JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Do Deuteriums Form Stronger CH−π Interactions?

Chen Zhao,[†] Robert M. Parrish,[‡] Mark D. Smith,[†] Perry J. Pellechia,[†] C. David Sherrill,[‡] and Ken D. Shimizu*,[†]

[†]Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina 29208, United States

[‡]School of Chemistry and Biochemistry and School of Computational Science and Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, United States

Supporting Information

ABSTRACT: The D/H isotope effect for the CH−π interaction was studied experimentally and computationally. First, a series of molecular balances that are very sensitive to changes in the strength of the CH−π interactions in solution were designed. Balances with deuterated and non-deuterated alkyl groups were synthesized, and their intramolecular CH−π interactions were compared. The geometries of their intramolecular CH−π and CD−π interactions were characterized in the solid state by X-ray analysis, and the strength of each interaction was characterized in solution by the folded/unfolded ratio as measured by ^{1}H NMR spectra. Second, the relative strengths of the CH−π and CD−π interactions were also assessed computationally using dispersion-corrected DFT (PDE-D2/6-31+G*). No significant differencee was observed in either the experimental or theoretical studies, indicating that the D/H isotope effect for the CH−π interaction is either very small or nonexistent.

CH−π interactions are attractive non-covalent interactions between the protons of an alkyl or aryl group and the π face of an aromatic ring.[1] Despite their weak nature, CH−π interactions play crucial roles in supramolecular chemistry,[2] asymmetric catalysis,[3] and the folding of small molecules[4] and proteins.[5] However, the study of CH−π interactions has been difficult because of their weak strengths (0.5−2.5 kcal/mol)[3] and highly variable geometries. A potentially powerful method for studying the interaction involves the use of D/H isotope effects, which have been successfully applied to the study of other non-covalent interactions.[6] The presence of a pronounced D/H isotope effect for the CH−π interactions could be used to verify their formation and to probe their stability trends. The enhanced CH−π interactions of deuterated molecules could also be used to design better pharmaceuticals and asymmetric catalysts.

However, whether H and D form CH−π interactions with different strengths remains unclear. Several studies have observed significant deuterium isotope effects: Rebek and co-workers[7] and Iwata and co-workers[8] found that deuterated species formed stronger interactions within different molecular capsules, and differences in the retention times of protic and deuterated species were observed in chromatographic studies.[9] Other studies have found little or no D/H isotope effect for the CH−π interaction.[10] A possible reason for these discrepancies is that many of these studies were carried out within the confined environments of molecular capsules, which are very sensitive to small differences in molecular volume. Thus, the observed enhancements in the stability of deuterated guests could be due to their reduced steric interactions arising from their shorter C−D bonds, as opposed to stronger attractive CD−π interactions.

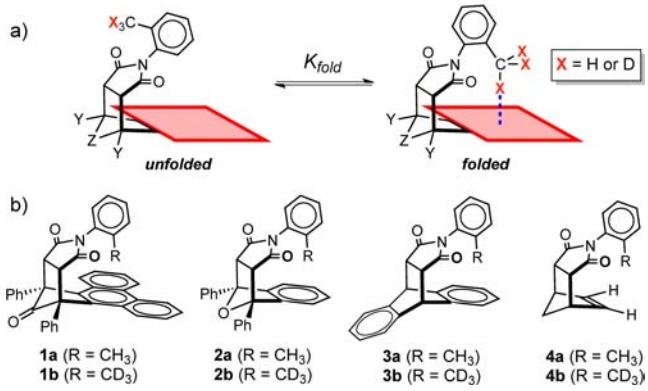

Figure 1. (a) Scheme showing the unfolded ⇄ folded conformational equilibrium of the molecular balances, which can be used to measure changes in the strength of the intramolecular CH−π interaction in the folded conformer. (b) Folded conformers of balances **1**−**3** designed to form intramolecular CH−π interactions and the control balance **4**.

Therefore, the goal of this study was to study the D/H isotope effect for CH−π interactions within less constrained environments in which steric interactions were minimized. First, an experimental study was carried out using small-molecule model systems. Second, a computational approach was carried out applying density functional theory (DFT) to a methane−benzene system. Both approaches found only minor differences between CD−π and CH−π interactions.

