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Experimental Study of the Cooperativity of CH−π Interactions

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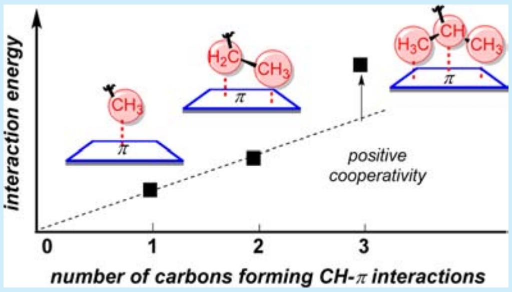
S Supporting Information

ABSTRACT: A series of new torsional molecular balances was designed to study the cooperativity of CH−π interaction in the solid state and in solution. The measured interaction energies correlated better to the number of participating alkyl carbons than to the number of CH−π contacts. The methyl and ethyl groups displayed additive interaction energies. However, the branched isopropyl group displayed strong positive cooperativity with higher than predicted interaction energies.



CH−π interactions are attractive interactions between alkyl and aromatic groups.[1] These weak noncovalent interactions play an important role in many systems, such as the structure of biomolecules and macromolecules,[2] the selectivity of supramolecular systems,[1b,3] and the reactivity of organic catalysts.[4] However, due to the weak nature and geometric variability of these interactions, many aspects of CH−π interactions are still not well understood. One of these is the cooperativity of CH−π interactions,[5] which is observed in crystal structures,[6] inside nanoporous hosts,[7] catenanes,[8] and enzyme active sites.[9] To study the cooperativity of CH−π interactions, we designed a small molecule model system that could systematically measure the CH−π interactions of different sized alkyl groups (Figure 1). We were particularly interested in whether larger alkyl groups that form multiple CH−π interactions would show positive or negative cooperativity.[10] These experimental studies would complement earlier computational studies that found decreasing interaction energy per carbon as the alkyl group increased in size (*vide infra*).[5]

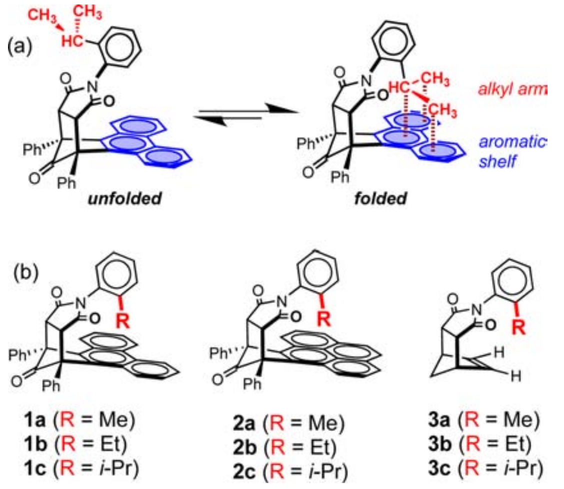


Figure 1. (a) *Folded*−*unfolded* conformational equilibrium of a representative molecular torsional balance (**1c**), which allows measurement of multiple CH−π interactions. (b) Structures of balances **1a**−**c** and **2a**−**c** and control balances **3a**−**c**.

A number of small molecule model systems have been developed to study CH−π interactions computationally[11] and experimentally.[12] However, few have examined the cooperativity of the interaction. Therefore, a series of new molecular torsional balances (**1**−**3**) were designed that could form multiple CH−π interactions, the strengths of which could be accurately measured in solution via their influence on a conformational equilibrium (Figure 1). In the *folded* conformation, the alkyl arm formed intramolecular CH−π interactions with the aromatic shelf. In the *unfolded* conformation, the alkyl arm and arene shelf were far apart and cannot form such CH−π interactions. Thus, the *folded*/*unfolded* ratios provided a sensitive measure of the strength of the intramolecular noncovalent interactions.

The new balances shared the same rigid bicyclic *N*-arylimide framework as our previous CH−π and π−π balances.[13,14] The oxygen linkers in the previous balances were removed, and the interacting alkyl groups were directly attached to the pivot ring. This positioned a greater proportion of the alkyl arms over the aromatic shelves, allowing up to three carbons on the arms to form CH−π interactions. The modular design and an efficient synthesis enabled the systematic variation of the alkyl arms and aromatic shelves. Balances **1a**−**c** and **2a**−**c** contained large phenanthrene or pyrene aromatic shelves and three different alkyl arms (Me, Et, and *i*-Pr). Control balances **3a**−**c** had the same alkyl arms but lacked an aromatic shelf of sufficient size for CH−π interaction. These were designed to measure the effects of solvation on the conformational equilibria in balances **1** and **2** in the absence of CH−π interactions. Moreover, these controls served to cancel out the possible framework effects over the conformational equilibria in balances with different sized alkyl

