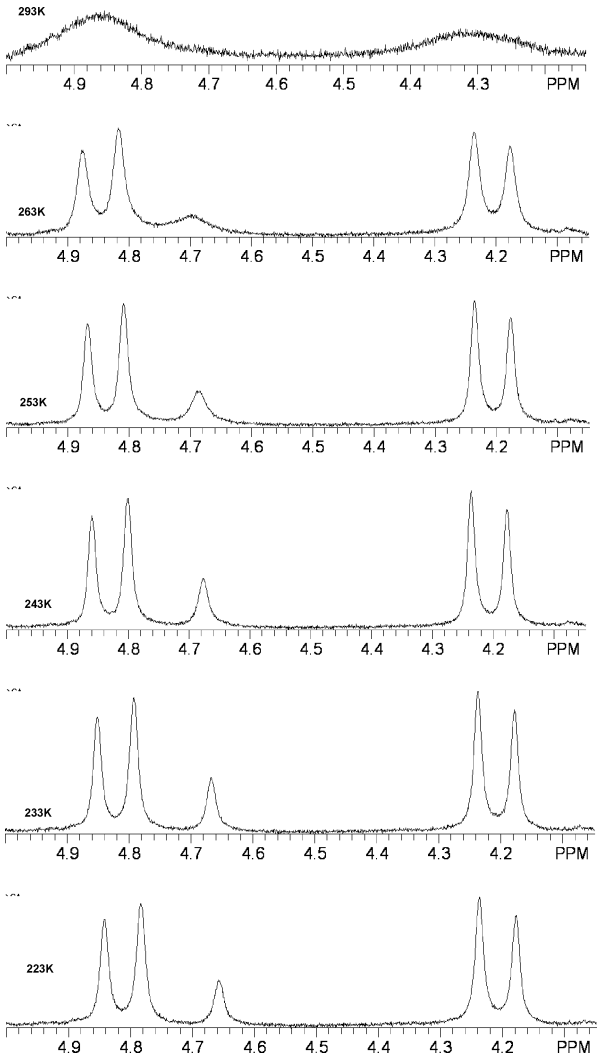


FIGURE 2. A representative temperature-dependent NMR signals (300 MHz in $CDCl_3$) from the bridgehead C(9)H_2 protons. The spectra shown are from compound **6e**, where the AB quartet is due to the syn conformation and the singlet at 4.6 ppm is due to the anti conformation.

In light of the apparent contradiction between the solution data and the crystal structure of **6f**, it is appropriate to report here our variable-concentration study performed at −50 °C in chloroform. The syn/anti ratios were examined by using low-temperature ^{1}H NMR on samples from a serial dilution performed on a sample of **6f** at an initial concentration of 0.2 M. A gradual increase of syn/anti ratio was observed as the sample concentration became more dilute (see Table 2). This observation indicates that intermolecular interactions are more prominent at higher concentration, which is expected and should reduce the preference for the syn conformation. This interpretation is further confirmed by careful examination of the X-ray structure of **6f**, which shows that two molecules of **6f** in the crystal cell align their pyrimidine ring with one of the benzene rings of the triptycene scaffold from the other molecule. Detailed discussion is presented in the following section.

Discussion

Gas-phase molecular mechanics calculations indicate that the syn conformations are preferred for the heterocyclic compounds examined in this study. Variable-temperature NMR data are consistent with this prediction and the syn/anti ratios are determined to be from 3.0 to ∼19.4 for the heterocycle-containing compounds (Table 1). Yet the crystal structure of **6f** indicates an anti conformation (Figure 4). A rational explanation can be reached by a close examination of the crystal structure. Figure 4 shows two adjacent molecules in the X-ray structure of compound **6f** in two perspectives, which indicates that the two molecules are reciprocally parallel, stacked with each other.

In other words, an offset stacking conformation positions C4 of the pyrimidine ring near the center of the benzene ring of the triptycene skeleton. The distance from the plane of the pyrimidine ring to the plane of the benzene ring is ∼3.5 Å. This relative position of the two stacked aromatic rings should be highly favorable with high electron density area of the benzene ring near the low electron density area of the pyrimidine ring. A secondary CH−O interaction from the most acidic proton of the pyrimidine ring to the phenolic oxygen of the adjacent molecule is also possible. However, stacking interaction is the dominant force because the H−O distance is 2.98 Å, which indicates a weak CH−O attraction. No apparent CH−π interaction could be identified in the crystal structure.