First, differences in CH−π and CD−π interactions were experimentally studied using molecular balances **1**−**3** (Figure 1). The balances form intramolecular CH−π interactions within relatively open environments with a minimum of steric interactions. Therefore, these model systems are less susceptible to repulsive interactions that could mask and attenuate the CH−π interactions of interest. The strengths of these interactions can be measured by following the folded/unfolded equilibrium ratios. Because of restricted rotation around the C_{aryl}−N_{imide} single bond, each balance adopts distinct folded and unfolded conformers. In the folded conformers, the *o*-methyl

Received: June 14, 2012
Published: August 17, 2012

   dx.doi.org/10.1021/ja305788p | *J. Am. Chem. Soc.* 2012, 134, 14306−14309

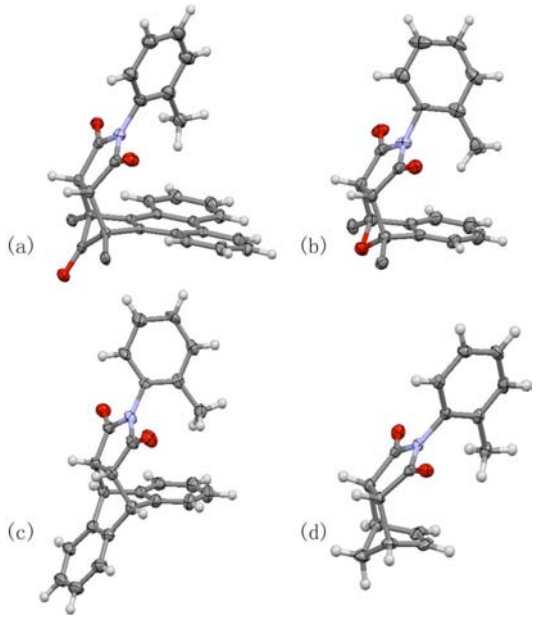

Figure 2. X-ray structures of the folded conformers of (a) **1a**,[14c] (b) **2a**, (c) **3a**,[14a] and (d) **4a**. The bridgehead phenyl groups in **1a** and **2a** are partially hidden for clarity. The unfolded conformers (not shown) were also present in the crystal structures of **2a**, **3a**, and **4a**.

groups (R) are perfectly positioned over the aromatic shelves to form intramolecular CH−π interactions. In the unfolded conformers, the *o*-methyl groups are held away from the aromatic shelves and cannot form intramolecular CH−π interactions. The two conformations are in slow exchange at room temperature on the ^{1}H NMR time scale. Therefore, the folded/unfolded ratio can be accurately measured from the integrations of the respective peaks.

Balances **1**−**3** provide a range of different CH−π interaction geometries and environments, affording a comprehensive study of the interaction. For example, balance **1** has a large phenanthrene aromatic shelf, whereas balances **2** and **3** have smaller benzene shelves. The geometry and steric interactions of the *o*-methyl group are attenuated by subtle differences in the bicyclic framework. Specifically, the different bridges −CO−, −O−, and −(*o*-C_6H_4)− (Z in Figure 1a) on the back sides of the balances attenuate the distance and steric interactions between the methyl group and the aromatic shelf.[11] Balance **4**, which cannot form a CH−π interaction because of the absence of an aromatic shelf, was used as a control.

Balances **1**−**4** were synthesized via similar modular routes allowing protic (**1a**−**4a**) and deuterated (**1b**−**4b**) forms to be prepared.[12] Protic balances **1a** and **3a** had been previously described in the literature, and **3a** had been used to study CH−π interactions.[13,14] The other six balances were new structures.

Initially, the structures of balances **1a**−**4a** were verified and characterized by X-ray structure analyses (Figure 2).[15] The crystal structures confirmed the formation of the endo bicyclic framework. As expected, well-defined intramolecular CH−π interactions were observed in the folded conformers of balances **1a**−**3a** (Figure 2a−c).[16] The methyl proton-to-arene plane distances (*d*) in **1a**−**3a** were all within the typical range for CH−π interactions (2.6−3.0 Å).[17] X-ray structure analysis also confirmed the absence of an intramolecular CH−π interaction in the folded conformation of control balance **4a** (Figure 2d). The X-ray structure of deuterated balance **1b** was also examined [see the Supporting Information (SI)] and compared to that of its protic counterpart **1a**. The structures were nearly identical.

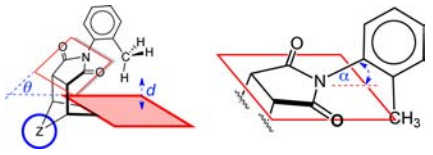

Figure 3. Distance *d* and angles θ and α used to characterize **1**−**4**.

