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A Rigid Molecular Balance for Measuring Face-to-Face Arene−Arene Interactions

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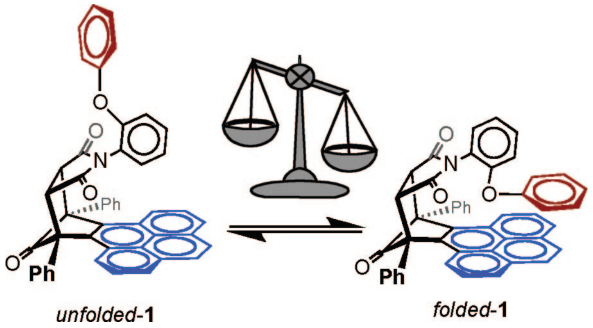
ABSTRACT



A new molecular balance was developed to measure face-to-face arene−arene interactions. The balance adopts distinct *folded* and *unfolded* conformations due to restricted rotation about a $C_{aryl}-N_{imide}$ bond. In the *folded* conformer, the rigid bicyclic framework enforces an offset face-to-face geometry to the exclusion of edge-to-face geometries, which was verified by X-ray crystallography. Measurement of the *folded* to *unfolded* ratio yields accurate values for the arene−arene interaction in a range of different solvents.

Arene−arene interactions play an important role in determining the conformation of organic molecules,[1] the structure and stability of proteins and polynucleotides,[2] and directing the stereoselectivity of organic transformations.[3] Thus, a better understanding of the origins and parameters of arene−arene interactions would lead to more accurate predictions of molecular structure and reactivity. One of the most effective methods to study the geometries and strengths of arene−arene interactions has been small molecule model systems.[4] These model systems have provided an important experimental basis for the development of computational models for the study of the arene−arene interaction.[5] Reported herein is the development of a new design of molecular balance systems (**1**−**3**) for measuring face-to-face arene−arene interactions (Scheme 1). The rigid bicyclic *N*-arylsuccinimide framework of these balances constrains the arene−arene interactions to an offset face-to-face geometry, which has been characterized in the solid-state via X-ray crystallography and in the solution via ^{1}H NMR. Strength of the arene−arene interaction was easily measured by quantification of the *folded/unfolded* ratio by integration of their ^{1}H NMR spectra. The balances are also readily assembled in modular fashion allowing examination of the influence of various sized arene groups and are readily

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[1] Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

[2] Hughes, R. M.; Waters, M. L. *Curr. Opin. Struct. Biol.* **2006**, *16*, 514.

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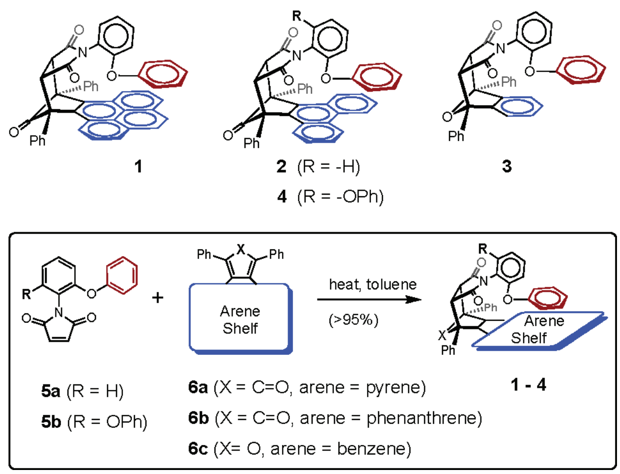
Scheme 1. Synthesis of the Molecular Balances **1**−**4** via the Diels−Alder Reaction between Maleimides **5** and Fused Bicyclic Dienes **6**[a]



[a] Balances **1**−**3** are shown in the *folded* state.

soluble in a wide range of organic solvents allowing study of the influence of solvent on the face-to-face arene−arene interaction.

A major difficulty in studying and quantifying arene−arene interactions is that two arene rings can adopt a continuum of different face-to-face and edge-to-face geometries (Figure 1).[6] Accordingly, model systems have been developed to independently study the edge-to-face[7] and face-to-face arene−arene geometries.[8] The development of model systems to study the face-to-face geometry have been particularly challenging. Often, the face-to-face geometry is dominant but the models are sufficiently flexible that edge-to-face interactions can also occur. In other cases, the model systems are too rigid and fix the arene surfaces in an unfavorable geometry.[4a]

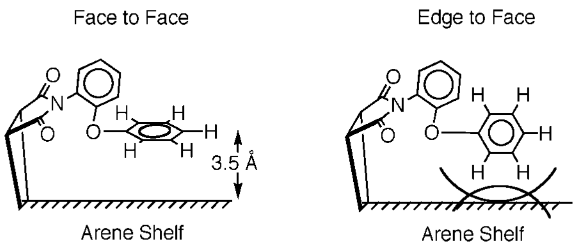


Figure 1. Representation of the geometric constraints in the folded conformers of systems **1**−**4**. The proximity of the phenyl arm to the arene shelf allows for effective formation the face-to-face geometry but prevents the formation of an edge-to-face geometry.

