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A Molecular Balance for Measuring Aliphatic CH−π Interactions

William R. Carroll, Chen Zhao, Mark D. Smith, Perry J. Pellechia, and Ken D. Shimizu*

*Department of Chemistry and Biochemistry, University of South Carolina, Columbia,
South Carolina 29208, United States*

shimizu@mail.chem.sc.edu

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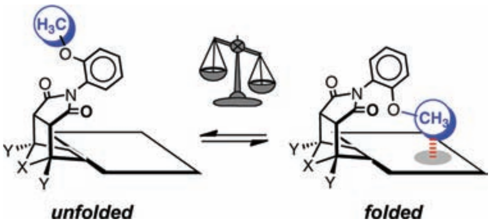
ABSTRACT



A series of conformationally flexible bicyclic *N*-arylimides were employed as molecular balances to study the weak aliphatic CH−π interaction between alkyl and arene groups. The formation of intramolecular CH−π interactions in the *folded* conformers was characterized by X-ray crystallography. The strengths of the interactions were characterized in CDCl$_3$ by the changes in the *folded*/*unfolded* ratios, as measured by ^{1}H NMR. The CH−π interaction between a methyl group and an aromatic surface was $\sim$1.0 kcal/mol and was easily disrupted or masked by conformational entropy and repulsive steric interactions.

The CH−π interactions between alkyl and arene groups play an important role in many active areas of research, including the conformation of small molecules,[1] assembly of host−guest complexes,[2] and folding of proteins and polynucleotides.[3] The CH−π interaction has been primarily characterized in crystal structures and computational studies.[1] One reason is that direct measurement of the CH−π has been difficult due to the weak and nondirectional nature of the interaction.[4,5] Here, we have synthesized and utilized a series of small molecule molecular torsional balances (**1**−**3**) to experimentally measure the strength of the CH−π interaction *in solution* (Figure 1).[6]

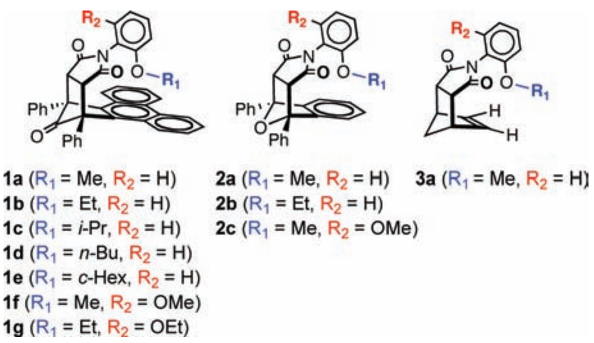


Figure 1. One-armed (**1a**−**e**), two-armed (**1f**, **1g**, and **2c**), and control (**2a**−**b**, **3a**) molecular balances designed to measure CH−π interactions.

The new CH−π molecular balances were built on a conformationally dynamic bicyclic *N*-arylimide framework

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(1) (a) Nishio, M.; Umezawa, Y.; Honda, K.; Tsuboyama, S.; Suezawa, H. *CrystEngComm* **2009**, *11*, 1757–1788. (b) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047–10056. (c) Mati, I. K.; Cockroft, S. L. *Chem. Soc. Rev.* **2010**, *39*, 4195–4205. (d) Bhayana, B.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6833–6836. (e) Shimohigashi, Y.; Maeda, I.; Nose, T.; Ikesue, K.; Sakamoto, H.; Ogawa, T.; Ide, Y.; Kawahara, M.; Nezu, T.; Terada, Y.; Kawano, K.; Ohno, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2479–2485. (f) Aliev, A. E.; Moise, J.; Motherwell, W. B.; Nic, M.; Courtier-Murias, D.; Tocher, D. A. *Phys. Chem. Chem. Phys.* **2009**, *11*, 97–100. (g) Motherwell, W. B.; Moise, J.; Aliev, A. E.; Nic, M.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B.; Chessari, G.; Hunter, C. A.; Vinter, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7823–7826. (h) Gung, B. W.; Emenike, B. U.; Lewis, M.; Kirschbaum, K. *Chem.—Eur. J.* **2010**, *16*, 12357–12362.