Table 1. Values of *d*, θ, and α from the Crystal Structures of Balances 1a−3a and the Folding Energies in Solution (ΔG_{fold}) for Protic and Deuterated Balances 1−4 in $CDCl_3$ at 25 °C

balance	*d* (Å)	θ (deg)	α (deg)	$\Delta G_{fold,H}$ (kcal/mol)	$\Delta G_{fold,D}$ (kcal/mol)	$\Delta\Delta G_{fold}$ (kcal/mol)[b]
1	2.68	58	5	−0.10	−0.13	+0.03
2[a]	2.69	52	21	0.84	0.81	+0.03
3	2.61	58	4	0.07	0.07	0.00
4	–	–	2	0.02	0.06	−0.04

[a] *d*, θ, and α for **2a** are averages of the values for the three unique folded conformers in the unit cell.[16] [b] $\Delta\Delta G_{fold} = \Delta G_{fold,H} - \Delta G_{fold,D}$.

Although balances **1a**−**3a** all formed intramolecular CH−π interactions, the number (one hydrogen vs two), geometry, and distance in these interactions varied considerably. The structural parameters *d*, θ, and α used to compare the balances are shown in Figure 3, and a comparison of the measurements from the crystal structures of the balances are shown in Table 1. The "hinge" angle θ defined by the succinimide and arene planes provides a measure of how closely the *o*-methyl group is held against the arene shelf. For example, balance **2a** has the smallest θ, fixing the *o*-methyl tightly against the arene shelf. This strain is evident from the fact that the *N*-aryl group is pushed upward out of the succinimide plane (α = +21°). In contrast, balances **1a** and **3a** have larger θ values, positioning their *o*-methyl groups at more optimal distances with less strain (α = +5 and +4°, respectively).

Next, the strengths of the CH−π interactions in balances **1**−**3** were measured in solution by ^{1}H NMR spectroscopy. In each case, separate peaks for the folded and unfolded conformers were observed at room temperature, enabling facile measurement of the folded/unfolded ratio. In particular, large upfield shifts were observed for the *o*-methyl groups in the folded conformers, consistent with the formation of CH−π interactions. The folded methyl singlets of **1a**−**3a** were shifted upfield by −2.08, −1.01, and −1.04 ppm, respectively, compared with the peaks for the unfolded methyl groups. By comparison, control balance **4a**, in which a CH−π interaction cannot form, had almost identical chemical shifts for the folded and unfolded methyl protons ($\Delta\delta$ = −0.03 ppm). The ^{1}H NMR spectra of the deuterated balances were identical to those of their protic counterparts except for the absence of the deuterated *o*-methyl peaks.

Comparison of the folded/unfolded ratios for the protic balances showed different strengths for their CH−π interactions (Figure 4). These ratios were measured from the integration of the singlets for the succinimide protons in the ^{1}H NMR spectra.[19] As expected, control **4** had a folded/unfolded ratio of nearly 1:1, suggesting that differences in dipole moment and solvation of the conformers did not bias the folded/unfolded ratios. Despite the presence of intramolecular CH−π interactions in **1**−**3**, only **1** displayed a preference for the folded conformer. We attribute this to destabilizing repulsive steric interactions that arise because the rigid bicyclic framework positions the methyl group slightly too close to the arene shelf. As

dx.doi.org/10.1021/ja305788p | J. Am. Chem. Soc. 2012, 134, 14306−14309

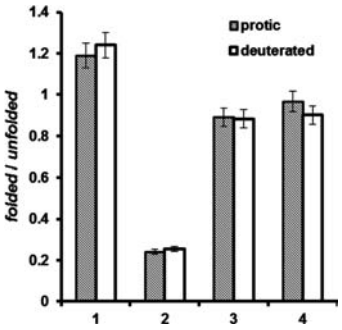

Figure 4. Folded/unfolded ratios for **1**−**4** in $CDCl_3$ at 25 °C measured by integration of the ^{1}H NMR spectra with a ±5% integration error.[18]

Table 2. Calculated ΔG_{fold} Values (in kcal/mol) for Protic and Deuterated Balances 1−3 in $CDCl_3$ and Acetone-d_6 at 25 °C

	$CDCl_3$		acetone-d_6	
	$\Delta G_{fold,H}$	$\Delta G_{fold,D}$	$\Delta G_{fold,H}$	$\Delta G_{fold,D}$
1	−0.12 ± 0.05	−0.14 ± 0.11	−0.23 ± 0.16	−0.26 ± 0.37
2	0.83 ± 0.28	0.80 ± 0.19	0.66 ± 0.07	0.65 ± 0.07
3	0.07 ± 0.14	0.08 ± 0.38	−0.05 ± 0.26	−0.06 ± 0.10

predicted from the crystal structures, the repulsive interaction was most evident in **2a**, which also had the lowest folded/unfolded ratio. The repulsive interactions complicate the measurement of the absolute strengths of the CH−π interactions but do not diminish the utility of **1**−**3** in measuring the isotope effects for the CH−π interactions.