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arms, such as the weak attractive interactions of the alkyl arms with the succinimide carbonyl groups in the *unfolded* conformers.[15]

X-ray crystal structure analysis confirmed the formation of CH−π interactions in balances **1a**, **1b**, **1c**, and **2a** that contained the large phenanthrene and pyrene aromatic shelves. Similar analysis also confirmed the absence of CH−π interactions in control balances **3a** and **3c** that contained the small olefinic shelves. (Figure 2). In **1a** and **2a**, the methyl groups formed CH−π interactions with their respective phenanthrene and pyrene shelves. In **1b**, both carbons of the ethyl group formed CH−π interactions with the phenanthrene shelf. In **1c**, all three carbons of the isopropyl group formed CH−π interactions with the phenanthrene shelf. Finally, the crystal structures of **3a** and **3c** established their viability as control structures. The methyl and isopropyl arms adopted similar *folded* structures as in balances **1** and **2** but did not form intramolecular CH−π interactions due to the lack of aromatic shelves.

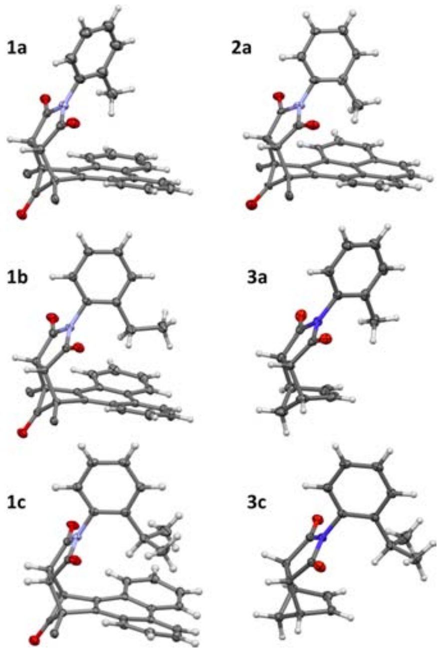

Figure 2. X-ray structures of the *folded* conformers for balances **1a**,[13b] **1b**, **1c**, and **2a** and control balances **3a**[13b] and **3c**. For X-ray structures that contained multiple conformers (**2a**, **3a**, and **3c**), a representative *folded* conformer is shown. Solvent molecules and the bridgehead phenyl groups for each balance were omitted for viewing clarity.

As predicted, the new balances adopted more stable *folded* conformers than our previous generation CH−π balances.[16] Replacement of the oxygen linker from our previous generation balances with CH_2 and CH units removed a repulsive lone pair−π interaction and introduced additional stabilizing CH−π interactions. The greater stability of the *folded* conformers was first observed in the solid state. The new balances **1a**−**c** and **2a** crystallized in the *folded* conformer or as a mixture of *folded* and *unfolded* conformers (Figure 2). This is in contrast to the previous generation of CH−π balances that exclusively crystallized in the *unfolded* conformer.[13,14] The enhanced stability of the *folded* conformers was later extensively characterized in solution (*vide infra*).

An interesting feature in the crystal structures of **1** and **2** was the presence of two distinct types of CH−π interactions. The first was a monodentate interaction where only one C−H bond on a carbon pointed directly toward an aromatic surface (Figure 3a) with shorter H-to-plane distances of <2.7 Å. This monodentate geometry was observed for the methyl group in **1a** and for the central carbon of the isopropyl group in **1c** (Figure 3d). The second was a bidentate interaction where two hydrogens attached to a carbon formed separate CH−π interactions with longer interaction distances (>2.7 Å) (Figure 3b). Examples of the bidentate geometry were the first carbon of the ethyl group in **1b** and the terminal methyl group in **2a**.

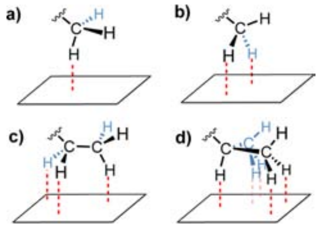

Figure 3. Schematic representations of the CH−π interactions of the alkyl arms highlighting the monodenate and bidentate geometries of the methyl (a, b), ethyl (c), and isopropyl (d) groups.