TABLE 1. Ratios of Syn/Anti Isomers at Different Temperatures for Model Compounds 6a−8f[a]

compd	C1Aryl	X	syn/anti ratio in $CDCl_3$ at different temperatures				
			−10 °C	−20 °C	−30 °C	−40 °C	−50 °C
6a	pyrimidine	NMe_2	12.7	13.3	15.5	17.9	19.4
6b	pyrimidine	OMe	6.2	6.4	7.8	7.8	8.9
6c	pyrimidine	Me	8.2	9.3	11.1	11.5	14.0
6d	pyrimidine	H	7.9	8.3	9.8	10.9	12.4
6e	pyrimidine	F	7.6	7.9	8.3	10.1	11.4
6f	pyrimidine	Br	9.6	11.4	13.7	16.3	18.9
7a	pyridine	NMe_2	3.1	3.4	3.4	3.7	4.1
7b	pyridine	OMe	4.7	4.9	5.3	5.6	5.7
7c	pyridine	Me	5.3	5.6	5.4	5.8	6.0
7d	pyridine	H	5.0	5.5	5.7	6.1	6.8
7e	pyridine	F	4.5	4.8	5.3	5.5	5.7
7f	pyridine	Br	7.6	7.8	8.4	8.5	9.3
7g	pyridine	NO_2	5.6	6.0	6.1	6.3	6.4
8a	C_6H_5	NMe_2	1.3	1.2	1.2	1.1	1.1
8b	C_6H_5	OMe	1.6	1.7	1.7	1.8	1.6
8c	C_6H_5	Me	2.1	1.9	1.8	1.8	1.8
8d	C_6H_5	H	1.8	1.9	1.9	2.0	2.0
8e	C_6H_5	F	2.0	2.1	2.3	2.4	2.5
8f	C_6H_5	Br	2.9	3.0	3.2	3.3	3.3

[a] The experiments were performed in $CDCl_3$ unless stated otherwise. All reported experimental data are averages of duplicate runs.

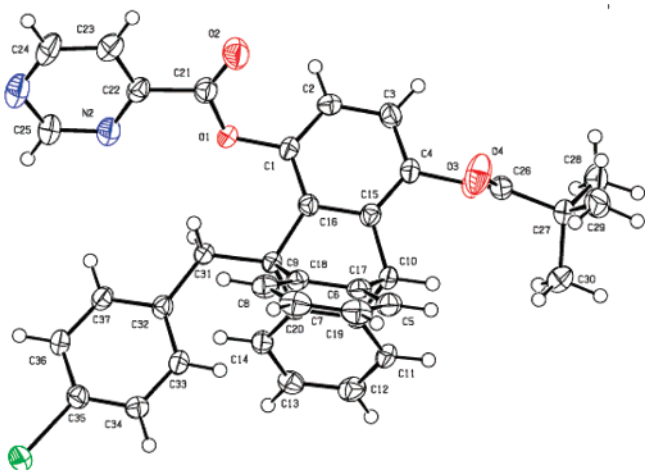


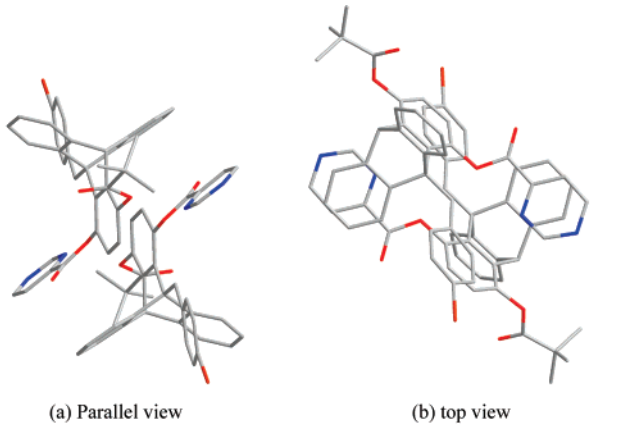
FIGURE 3. X-ray structure of compound **6f** shown in ellipsoid plot. In contrast to the solution ^1H NMR data, an anti conformation is observed in the crystal structure.

TABLE 2. Ratios of Syn/Anti Isomers at Different Concentrations for Model Compound 6f (in $CDCl_3$)[a]

	0.2 M	0.1 M	0.05 M	0.03 M	0.02 M	0.01 M
syn/anti ratio	13.6	13.9	14.1	14.9	15.9	18.4

[a] The experiment was performed at −50 °C.