Differences in the strengths of the intramolecular CH−π and CD−π interactions were assessed by comparison of the folded/unfolded ratios and the corresponding folding energies (Table 1). The folding energies for protic and deuterated balances **1**−**3** were almost identical. The differences ($\Delta\Delta G_{fold}$) were very small and within the error of the analysis (±0.03 kcal/mol), which was calculated on the basis of a conservative estimate of ±5% for the ^{1}H NMR integration error.[18] The folding energies in acetone-d_6 were also compared (see the SI). Again, nearly identical folding energies were observed, with even smaller errors.

To confirm the above single-point measurements, more comprehensive multipoint van't Hoff analyses were carried out. The folded/unfolded ratios for balances **1**−**3** were measured over a range of temperatures (25−55 °C) in $CDCl_3$ and acetone-d_6, and the ΔG_{fold} values were calculated from the measured ΔH and ΔS values (Table 2). This study led to the same conclusion that the small differences in the ΔG_{fold} values for the protic and deuterated balances were well within the error of the analysis.

The above experimental studies found only small differences in the strengths of the CH−π and CD−π interactions that were smaller than the experimental error of the analyses. Therefore, we concluded that either there was no deuterium isotope effect for the CH−π interaction or that the effect was too small to be measured accurately using our model systems. Another possible explanation would be that the isotope effects for the attractive CH−π and repulsive steric interactions perfectly canceled out in all three balances. However, this possibility was deemed unlikely. First, the attractive and repulsive isotope effects would have to balance perfectly for all three model systems, despite the differences in their geometries and conformational constraints. Second, the repulsive steric interactions in balances **1**−**3** are very small (<1.0 kcal/mol) and do not change significantly with small differences in the lengths of the C−D and C−H bonds.[20]

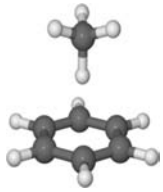

Figure 5. Model benzene−methane system used in the computational studies of the D/H isotope effect for the CH−π interaction.

To investigate further the isotope effect for the CH−π interaction, computational studies were carried out using a simple model system of methane interacting with benzene (Figure 5). Under the Born−Oppenheimer approximation, CH−π and CD−π interactions take place on the same electronic potential energy surface. The primary difference should come from the fact that a C−D stretch has a significantly lower vibrational frequency than a C−H stretch; this would be reflected as a difference in the corrections added to the electronic energies to obtain the enthalpies. Secondarily, one could also consider shifts due to the slight difference in the C−H and C−D bond lengths. We investigated the order of magnitude of both possible effects using DFT with the Perdew−Becke−Ernzerhof (PBE) exchange−correlation functional.[21] Because standard DFT does not account for long-range dispersion interactions that are important in intermolecular interactions, we added Grimme's D2 empirical pairwise dispersion correction with the parameters recommended for PBE;[22] this approach is denoted PBE-D2. Pople's standard 6-31+G* basis set was used.

The geometry of the interaction model was optimized at the PBE-D2/6-31+G* level. The C_{3v}-symmetric model chosen was not a potential energy minimum (the energy was lower when the CH_4 was tilted so one of the other hydrogens could also interact with the benzene ring), but the associated small imaginary vibrational frequencies should not significantly impact our exploration of isotope effects (an alternative structure in which the methane C−H bonds lie between benzene C−C bonds was essentially isoenergetic and featured analogous small imaginary frequencies). Replacing the interacting H of CH_4 with D in the complex led to an increase in binding energy of only 0.02 kcal/mol due to mass-dependent changes in the 298 K enthalpy correction (replacing all of the H's in CH_4 with D's decreased the binding energy by 0.01 kcal/mol).