(2) (a) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185–6191. (b) Zhao, R.; Matsumoto, S.; Akazome, M.; Ogura, K. *Tetrahedron* **2002**, *58*, 10233–10241.

(3) (a) Brandl, M.; Weiss, M. S.; Jabs, A.; Suhnel, J.; Hilgenfeld, R. *J. Mol. Biol.* **2001**, *307*, 357–377. (b) Umezawa, Y.; Nishio, M. *Bioorg. Med. Chem.* **1998**, *6*, 2507–2515. (c) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Bioorg. Med. Chem.* **1999**, *7*, 2021–2026.

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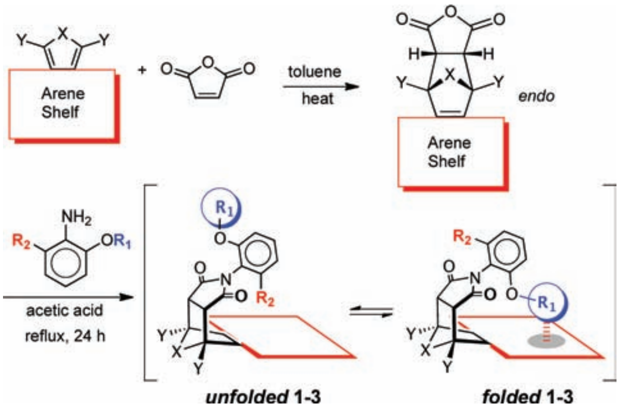
that we previously developed to study face-to-face π-stacking interactions.[7] Restricted rotation about the $C_{aryl}-N_{imide}$ bond leads to the formation of two distinct conformers. In the *folded* conformation, the *ortho*-alkoxy group (OR_1) is positioned over the arene shelf forming an intramolecular CH−π interaction. In the *unfolded* conformation, the OR_1 group is positioned far away from the arene shelf. Therefore, changes in the *folded*/*unfolded* ratios of the molecular balances provide an accurate measure of the strength of the intramolecular CH−π interaction. Three types of balances were studied. Balances **1a**−**e** have alkoxy groups of varying size that can interact with a large phenanthrene surface. Control balances **2a**−**b** and **3a** have alkoxy groups that can interact with smaller benzene or ethylene surfaces. Finally, 'two-armed' balances **1f**, **1g**, and **2c** have two identical *ortho*-alkoxy arms, which forces the balances to always position one of the alkoxy groups over the arene shelf.

One of the most attractive features of the *N*-arylimide molecular balances was that they all could be quickly assembled via the same two-step route (Scheme 1). First, a Diels−Alder reaction between a cyclic diene containing an arene shelf and maleic anhydride yielded an *endo*-bicyclic anhydride. Second, thermal condensation of the bicyclic anhydride with an *ortho*-substituted aniline formed the *N*-arylimide of the molecular balance. Both reactions proceeded in high yields (>80%). This modular synthesis enabled the systematic variation of the size of the alkyl group (R_1 = Me, Et, *i*-Pr, *n*-Bu, *c*-Hex) and the arene shelf (arene shelf = phenanthrene, benzene, ethylene).

Scheme 1. General Synthesis of Balances **1**−**3** (X = CO, O, or CH_2; Y = H or Ph)



To verify the formation of an intramolecular CH−π interaction in the *folded* conformers, the solid-state structures of the balances were analyzed by X-ray crystallography. Unfortunately, the one-armed balances preferred to crystallize in the *unfolded* conformation, due to the repulsive interaction between the ether oxygen linker and the arene shelf. To force the molecule to crystallize in the *folded* conformation, two-armed balances **1f**, **1g**, and **2b** were synthesized that have identical alkyl-ether substituents at both *ortho*-aryl positions. Therefore, one of the two arms would always point toward the aryl shelf.