We have designed a new molecular balance based on the rigid bicyclic *N*-arylimide framework that restricts the arene−arene interaction to a face-to-face geometry.[9] Balances **1**−**3** adopt distinct *folded* and *unfolded* conformations due to restricted rotation about a central C_{aryl}−N_{imide} bond. Molecular modeling studies predicted that the benzene ring of the phenyl ether arm was perfectly positioned in the *folded*-conformer to form an effective offset face-to-face interaction with the arene shelf (Figure 1, left). More importantly, the modeling studies also predicted that the phenyl ether arm cannot adopt an edge-to-face geometry in the *folded*-conformer because it is held too closely (Figure 1, right) to the arene shelf (<4.0 Å) to allow edge-to-face interactions, which normally require 5−6 Å (centroid to centroid).[10] In the *unfolded* conformer, the phenyl ether arm is far from the arene shelf and cannot interact with the arene shelf. Thus, the strength of the face-to-face arene−arene interaction can be assessed by measuring the ratio of *folded* to *unfolded* conformers by ^{1}H NMR. Balances **1**−**3** differ in the size of their arene shelves. Molecular models predicted that the larger pyrene and phenanthrene shelves of **1** and **2** could form effective arene−arene interactions with the phenyl ether arm. In the case of balance **3**, the benzene shelf is too short to form stacking interactions, and thus, balance **3** was used as a control system to assess the influence of additional attractive or repulsive interactions between the arm and the arene shelf.

The study of balances **1**−**3** was facilitated by their facile and modular synthesis (Scheme 1). The rigid bicyclic framework was assembled in one step via a Diels−Alder reaction between *N*-aryl maleimide **5** and cyclic diene **6**. In each case, the reaction proceeded in high yields (>95%).[11] In the case of the benzene and phenanthrene balances **2**−**4**, the cyclic dienes (**6b** and **6c**) were commercially available. The pyrene-based diene **6a** was synthesized in two steps from pyrene.[12]

First, crystallographic studies were carried out in order to confirm the nature of the arene−arene interactions in the new balances in the folded structures. Crystals of **2** were obtained from various solvents. However, balance **2** consistently crystallized in the *unfolded* conformer (Supporting Information). The structure of *unfolded* **2** confirmed the *endo*-stereochemistry of the balance, and the inability of the

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(9) This framework has been used to measure C−H−arene interactions, but this is the first example of its use to measure face-to-face arene−arene interactions. (a) Sklyut, O.; Prip, R.; Azar, N.; Callahan, R.; Rothchild, R. *Spectrosc. Lett.* **2004**, *37*, 493. (b) 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. (c) Kishikawa, K.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamaguchi, K.; Yamada, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1233.

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unfolded conformer to form an intramolecular arene−arene interaction. In order to fix the balance into the *folded*-conformer, the balance **4** was prepared with two identical phenyl ether arms, which ensured that one arm was always in the *folded* conformation. The crystal structure of balance **4** established that the *folded* conformer adopts the predicted face-to-face interaction with the arene shelf (Figure 2). The benzene of the ether arm is off-center in order to maximize contact with one of the benzenes of the phenanthrene shelf. The phenyl ether arm centroid to arene shelf plane distance is 3.75 Å with a closest atom to atom contact of 3.56 Å. The phenyl ring of the arm is also offset from the benzene of the shelf by 0.85 Å. Finally, the phenyl ether oxygen is positioned sufficiently close to the arene shelf (3.46 Å), preventing the adoption of the edge-to-face geometry.