A computational study by Houk and co-workers used this same model system to estimate isotope effects in *p*-xylene-d_3 as a guest (along with CCl_4 as a coguest) in a dimeric capsule complex;[7b] they found a considerably larger effect due to vibrational energy contributions. One major difference, however, is that the host capsule in that study presented three aromatic faces to interact with one methyl group of *p*-xylene, thus tripling the size of the isotope effect in their additive estimates. Another is that their MP2/6-311++G(d,p) level of theory predicted 3 times the zero-point vibrational energy stabilization of CH_3D/C_6H_6 versus CH_4/C_6H_6. Our binding energy for this complex, 1.78 kcal/mol, is closer to coupled-cluster complete-basis-set estimates of 1.45 kcal/mol[23] than their value of 0.85 kcal/mol, suggesting that our value for this quantity is likely to be more reliable. Finally, our results also include finite-temperature effects on the enthalpy that were neglected in the previous study, which further reduce the computed isotope effect.

Another possible source of D/H isotope effects for CH−π interactions is a steric effect due to the fact that the vibrationally

averaged bond length of C−H is longer than that of C−D by ∼0.005 Å. To obtain a rough estimate the size of this steric effect on the CH−π interactions, we computed interaction energies for our methane−benzene model while stretching or compressing the interacting methane C−H bond (Δr = ±0.005 Å). The distance R between the plane of the benzene and the methyl carbon was set to 3.493 Å (the closest approach for **1a**) and varied by ±0.2 Å. The results are plotted in Figure S9 in the SI. The interaction between methane and benzene became more favorable ($\Delta\Delta E_{int} < 0$) as the C−H bond was compressed (mimicking C−D bonds). The effect was negligible (∼0.01 kcal/mol or less) for $R \geq 3.493$ Å, but it grew as the benzene came closer to the methane ($\Delta R < 0$), becoming as large as 0.04 kcal/mol for $\Delta R = -0.2$ Å and $\Delta r = -0.005$ Å. Hence, this "steric isotope effect" is negligible for the present systems but may become significant in other systems with closer CH−π contacts. *The steric origin of this effect was confirmed using our symmetry-adapted perturbation theory (SAPT) program* (Figure S27).[24]

In conclusion, D/H isotope effects were not observed for the CH−π interaction within three very sensitive small-molecule model systems containing different CH−π interaction geometries and environments. The experimental results were corroborated by theoretical calculations that compared the interaction energies of methane and benzene. The experimental and theoretical systems in this study were designed to minimize steric interactions. Thus, previous reports of isotope effects were probably due to other factors (e.g., the different sizes of CH_3 and CD_3 groups placed within more confined environments) rather than attenuation of the CH−π interaction.[25] This steric hypothesis was supported by the calculations, which showed that differences in energy arose when the interacting groups were brought closer than the optimal CH−π interaction distance. While the lack of an isotope effect eliminates the possibility of using deuteration to enhance the CH−π interaction, it validates the use of deuteration for spectroscopic and labeling purposes, as this introduces a minimal perturbation of the system.[26]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, ^{1}H and ^{13}C NMR spectra, X-ray data (CIF), and van't Hoff plots for balances **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

shimizu@mail.chem.sc.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CHE 0911616 and CHE 1011360).

■ REFERENCES

(1) (a) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π Interaction. Evidence, Nature, and Consequences*; Wiley-VCH: New York, 1998. (b) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201. (c) Nishio, M.; Umezawa, Y.; Honda, K.; Tsuboyama, S.; Suezawa, H. *CrystEngComm* **2009**, *11*, 1757. (d) Nishio, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873. (e) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808.

(2) (a) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665. (b) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185. (c) Tewari, A. K.; Dubey, R. *Bioorg. Med. Chem.* **2008**, *16*, 126. (d) Ozawa, T.; Okazaki, K.; Kitaura, K. *J. Comput. Chem.* **2011**, *32*, 2774. (e) Ozawa, T.; Okazaki, K.; Kitaura, K. *Bioorg. Med. Chem.* **2011**, *19*, 5231.

(3) Nishio, M. *Tetrahedron* **2005**, *61*, 6923.

(4) (a) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Bioorg. Med. Chem.* **1999**, *7*, 2021. (b) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047. (c) Takahashi, O.; Kohno, Y.; Nishio, M. *Chem. Rev.* **2010**, *110*, 6049.

(5) (a) Brandl, M.; Weiss, M. S.; Jabs, A.; Suhnel, J.; Hilgenfeld, R. *J. Mol. Biol.* **2001**, *307*, 357. (b) Fernandez, M. D.; Canada, F. J.; Jimenez-Barbero, J.; Cuevas, G. *J. Am. Chem. Soc.* **2005**, *127*, 7379.

(6) Wade, D. *Chem.-Biol. Interact.* **1999**, *117*, 191.