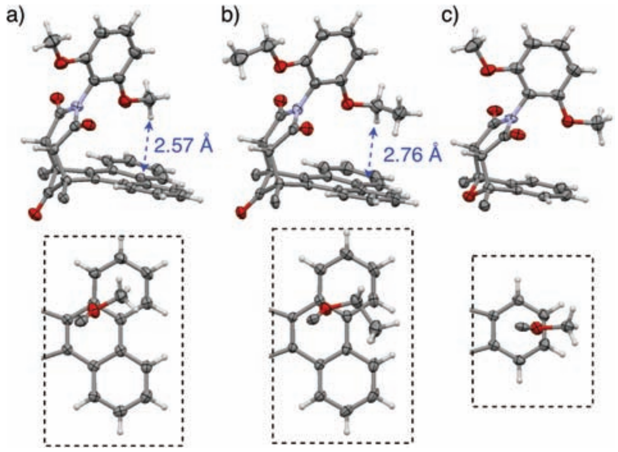


Figure 2. X-ray structures of two-armed balances (a) **1f**, (b) **1g**, and (c) **2c**. The solvent molecules and the bridgehead phenyl groups are hidden for viewing clarity. The inset boxes show top views of the interacting alkoxy and arene surfaces in each balance.

X-ray crystal structures of the two-arm balances **1f**, **1g**, and **2c** were obtained (Figure 2). The OMe and OEt groups in **1f,g** each form well-defined CH−π interactions. A proton on the carbon bonded to the ether oxygen points toward the face of the outer ring of the phenanthrene shelf with atom-to-plane distances of 2.57 and 2.76 Å, respectively. These distances are less than the sum of the van der Waals radii of the interacting H and C atoms (2.90 Å) and are also within the commonly used distance cutoff of 3.05 Å for the CH−π interaction.[1a] The terminal carbon of the OEt group in **1g** extends beyond the phenanthrene surface; thus it can only form a weak second CH−π interaction.

Control balance **2c** with the shorter benzene surface (Figure 2c) does not form a CH−π interaction, as the methyl group extends beyond the benzene shelf in both ball-and-stick and space-filling models. However, **2c** retains the lone pair−π interaction between the oxygen of the ether linker and the arene shelf that is also present in balance **1**.[8] Thus, comparison of the folding propensities of

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(4) (a) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498. (b) Hughes, R. M.; Waters, M. L. *Curr. Opin. Struct. Biol* **2006**, *16*, 514–524. (c) Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem.* **2003**, *1*, 157–162. (d) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665–8701.

(5) Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057–7065.

(6) These studies of the CH−π interaction were carried out in the condensed phase, and attributes of the CH−π interactions include solvation effects.

(7) Carroll, W. R.; Pellechia, P.; Shimizu, K. D. *Org. Lett.* **2008**, *10*, 3547–3550.

(8) In **2b**, the oxygen to aromatic plane distance is 3.37 Å distance, which is similar to distances for **1f** and **1g** (3.519 Å for OEt, 3.374 Å for OMe)

balances **1** and **2** provides a direct measure of strength of the intramolecular CH−π interaction.

The strengths of the CH−π interactions were measured by monitoring the *folded*/*unfolded* conformational equilibrium by ^{1}H NMR. Due to restricted rotation around the C_{aryl}−N_{imide} single bonds, the *folded* and *unfolded* conformations were in slow exchange at rt[9] and separate peaks for the alkoxy groups in each conformation were observed in the ^{1}H NMR spectra. For phenanthrene balances **1a**−**g** that form intramolecular CH−π interactions, large upfield shifts of 1.4−1.6 ppm were observed for the alkoxy protons in the *folded* conformers due to the proximity of the arene shelf. In contrast, only small upfield shifts were observed for the *folded* conformers of control balances **2** (0.1−0.3 ppm) and **3** (0.01 ppm).