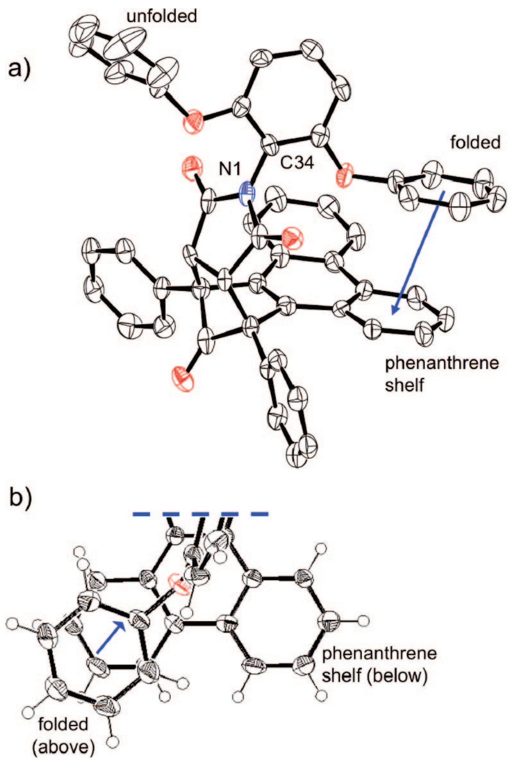

Figure 2. (a) Side view of the crystal structure of two-armed balance **4**. The arene−arene interaction in the *folded*-arm are highlighted with a blue arrow. Hydrogens were omitted for viewing clarity. (b) Truncated top-view of the arene−arene interaction between the phenylether arm (above) and phenanthrene shelf (below) in balance **4**.

Next, the arene−arene interactions were characterized in solution by ^{1}H NMR. An attractive attribute of these N-arylimide balances was that the rotational barrier was sufficiently high that the NMR spectra of the *folded* and *unfolded* conformers were in slow exchange at room temperature and the *folded/unfolded* ratio could be measured by simple integration of the corresponding peaks (Figure 3).[13] This was principally through the signals corresponding to H_b (Figure 3), which were singlets in an unobstructed region of the spectra. The upfield singlet was assigned as the *unfolded* conformer due to the proximity of the phenyl ether arm in the *unfolded* conformer. The integration of the upfield singlet was consistent with that of the doublet of doublets for H_a, which is shifted dramatically upfield to ~4.6 ppm in the *unfolded* conformer due its position over the arene shelf.[14] Variable temperature NMR of balances **1**−**3** in TCE-d_2 confirmed that the *folded* and *unfolded* conformers were in equilibrium due to the observation of coalescence of the peaks corresponding to the two isomers. This study also enabled measurement of the rotational barrier ($\Delta G = 20.9$ kcal/mol for **2**) from the temperature dependent peak widths.[15] The barrier was sufficiently high that the *folded/unfolded* ratio could be measured over a range of temperatures from rt to 130 °C. The barrier was not too high as the *folded-unfolded* equilibrium could be reached at 23 °C in 30 min (~10 half-lives).

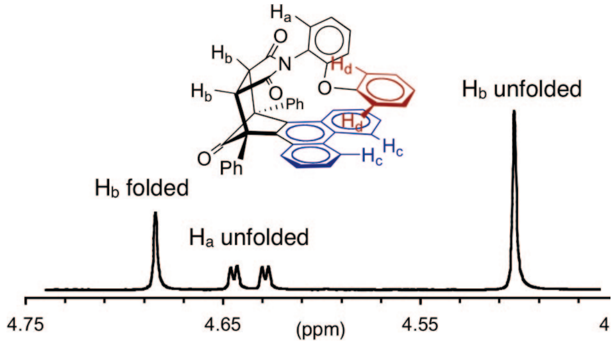

Figure 3. ^{1}H NMR of balance system **2** in $CDCl_3$ allows for quantification of *folded* and *unfolded* states via integration.

The differences in chemical shift between the *folded* and *unfolded* conformers also assisted in verifying the formation of the arene−arene interaction in solution. Specifically, the expected upfield shifts in the folded conformer were observed for protons on the phenyl arm and arene shelf. For example, the phenanthrene protons H_c and phenylether protons H_d were shifted 0.68 and 1.20 ppm upfield in the *folded* versus *unfolded* conformer (Figure 3). The magnitude of upfield shifts were also consistent the strengths of the local magnetic fields generated by the opposing arene surfaces.

The measured *folded/unfolded* ratios of balances **1**−**3** in $CDCl_3$ (Figure 4) showed a strong correlation between the size of the arene shelf, which is consistent with the presence of an arene−arene interaction. Balances **1** and **2** with the larger pyrene and phenanthrene shelves displayed higher degrees of folding

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(13) Marshall, K.; Rothchild, R. *Spectrosc. Lett.* **2004**, *37*, 469.

(14) To exclude the influence of intramolecular aggregates on the *folded/unfolded* ratios NMR spectra were taken at varying concentrations of **2** (0.3 mM to 3 mM in $CDCl_3$). No variation in the *folded/unfolded* was observed.