The formation of two distinct interaction geometries complicated our analyses. We initially correlated the interaction strengths with the number of CH−π contracts. However, the variability in the number of interactions per carbon led to inconsistent results. Thus, we switched to correlating the interaction energies with the number of carbons forming CH−π interactions. This simplification was justified on the basis of the following arguments. First, previous theoretical studies[5a,11e] have observed a good correlation between interaction energies of the CH−π interaction and the polarizability of the alkane, which is approximately proportional to the number of carbons for simple alkanes. Second, the two types of CH−π interactions appear to be very close in energy. Computational studies predicted that the more stable interaction geometry switches from system to system.[11d,17] Similarly, we observed both geometries for the methyl arms in the crystal structures of **1a** and **2a**, suggesting that the two interaction types were energetically interchangeable. Third, the two interaction geometries are fundamental features of cooperative CH−π systems because each interaction type is typically found on adjacent carbons. Alkyl chains favor a staggered *anti*-conformation (Figure 3c and d), which rotates adjacent carbons to have one and two hydrogens projecting from a particular face. This alternating pattern of mono- and bidentate interactions was observed for adjacent carbons in the crystal structures of **1b** and **1c**.

Next, the intramolecular CH−π interactions were characterized in solution ($CDCl_3$). The analysis was facilitated by the presence of a distinct set of peaks for the *folded* and *unfolded* conformers in the ^{1}H NMR spectra. These conformers were in slow exchange at rt due to the restricted rotation of the pivot arm. First, the formation of intramolecular CH−π interactions in solution was confirmed by the differences in chemical shift for specific protons in the *folded* and *unfolded* conformers. Large upfield shifts were observed for the protons on the alkyl arms of *folded*-**1a**−**c** and *folded*-**2a**−**c**, which were consistent with the alkyl groups being positioned over the aromatic shelves and forming CH−π interactions. For example, the protons for the CH_3 groups in *folded*-**1a** and *folded*-**2a** were shifted 2.08 and 2.60 ppm upfield, respectively. The magnitudes of these shifts were in good agreement with those calculated for the methane-benzene CH−π complex (2.29 ppm). Similarly, large upfield shifts were also observed for terminal *folded* CH_3 protons of the ethyl and isopropyl arms in balances **1b,c** (1.24 and 1.38 ppm) and **2b,c** (1.95 and 2.03 ppm).

The strengths of the intramolecular CH−π interactions in solution were calculated from the *folded*/*unfolded* ratios ($\Delta G = -RT\cdot\ln[folded/unfolded]$). Integration of the individual conformers on the ^1H NMR spectra ($CDCl_3$, 23 °C) yielded the *folded*/*unfolded* ratios and corresponding folding energies. An initial analysis of the folding energies confirmed that the balances could effectively measure the intramolecular CH−π interactions. First, the three control balances **3a−c**, which could not form CH−π interactions in their *folded* conformers, had very similar near -zero folding energies (+0.02 to +0.08 kcal/mol). Thus, the framework and solvation effects of the different alkyl arms did not impose a large bias on the *folded*/*unfolded* ratios. By comparison, balances **1a−c** and **2a−c** with arene shelves displayed successively larger negative folding energies with increasing size of the alkyl arms. For example, the isopropyl balance **1c** had the largest folding energy, and the methyl balance **1a** had the smallest folding energy for the phenanthrene series. The same size trend was observed for the pyrene balances **2a−c**.

The folding energies for balances **1** and **2** (Figure 4) did not display the negative cooperativity inferred from the computational studies. The smaller methyl and ethyl balances (**1a,b, 2a,b**) showed no cooperativity, as their folding energies were almost perfectly additive, and the larger isopropyl balances (**1c** and **2c**) showed strong positive cooperativity. The additivity of the methyl and ethyl balances was evident from the stepwise increases in their folding energies. For example, ethyl balance **1b** had a folding energy (−0.27 kcal/mol) that was almost exactly twice the folding energy of methyl balance **1a** (−0.13 kcal/mol). The same stepwise trend was observed between the ethyl and methyl pyrene balances **2b** and **2a**, which had folding energies of −0.51 and −0.23 kcal/mol, respectively.

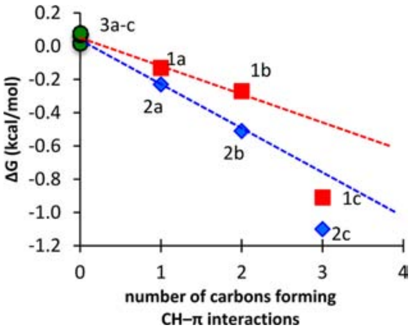

Figure 4. Plot of the measured folding energies (Δ*G*) of balances **1a−c** and **2a−c** and control balances **3a−c** versus the number of alkyl carbons forming intramolecular CH−π interactions. The two linear fits were drawn from data points **3a,b**, **1a**, and **1b** (red dashed line) and **3a,b**, **2a**, and **2b** (blue dashed line), respectively. The folding energies were measured by integration of the ^1H NMR spectra (23 °C, $CDCl_3$) and had an estimated error of ±0.03 kcal/mol.