Table 1. Comparison of the *Folded*/*Unfolded* Ratios and ΔG_{fold} Values for the One-Armed Balances As Measured by ^{1}H NMR Integration, in $CDCl_3$ at 23 °C

balances	alkoxy-arm	arene-shelf	K_{eq} [*folded*]/[*unfolded*]	ΔG_{fold} (kcal/mol)
1a	OMe	phenanthrene	0.46	0.45
1b	OEt	phenanthrene	0.20	0.94
1c	O*i*-Pr	phenanthrene	<0.05[a]	>1.8
1d	O*n*-Bu	phenanthrene	0.13	1.2
1e	O*c*-*Hex*	phenanthrene	<0.05[a]	>1.8
2a	OMe	benzene	0.09	1.40
2b	OEt	benzene	0.036	1.96
3a	OMe	ethene	0.73	0.18

[a] For balances **1c** and **1e**, only the *unfolded* conformer was observed, and thus a maximum *folded*/*unfolded* ratio of 0.05 was estimated based on a ^{1}H NMR integration accuracy of ±2%.

The folding propensities of the balances **1a**−**e** and control balances **2a**−**b** and **3a** were measured. Integration of the peaks for the respective conformers yielded the *folded*/*unfolded* ratios and ΔG_{fold} values (Table 1).[10] The singlets corresponding to two *syn*-protons on the succinimide rings of the balances provided the most accurate *folded*/*unfolded* ratios as they fell in a clear region of the ^{1}H NMR spectra (4.2−4.8 ppm) and were well differentiated in most solvents. The conformers with aromatic shelves (**1a**−**e** and **2a**−**b**) were assigned by the upfield shifts of the alkoxy protons in the *folded* conformers.[11]

The differences in the folding energies ($\Delta\Delta G$) of balances **1** and **2** that can and cannot form CH−π interactions, respectively, provide a measure of the CH−π interactions. Therefore, the $\Delta\Delta G$ for methoxy balances **1a** and **2a** yields an estimate of −0.95 kcal/mol for the CH−π interaction in $CDCl_3$ ($\Delta\Delta G$ = 0.45−1.40 kcal/mol). An analogous analysis with ethoxy balances **1b** and **2b** yielded a value of −1.04 kcal/mol. The magnitude of the CH−π interaction also compares favorably to previous measurements by Wilcox of −0.44 kcal/mol for an intramolecular alkyl CH−π interaction in $CDCl_3$.[4]

Although the CH−π interactions in **1a** and **1b** were attractive, the *folded* conformers were still not the major conformers ($K_{\text{eq}} < 1.0$). We hypothesized that this was due to an opposing repulsive lone pair−π interaction between the ether oxygen linkers and the arene surfaces. Although the lone pair−π interaction was considered to be attractive by many researchers,[12] our result showed that it can be repulsive. To measure the strength of the repulsive interaction, control balance **3a** was prepared, which lacked an aromatic surface. Therefore, the K_{eq} of **3a** provided a measure of the intrinsic conformational bias of the *N*-arylimide framework in the absence of the attractive CH−π and the repulsive oxygen−arene interaction. As expected, K_{eq} of **3a** was close to unity (0.73). The slight bias for the *unfolded* conformer was attributed to differences in dipole and solvation energy of the conformers. The $\Delta\Delta G_{\text{fold}}$ for **2a** and **3a** was +1.22 kcal/mol. This repulsive oxygen−π interaction was slightly larger than the attractive CH−π interactions in **1a** and **1b**, providing an explanation for the overall bias for the *unfolded* conformers in both balances.