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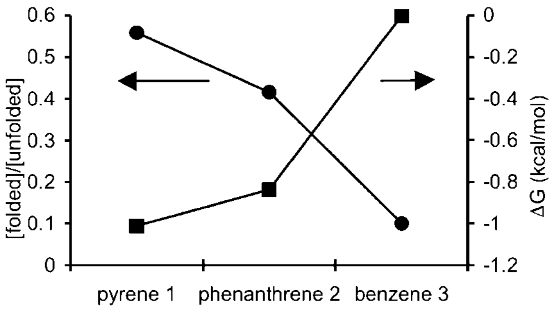

Figure 4. *Folded/unfolded* ratios (●) and ΔG (■) for balance systems **1**−**3** relative to balance **3** measured by ^{1}H NMR at 23 °C in $CDCl_3$.

with *folded/unfolded* ratios of 0.56 and 0.42 respectively. The smaller benzene shelf of balance **3** is too small to form arene−arene interactions with the phenyl arm and thus had a significantly lower *folded/unfolded* ratio of 0.11.

The inability of balance **3** to form an arene−arene interaction in the folded conformer makes it useful as a control system. The strong bias in balance **3** for the *unfolded* conformer is a measure of the repulsive interaction between the phenylether oxygen and the arene shelf. This interaction is present in all of the balances. Thus the *folded/unfolded* ratios for balance **3** can be used as the zero point value for this balance system.[16] The corrected values of ΔG values for the arene−arene interactions in **1** and **2**, in $CDCl_3$ were −1.01 and −0.84 kcal/mol, respectively (298 K) (Figure 4). These values are consistent with the range of values previously reported for similar arene−arene interactions.[4,8] This conformation bias makes the measurement of the arene−arene interaction more accurate because it keeps the *unfolded/folded* ratio closer to unity where the NMR integrations are more accurate.

Finally, the excellent solubility of the balances enabled examination of solvent effects on the arene−arene interactions (Figure 5). Consistent with previous studies, we have observed that more polar solvents drive systems **1**−**3** to greater degrees of folding. The energy of the observed interactions has a linear correlation with the $E_T(30)$ value of the solvent.[17] In order to rule out possibility that the solvent trends were due to differences in dipole moments between the *folded* and *unfolded* conformers, MOPAC semi empirical calculations were carried out on balance **2**. The difference in dipole moments were 0.4 D with the *unfolded* conformer being more polar. This is opposite to the observed trend in which the *folded* conformer were more favored in polar solvents. Interestingly, the trend lines in Figure 5 were all parallel as the differences in energy between the balances was relatively constant over the range of solvent systems that were examined. One explanation is that variations in the ΔG are due to the differences in solvation energy of the unfolded conformers. This is consistent with the phenylether arm in the *unfolded* conformer being the most solvent accessible surface and also being a conserved structure in all three balances. The differences in ΔG between balances are then due to the arene−arene energies of the *folded* conformers in different solvents. The arene surfaces in the *folded* conformer are more solvent shielded and thus have very similar solvation energies in different solvents.[18]

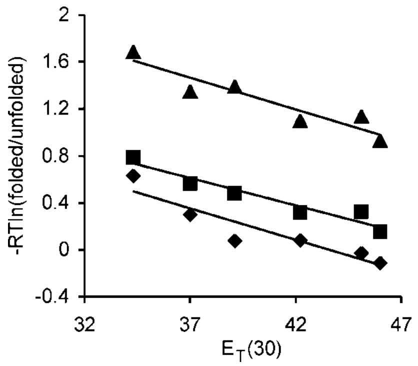

Figure 5. Measured ΔG for balances **1** (◆), **2** (■), and **3** (▲) in a variety of solvents plotted versus the $E_T(30)$ value for each solvent. Solvents from left to right are benzene, THF, chloroform, acetone, DMSO, and acetonitrile at 23 °C.

In conclusion, a series of molecular balance was prepared based on a rigid bicyclic *N*-aryl succinimide that can adopt distinct *folded* and *unfolded* conformations. We have observed in the solid-state that the *folded* conformer displays an offset face-to-face arene−arene interaction while no intramolecular interaction is possible in the *unfolded* conformation. The balance can be assembled by an efficient modular synthesis that allowed for the interconversion of a number of arene shelves. Excellent solubility allowed for quantification of the *folded/unfolded* ratio in a wide variety of organic solvents. Future studies will focus on the substituent effects on the face-to-face arene−arene interaction via variation of the phenylether arm and also will examine the thermodynamics of the arene−arene interactions in different solvents.

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Supporting Information Available: Experimental procedures and compound characterization for **1-4**, X-ray structures of **5a**, **2**, and **4**, and NMR studies of **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Smithrud, D. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339.

(18) Alternatively, the similar differences in folding energies of the balances in various solvents maybe a surreptitious occurence. Balances with different arene arms and surfaces are being synthesized and will be tested to see whether this trend is observed in other systems.