The intermolecular stacking arrangement is more likely to be free of strain than the intramolecular stacking arrangement. In the absence of entropic factors, the intermolecular stacking interaction becomes more favorable in the solid state environment. In addition, the benzene ring of the triptycene scaffold should have a higher electron density than the bromo-substituted benzene ring in **6f**. From the syn/anti ratio data in Table 1, the pyrimidine ring is electron-deficient enough to favor interactions with electron-rich aromatic rings such as the $Me_2NC_6H_4$ group (**6a**, Table 1). Therefore, it is not surprising that the pyrimidine ring aligns with an electron-rich benzene ring intermolecularly in the solid state. However, due to structural restraint it is not possible for the C1 pyrimidine group to align with a benzene ring of the triptycene scaffold intramolecularly. Thus, we are observing intramolecular interactions in solution due to entropic effects while the crystal structure reflects intermolecular interactions. This interpretation is supported by the variable-concentration data in Table 2. A gradual increase in syn/anti ratio was observed when the sample concentration was incrementally diluted. However, even at the highest concentration examined, the syn conformation is still nearly 14 times that of the anti isomer for compound **6f**. Intermolecular interactions are largely eliminated in solution due to entropic and solvent effects. The following discussion will be centered on solution study.



(a) Parallel view (b) top view

6f (Key: C, gray; O, red; N, blue; and Br, orange), hydrogen omitted for clarity.

FIGURE 4. X-ray structure of compound **6f** displayed as a stick model in two perspectives. The structure shows that the pyrimidine ring is parallel stacked with a benzene ring from an adjacent molecule in the crystal cell. The distance from the plane of the pyrimidine ring to the plane of the benzene ring is ~3.5 Å. The 4-bromobenzyl group is anti to the pyrimidine ring.

Once we can concentrate on the intramolecular interactions between the 6-member nitrogen-containing heterocycle and the C9 benzyl group using the solution NMR data presented in Table 1, the substituent effects on the benzene ring can be examined. For the pyrimidine derivatives (**6a**−**f**), the syn/anti ratio changes significantly with temperature. This enables us to obtain both ΔH and ΔS by using the van't Hoff eq 1.

$$\ln K_{eq} = -\Delta H°/RT + \Delta S°/R \qquad (1)$$

where $K_{eq} = {}^1/_2$(syn/anti) and R is the gas constant.

Entropic effects in noncovalent interactions are considered vitally important for studies in guest−host chemistry.[19,20] This study provides some entropic information for π-stacking between a heterocycle and a benzene ring. Thermodynamic parameters are collected in Table 3. Some caution should be taken with these data since the enthalpy and entropy obtained when using the van't Hoff equation assume a constant enthalpy value in the surveyed temperature range that may or may not be true.

The thermodynamic data obtained are summarized in Table 3 along with those of six compounds from our previous study

(19) Searle, M. S.; Williams, D. H. The Cost of Conformational Order—Entropy Changes in Molecular Associations. *J. Am. Chem. Soc.* **1992**, *114*, 10690−10697.

(20) Martinez, A. G.; Barcina, J. O.; Cerezo, A. D. Influence of highly preorganised 7,7-diphenylnorbornane in the free energy of edge-to-face aromatic interactions. *Chem.-Eur. J.* **2001**, *7*, 1171−1175.

TABLE 3. Thermodynamic Parameters Obtained through Variable-Temperature ^{1}H NMR Studies in $CDCl_3$[a]

compd	C1Aryl	X	$\Delta H°$ [c]	$\Delta S°$ [d]	$\Delta G°$ [c]
6a	pyrimidine	NMe_2	-1.34 ± 0.06	-1.5 ± 0.5	-0.91 ± 0.3
6b	pyrimidine	OMe	−1.08	−1.9	−0.52
6c	pyrimidine	Me	−1.51	−2.9	−0.64
6d	pyrimidine	H	−1.38	−2.6	−0.62
6e	pyrimidine	F	−1.24	−2.1	−0.64
6f	pyrimidine	Br	−2.0	−4.5	−0.7
7a	pyridine	NMe_2	−0.75	−2.0	−0.16
7b	pyridine	OMe	−0.60	−0.6	−0.43
7c	pyridine	Me	−0.34	0.6	−0.53
7d	pyridine	H	−0.84	−1.4	−0.44
7e	pyridine	F	−0.71	−1.0	−0.40
7f	pyridine	Br	−0.58	0.5	−0.71
7g	pyridine	NO_2	−0.36	0.7	−0.57
8c	C_6H_5	Me	0.44	1.6	−0.03
8d	C_6H_5	H	0.19	0.7	−0.03
8e	C_6H_5	F	0.0	0.4	−0.13
9c[b]	C_6H_4CN	Me	−0.03	1.4	−0.46
9d[b]	C_6H_4CN	H	−0.04	2.2	−0.69
9e[b]	C_6H_4CN	F	−0.1	2.4	-0.82