Next, balances **1a**−**e** with alkoxy arms (OMe, OEt, O*i*-Pr, O*n*-Bu, and O*c*-Hex) of varying lengths and widths were prepared and studied (Table 1). In general, larger alkoxy arms appeared to weaken the intramolecular CH−π interactions. This trend could be explained for the branched O*i*-Pr and O*c*-Hex groups in **1c** and **1d**. Modeling showed that these secondary alkoxy groups create significant steric strain in the *folded* conformation. One of the two alkyl groups attached to the branch point was always pressed into the arene shelf. The destabilization of the balances with the longer linear alkoxy arms **1b** (OEt) and **1d** (O*n*-Bu) was more difficult to explain. X-ray and molecular modeling studies predicted that **1a**, **1b**, and **1d** should have similar folding energies because (1) they all form one strong CH−π interaction between the protons on the carbon attached to the ether oxygen and the phenanthrene surface and a second weaker CH−π interaction for the longer OEt and O*n*-Bu balances[13] and (2) the more flexible linear alkoxy groups can adopt conformations that minimize any destabilizing steric interactions. A possible explanation was that the observed differences in ΔG_{fold} were due to differences in conformational entropy (ΔS) of the alkoxy arms.

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(9) For example, the rotational barrier about the C_{aryl}−N_{imide} bond in balance **1a** was measured to be 20.5 kcal/mol by VT NMR method (coalescence temp = 135 °C). This equates to a half-life of 1.4 min at 23 °C.

(10) To verify that aggregation did not also attenuate the *folded*/*unfolded* ratio, the K_{eq} of balance **1a** was measured over a wide concentration range. The *folded*/*unfolded* ratio remained constant from 1.9 to 17 mM in $CDCl_3$, confirming that aggregation did not affect the *folded*/*unfolded* ratio.

(11) For balance **3a**, the conformers were assigned by NOEs between the methyl ether and vinyl protons in the *folded* conformer.

(12) (a) Schneider, H. J.; Werner, F.; Blatter, T. *J. Phys. Org. Chem.* **1993**, *6*, 590–594. (b) Egli, M.; Sarkhel, S. *Acc. Chem. Res.* **2007**, *40*, 197–205. (c) Gung, B. W.; Zou, Y.; Xu, Z. G.; Amicangelo, J. C.; Irwin, D. G.; Ma, S. Q.; Zhou, H. C. *J. Org. Chem.* **2008**, *73*, 689–693. (d) Korenaga, T.; Tanaka, H.; Ema, T.; Sakai, T. *J. Flourine Chem.* **2003**, *122*, 201–205. (e) Annunziata, R.; Benaglia, M.; Cozzi, F.; Mazzanti, A. *Chem.—Eur. J.* **2009**, *15*, 4373–4381. (f) Benaglia, M.; Cozzi, F.; Mancinelli, M.; Mazzanti, A. *Chem.—Eur. J.* **2010**, *16*, 7456–7468.

(13) The second CH−π interaction is near the edge of an arene shelf, where it is much less electron-rich than the center of the shelf; thus it is not as strong as the first CH−π contact.

To test this theory, the entropic and enthalpic terms of the folding equilibria were measured for balances **1a**, **1b**, **2a**, **2b**, and **3a** (Figure 3).[14] The analysis confirmed that the apparent differences in the CH$-\pi$ interactions of the OMe and OEt balances were due to differences in conformational entropy. For example, the $\Delta\Delta G$ of 0.47 kcal/mol for OEt and OMe balances, **1b** and **1a**, was due primarily to the differences in the entropic term, as $-T\Delta\Delta S > \Delta\Delta H$ (Table 2, entry 1). The additional methylene group of the OEt arm of **1b** forms only a slightly stronger CH$-\pi$ interaction, as $\Delta\Delta H$ was small. The larger change was in the entropic term (0.61 kcal/mol), which can be attributed the loss of rotational freedom in the OEt arm when it is held against the phenanthrene shelf in the *folded* conformation. The same entropic penalty was observed for the smaller benzene-shelf balances **2b** and **2a** (Table 2, entry 2) that cannot form CH$-\pi$ interactions, confirming that the entropic penalty in the OEt group was due to rotational isomerism around the O$-$CH$_2$ bond and not the CH$_2-$CH$_3$. The magnitude of the entropic penalty was also consistent with estimates of loss of rotational freedom around the O$-$C bond of an ethoxy group ($-T\Delta\Delta S = 0.43$ kcal/mol).[15]