(7) (a) Rechavi, D.; Scarso, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7738. (b) Zhao, Y. L.; Houk, K. N.; Rechavi, D.; Scarso, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 11428.

(8) Haino, T.; Fukuta, K.; Iwamoto, H.; Iwata, S. *Chem.—Eur. J.* **2009**, *15*, 13286.

(9) (a) Turowski, M.; Yamakawa, N.; Meller, J.; Kimata, K.; Ikegami, T.; Hosoya, K.; Tanaka, N.; Thornton, E. R. *J. Am. Chem. Soc.* **2003**, *125*, 13836. (b) Iyer, S. S.; Zhang, Z. P.; Kellogg, G. E.; Karnes, H. T. *J. Chromatogr. Sci.* **2004**, *42*, 383.

(10) (a) Liu, Y.; Warmuth, R. *Org. Lett.* **2007**, *9*, 2883. (b) Mugridge, J. S.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1182.

(11) Bhayana, B.; Ams, M. R. *J. Org. Chem.* **2011**, *76*, 3594.

(12) (a) Carroll, W. R.; Pellechia, P.; Shimizu, K. D. *Org. Lett.* **2008**, *10*, 3547. (b) Carroll, W. R.; Zhao, C.; Smith, M. D.; Pellechia, P. J.; Shimizu, K. D. *Org. Lett.* **2011**, *13*, 4320.

(13) (a) Eto, M.; Setoguchi, K.; Harada, A.; Sugiyama, E.; Harano, K. *Tetrahedron Lett.* **1998**, *39*, 9751. (b) Yoshitake, Y.; Misaka, J.; Setoguchi, K.; Abe, M.; Kawaji, T.; Eto, M.; Harano, K. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1611.

(14) (a) Grossmann, G.; Potrzebowski, M. J.; Olejniczak, S.; Ziolkowska, N. E.; Bujacz, G. D.; Ciesielski, W.; Prezdo, W.; Nazarov, V.; Golovko, V. *New J. Chem.* **2003**, *27*, 1095. (b) Srivastav, K. K.; Verma, A. K.; Verma, S. M. *Indian J. Chem., Sect. B* **1993**, *32*, 1143. (c) Kishikawa, K.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamaguchi, K.; Yamadab, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1233.

(15) The crystal structures of **1a** and **3a** were reported previously.[14a,c]

(16) The crystal structure of **2a** contained three different folded conformers that formed intramolecular CH−π interactions with slightly different geometries and distances; only one is shown in Figure 1b.

(17) (a) Hobza, P.; Havlas, Z. *Chem. Rev.* **2000**, *100*, 4253. (b) Nishio, M. *CrystEngComm* **2004**, *6*, 130.

(18) (a) Bauer, M.; Bertario, A.; Boccardi, G.; Fontaine, X.; Rao, R.; Verrier, D. *J. Pharm. Biomed. Anal.* **1998**, *17*, 419. (b) Rizzo, V.; Pinciroli, V. *J. Pharm. Biomed. Anal.* **2005**, *38*, 851. (c) Soininen, P.; Haarala, J.; Vepsalainen, J.; Niemitz, M.; Laatikainen, R. *Anal. Chim. Acta* **2005**, *542*, 178.

(19) Integration of *o*-methyl groups gave similar folded/unfolded ratios. However, *o*-methyl peak integrations could not be used for comparisons because this peak is absent in the deuterated balances.

(20) A third reason that this explanation is unlikely is that it requires the attractive CD−π interaction to be weaker than the CH−π interaction. However, all reports that have observed deuterium isotope effects for the CH−π interaction have found the opposite trend.

(21) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.

(22) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787.

(23) Ringer, A. L.; Figgs, M. S.; Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2006**, *110*, 10822−10828.

(24) Hohenstein, E. G.; Parrish, R. M.; Sherrill, C. D.; Turney, J. M.; Schaefer, H. F., III. *J. Chem. Phys.* **2011**, *135*, No. 174107.

(25) (a) Turowski, M.; Yamakawa, N.; Meller, J.; Kimata, K.; Ikegami, T.; Hosoya, K.; Tanaka, N.; Thornton, E. R. *J. Am. Chem. Soc.* **2003**, *125*, 13836. (b) Iyer, S. S.; Zhang, Z. P.; Kellogg, G. E.; Karnes, H. T. *J. Chromatogr. Sci.* **2004**, *42*, 383.

(26) Ruschak, A. M.; Kay, L. E. *J. Biomol. NMR* **2010**, *46*, 75.