[a] $\Delta G°$ values were calculated at $T = 298$ K. The experimental errors are calculated using linear regression analysis of the data points over the experimental temperature range.[21] [b] Reference 13. [c] Units: kcal mol^{-1}. [d] Units: cal mol^{-1} K^{-1}.

to serve as control experiments. The experimental errors are calculated by using linear regression analysis of the data points over the experimental temperature range.[21] In general, the enthalpy values have much smaller errors than the entropy values because the former was calculated from the slope and the latter from the intercept.

All heterocyclic model compounds (**6a**−**7f**) studied show attractive interactions between the C9-substituted aromatic ring and the C1 heterocycle group. The strongest interaction is observed between the pyrimidine group and the electron-rich $Me_2NC_6H_4$ group (**6a**, Table 2). Hammett plots did not give a good correlation between the substituent constants (σ_{para} or σ_{meta}) and the free energies obtained.[22] 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.[10,23] While there is hardly any trend in substituent effects, the electron-rich $Me_2NC_6H_4$ group is most attractive with the pyrimidine ring and least attractive with the pyridine ring (**6a** and **7a**, entries 1 and 7, Table 3). These observations can be attributed to an attractive donor−acceptor interaction in **6a** and repulsive electrostatic interactions in **7a**. In general, in order to have a donor−acceptor type of interaction, the acceptor must meet a certain threshold in electron deficiency. Previously we have observed similar types of donor−acceptor interactions in the corresponding $C_6F_5CO_2$ derivative.[15]

The entries 17 to 19 in Table 3 are taken from our previous study[13] and along with compounds **8c**−**e** they serve as control compounds and provide some illuminating comparisons. When an unsubstituted benzene ring is in the position of the heterocycle, repulsive enthalpies and favorable entropies were observed for X = Me or H and a very small attractive interaction was observed for X = F (compounds **8c**−**8e**, Table 3). When the benzene ring is substituted with an electron-withdrawing group (such as a CN, compounds **9c**−**9e**, Table 3), a small favorable enthalpy and favorable entropic interactions were observed. The CN-substituted benzene derivatives give an overall attractive interaction comparable to that of the heterocycles. Notwithstanding the different proportions of contributions from enthalpic and entropic components, the free energy results appear to be consistent with the concept that a −N═ group for −C═ substitution in a 6-membered aromatic ring reduces the electron density from the π-system.[24]

From the data in Table 3, the pyrimidine ring interacts with the substituted benzene ring mainly by an enthalpy-driven process. The entropies for the stacking interactions are all negative. On the contrary, it is interesting to note that the stacking interactions between two benzene rings although small are all favored by entropy effects (compounds **8c**−**9e**, Table 3). The pyridine derivatives are somewhere in between, some have a positive entropy and others a negative entropy term. Our interpretation for these differences is solvent effects, i.e., the stacked conformation between a pyrimidine ring and a benzene ring, is entropically more disfavored than when the two rings are separated. This is similar to many host−guest systems where enthalpy−entropy compensation is often observed.[2] On the other hand, the stacked conformation between two benzene rings is slightly more entropically favored than when the two rings are separated. The difference lies in the interactions with the solvent molecule $CDCl_3$. The stacking interactions in normal benzene rings appear to be slightly favored by a desolvation entropy.[2]

For aromatic rings without strong electron density-altering substituents, previous studies have in general supported the notion that simple electrostatic forces are dominant in arene−arene stacking interactions.[13,25,26] One of the supporting pieces of evidence is that all arene−arene interactions display similar substituent effects that gave good correlation in a Hammett plot. The lack of a general trend in substituent effects in the heterocycle series indicates that more complex forces are involved in the heterocycle−benzene stacking interactions. These forces likely include London dispersion and local dipole−dipole and donor−acceptor interactions. The normally useful simplification to treat an aromatic ring as a quadrupolar subject does not work on these nitrogen-containing heterocycles.[27,28] To identify these forces involved, more studies are planned. One such plan involves the change of the substituent position on the C9 benzene ring. This could detect the importance of the directionality of the local dipoles introduced by the heteroatom. High-level computational studies are also planned and a partition of the calculated total interaction energy into relevant components should help to reveal the interplay of various physical forces in heterocycle−benzene interactions.