The additivity of the CH−π interactions in the methyl and ethyl arms was also analyzed graphically (Figure 4). A linear correlation was observed between the folding energies and the number of carbons forming CH−π interactions. For this analysis, the folding energy for a balance with no carbons forming CH−π interactions was calculated from the average of the three control balances **3a**, **3b**, and **3c** (+0.06 kcal/mol). From the slope of these correlations, we could estimate a CH−π interaction energy of −0.16 and −0.28 kcal/mol per carbon for the phenanthrene and pyrene surfaces. As expected, these solution-phase values were significantly smaller than the *in vacuo* computational values of −1 to −1.5 kcal/mol per carbon.[1]

In contrast to the additive trends of the methyl and ethyl balances, the isopropyl balances **1c** and **2c** displayed higher than expected folding energies, which were consistent with positive cooperativity. Based on the CH−π interaction energy of −0.16 kcal/mol per carbon for the **1a** and **1b**, we predicted a folding energy of −0.48 kcal/mol for the three-carbon isopropyl **1c**. However, a much larger folding energy of −0.91 kcal/mol was measured for **1c**. Positive cooperativity was also observed for the isopropyl pyrene balance **2c**. Balance **2c** had a folding energy of −1.10 kcal/mol, which was larger than the −0.84 kcal/mol value extrapolated from the methyl and ethyl pyrene balances **2a−b**. The origins for the positive cooperativity of the larger isopropyl arms are unclear. One possible explanation is that branched alkyl groups such as the isopropyl group form stronger CH−π interactions than linear groups. This trend could be attributed to the higher polarizability of the branched alkyl groups over the linear ones. Support for this hypothesis comes from the computational studies, which show slightly stronger CH−π interactions for cyclic versus linear alkanes.[5]

Overall this experimental study found that multiple CH−π interactions were either additive or showed positive cooperativity. This is in contrast to the negative cooperativity seen in the computational studies, which found that the interaction energy per carbon decreased as the size of the alkyl group increased.[5] There are two possible reasons for this discrepancy with the computational studies. First, the two studies were conducted in different environments. The computational studies were carried out *in vacuo*, and the experimental studies were carried out in organic solvents. As Cockroft recently demonstrated,[18] non-covalent interactions that are primarily dominated by their dispersion term are greatly diminished in solution and are instead dominated by solvophobic effects. A second reason for the discrepancies are the differences in the geometries of the CH−π interactions in the computational and experimental studies. The geometry of the CH−π interactions in this study is closer to the optimal interaction geometry. Each carbon participating in a CH−π interaction is positioned over the center of a separate benzene ring. In contrast, the computational studies were carried out using a small benzene or naphthalene surface. Thus, larger alkanes and carbohydrates were crowded on top of these small aromatic surfaces and had to form weaker CH−π interactions with the edges of the rings.[5]

Although the stability trends for the pyrene balances paralleled those of the phenanthrene balances, the CH−π interactions for the larger pyrene surface were consistently stronger. For example, the methyl arm formed a −0.10 kcal/mol stronger interaction with the pyrene shelf (**2a**) than with the phenanthrene shelf (**1a**). Similarly, the ethyl and isopropyl arms formed −0.24 and −0.19 kcal/mol stronger interactions with the pyrene shelves than with the phenanthrene shelves. This size trend was consistent with a recent computational study by Patkowski that found that larger aromatic surfaces formed stronger CH−π interactions.[17b] As CH−π interactions are largely dominated by dispersion interactions, these size effects were attributed to the enhanced dispersion interactions of the larger aromatic surfaces.[11e,17c]

In summary, a series of molecular balances were synthesized and applied to the study of CH−π interactions and their cooperativity. A strong correlation was found between the interaction energies and the number of participating alkyl carbons. In contrast to theoretical precedents, the CH−π interactions in our balance systems displayed additivity for short alkyl groups (methyl and ethyl) and positive cooperativity for branched alkyl groups (isopropyl). These cooperativity trends were observed for two series of balances with phenanthrene and pyrene shelves. Finally, balances with larger pyrene shelves form consistently stronger CH−π interactions than those with smaller phenanthrene shelves. This suggests that larger aromatic surfaces will form stronger noncovalent interactions with alkanes though they may not form any additional CH−π interactions. The above study was carried out using a model and control balance with very similar frameworks. While the overall trends we observed should stay consistent, the magnitudes of the trends could be measured with higher accuracy if the control and model systems had identical frameworks. Such a system is currently being developed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for all newly reported compounds, and X-ray crystal data for **1b**, **1c**, **2a**, and **3c**, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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