Table 2. Comparison of $\Delta\Delta G$, $\Delta\Delta H$, and $-T\Delta\Delta S$ Values for Balances for Selected Pairs of Balances (in CDCl$_3$, 25 °C)

entry	Comparison	$\Delta\Delta G$ (kcal·mol^{-1})	$\Delta\Delta H$ (kcal·mol^{-1})	$-T\Delta\Delta S$ (kcal·mol^{-1})
1	**1b**$-$**1a**	0.47	-0.14	0.61
2	**2b**$-$**2a**	0.62	-0.03	0.60
3	**1a**$-$**2a**	-0.95	-0.79	-0.15
4	**1b**$-$**2b**	-1.10	-0.96	-0.14
5	**2a**$-$**3a**	1.23	0.42	0.81

The analyses in Table 2 also confirmed the validity of measuring the CH$-\pi$ interaction via the difference in folding energies of the phenanthrene and benzene-shelved balances **1** and **2** (Table 2, entries 3 and 4). This comparison effectively removes the differences in conformational entropy in the *folded* and *unfolded* conformers, isolating the enthalpic differences associated with the CH$-\pi$ interaction. This can be seen by the dominant enthalpic terms ($|\Delta\Delta H| > |T\Delta\Delta S|$). Also, the -0.17 kcal/mol difference between $\Delta\Delta H$ terms for **1a**$-$**2a** and **1b**$-$**2b** (-0.79 and -0.96 kcal/mol) indicated a slightly stronger CH$-\pi$ interaction for **1b** vs **1a**, consistent with the additional CH$-\pi$ contact identified above in the solid structure of **1g**.

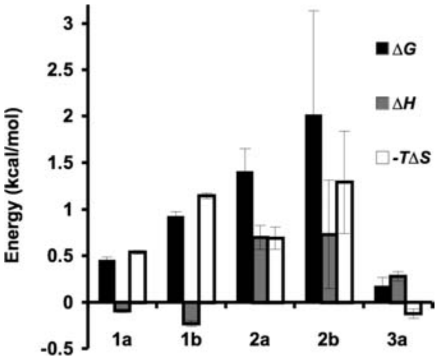

Figure 3. Folding energy (ΔG), enthalpy (ΔH), and entropy ($T\Delta S$) values in CDCl$_3$ for balances **1a**, **2a**, **1b**, **2b**, **3a** measured from van't Hoff plots (25$-$55 °C).

In conclusion, a series of molecular balances based on the versatile bicyclic *N*-arylimide framework were designed, which can accurately measure intramolecular CH$-\pi$ interactions. Due to the weak nature of the CH$-\pi$ interaction (~1.0 kcal/mol) and the sensitivity of the balances, stability trends were easily masked by other weak forces such as rotational entropy and repulsive lone pair$-\pi$ interactions. However, through comparison with carefully designed control balances, we can isolate the relative contribution of the CH$-\pi$ interaction to the ΔG_{fold}. For example, the 0.45 kcal/mol ΔG_{fold} measured for balance **1a** is the sum of three terms: (1) the attractive CH$-\pi$ interaction between the methyl and phenanthrene surfaces (-0.95 kcal/mol), (2) the repulsive oxygen$-\pi$ interaction (1.23 kcal/mol), and (3) the slight conformational bias of the balances for the *unfolded* conformer (0.17 kcal/mol).[16]

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

Supporting Information Available. Full experimental details, ^{1}H and ^{13}C NMR spectra, and X-ray data are provided for compounds **1a**$-$**e**, **2a**$-$**b**, and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] The van't Hoff analysis for balances **1c**, **1d**, and **1e** were not performed because of the large errors in the analysis for balances with *folded*/*unfolded* ratios that were < 0.1 or > 10.

[15] Mammen, M; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem.* **1998**, *63*, 3168–3175.

[16] The magnitude of the conformational bias for the bicyclic *N*-aryl imide framework was estimated based on the *folded*/*unfolded* ratio for control balance **3a**, which does not form a CH$-\pi$ interaction and allows free rotation around the bonds of the alkoxy arm in both conformers.