(21) Shoemaker, D. P.; Garland, C. W.; Nibler, J. W. *Experiments in Physical Chemistry*, 6th ed.; McGraw-Hill: New York, 1996.

(22) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195.

(23) Mecozzi, S.; West, A. P.; Dougherty, D. A. "Cation-π interactions in aromatics of biological and medicinal interest: Electrostatic potential surfaces as a useful qualitative guide. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566−10571.

(24) Albert, A. *Heterocyclic Chemistry*: *an Introduction*, 2nd ed.; The Athlone Press: New York, 1968.

(25) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. Dominance of Polar/π over Charge-Transfer Effects in Stacked Phenyl Interactions. *J. Am. Chem. Soc.* **1993**, *115*, 5330−5331.

(26) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. "Polar/π Interactions between Stacked Aryls in 1,8-Diarylnaphthalenes. *J. Am. Chem. Soc.* **1992**, *114*, 5729−5733.

(27) Luhmer, M.; Bartik, K.; Dejaegere, A.; Bovy, P.; Reisse, J. The Importance Of Quadrupolar Interactions In Molecular Recognition Processes Involving A Phenyl Group. *Bull. Soc. Chim. Fr.* **1994**, *131*, 603−606.

(28) Ma, J. C.; Dougherty, D. A. The cation−π interaction. *Chem. Rev.* **1997**, *97*, 1303−1324.

Summary

Parallel displaced stacking interactions between a six-membered heterocycle (pyridine or pyrimidine) and a substituted benzene ring were quantitatively studied in solution. Both pyridine and pyrimidine were found to have a greater attractive interaction with a substituted benzene ring than the corresponding arene−arene interactions. An X-ray structure analysis of compound **6f** shows that two molecules are reciprocally parallel stacked with each other with their pyrimidine ring and one of the triptycene scaffold benzene rings. Although the anti conformation is observed in the crystal structure, the syn conformation was observed for **6f** overwhelmingly in solution, which is attributed to entropic effects. Namely, entropy disfavors intermolecular interactions which lead to favorable intramolecular stacking interactions. A Hammett plot did not give a good correlation with the free energies obtained. This is viewed as evidence for more complex physical forces involved in the heterocycle−benzene interactions. These forces may include London dispersion and local dipole−dipole and donor−acceptor interactions. Further studies are planned to change the position of the substituent on the C9 benzene ring in an attempt to identify the predominant physical forces.

Experimental Section

Representative Procedure for the Preparation of the Model Compounds: 9-(4-(Dimethylamino)benzyl)-1-pyrimidinoyloxy-4-(pivaloyloxy)triptycene (6a). To a suspension of 4-pyrimidine carboxylic acid (2.07 mmol) and oxalyl chloride (0.25 mL) in dichloromethane (5 mL) was added one drop of *N*,*N*-dimethylformamide and the resulting solution was stirred at room temperature under N_2 overnight. Solvent was removed under reduced pressure and the residue was redissolved in 5 mL of dichloromethane. This solution was then added dropwise to a solution of **5a** (1.43 mmol) with a catalytic amount of *N*,*N*-dimethylaminopyridine in dichloromethane (3 mL) and triethylamine (3 mL) at room temperature. The mixture was stirred at room temperature for 10 min and then refluxed (50 °C) for 2 h. The reaction was allowed to cool to room temperature, quenched with 20 mL of water, and extracted with dichloromethane (3 × 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography to afford **6a** as a yellow solid: mp 190−191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (9H, s), 3.70 (3H, s), 4.25 (2H, br), 5.49 (1H, s), 6.32−6.48 (2H, br), 6.61−7.10 (10H, m), 7.30−7.59 (3H, m), 8.85 (1H, br), 9.39 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ, 27.4, 29.7, 33.6, 39.4, 40.7, 48.6, 112.2, 120.0, 121.3, 122.8, 123.1, 123.6, 124.9, 125.3, 125.4, 130.2, 136.2, 136.5, 143.3, 143.4, 148.6, 150.3, 150.6, 163.4, 176.4; HRMS calcd for $C_{39}H_{35}N_3O_4$ + Na 632.2525, found 632.2530.

Acknowledgment. We are grateful for support from the National Institutes of Health (GM069441). We thank Professor Rainer Glaser for helpful discussion and for facilitating the X-ray structure analysis.

Supporting Information Available: Experimental procedures including low-temperature NMR spectroscopy and X-ray structure analysis including a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702354X