Electrostatic Interactions

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Stabilizing Fluorine–π Interactions

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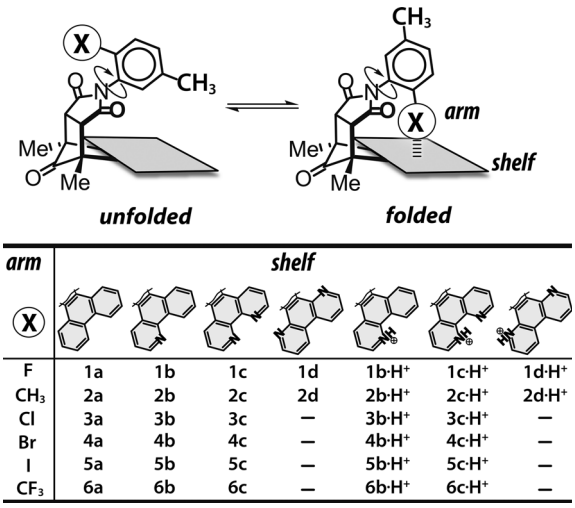
Abstract: *A series of N-arylimide molecular balances were designed to study and measure fluorine–aromatic (F–π) interactions. Fluorine substituents gave rise to increasingly more stabilizing interactions with more electron-deficient aromatic surfaces. The attractive F–π interaction is electrostatically driven and is stronger than other halogen–π interactions.*

Organofluorine compounds[1] are widely used in synthesis,[2] materials,[3] and medicine.[4] The high electronegativity and small size of the fluorine atom endow organofluorine compounds with unique noncovalent interactions,[5,6] chemical stability,[7] and distinct conformational preferences.[8] For example, F–π interactions have been shown to be capable of controlling the regioselectivity of reactions of aromatic rings.[9] However, the ability of C–F bonds to form attractive interactions with π-systems has been a subject of debate.[10] Diederich and co-workers observed attractive interactions between C–F and C=O π-systems experimentally[11] and in a database survey.[12] However, few studies[13] have examined the interactions between organofluorides and aromatic surfaces (F–π interactions).[14] Therefore, the goal of this work was to systematically measure the F–π interactions within a series of *N*-arylimide "molecular balances".[15] The questions addressed were: 1) Can fluorine and organofluorine substituents form stabilizing interactions with aromatic surfaces? 2) What is the nature of the interaction? 3) Are F–π interactions different from other halogen–π interactions?

The F–π interaction stability trends were measured using a series of molecular balances **1a**–**1d** (Scheme 1). Restricted rotation of the *N*-aryl rotor generates distinct folded and unfolded conformers in which an intramolecular interaction is formed and broken. Thus variations in the arm–shelf interaction energies can be quantitatively measured by determining the folded–unfolded equilibrium. The *N*-arylimide molecular balance model has been successfully employed to study many noncovalent interactions, including aromatic stacking,[16] CH–π,[17] heterocycle–π,[18] and metal–π interactions.[19] In this work, a fluorine substituent (X = F) was affixed to the rotor of balances containing a series of different aromatic surfaces (**1a**–**1d**) of varying electrostatic potential. The



arm \ shelf							
X							
F	1a	1b	1c	1d	1b·H⁺	1c·H⁺	1d·H⁺
CH_3	2a	2b	2c	2d	2b·H⁺	2c·H⁺	2d·H⁺
Cl	3a	3b	3c	—	3b·H⁺	3c·H⁺	—
Br	4a	4b	4c	—	4b·H⁺	4c·H⁺	—
I	5a	5b	5c	—	5b·H⁺	5c·H⁺	—
CF_3	6a	6b	6c	—	6b·H⁺	6c·H⁺	—

Scheme 1. The equilibrium between the unfolded and folded isomers of the *N*-arylimide atropisomeric molecular balances for quantitative comparison of the electrostatic trends of F–π (**1**), CH–π (**2**), halogen–π (**3**–**5**), and perfluoroalkyl–π (**6**) interactions.

systematic incorporation of nitrogen atoms and positive charges yielded seven aromatic shelves ranging from "normal" (**1b**) to strongly electron-deficient (**1c**·H^+ and **1d**·H^+).[20] The aromatic shelves had very similar steric properties, which greatly simplified the analyses. Finally, to examine the nature of the F–π interactions in **1**, five additional series of balances **2**–**6** were prepared with different arms (CH_3, Cl, Br, I, and CF_3) and the same aromatic shelves (Scheme 1).

The folding ratios of the molecular balances **1**–**6** were determined by integration of their ^1H or ^{19}F NMR spectra in CD_2Cl_2.[21] The folded and unfolded conformers were in slow exchange at 23 °C, leading to distinct sets of peaks. The reporter 5-methyl group provided easily measurable sets of singlets at 2.1 and 1.7 ppm. Solution studies and crystal-structure analysis confirmed that the 5-methyl group had minimal influence on the folding equilibrium.

Molecular balance **1** gave rise to a wide range of folding energies with the different aromatic shelves (Figure 1). Parent molecular balance **1a** formed a moderately destabilizing F–π interaction ($\Delta G = +0.7$ kcal mol^{-1}). In contrast, the cationic balances **1c**·H^+ and **1d**·H^+ gave rise to strongly stabilizing F–π interactions ($\Delta G = -1.4$ to -1.5 kcal mol^{-1}). Overall, the folding energy trends for **1a**–**1d** were consistent with an electrostatic interaction as the folded conformers became increasingly more stabilized with more electron-poor aromatic shelves.[6,8a] Similar stability trends were also observed in other organic solvents (see the Supporting Information, Figure S11). These experimental trends mirrored computa-

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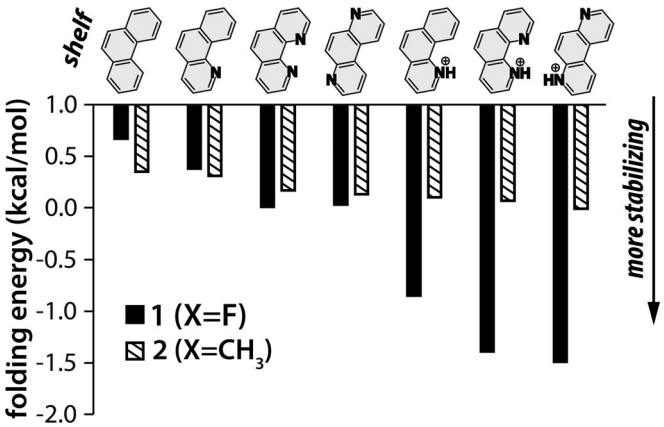

Figure 1. Folding energies (in CD_2Cl_2) of the fluorine- (black) and CH_3-substituted (striped) molecular balances **1** and **2**.

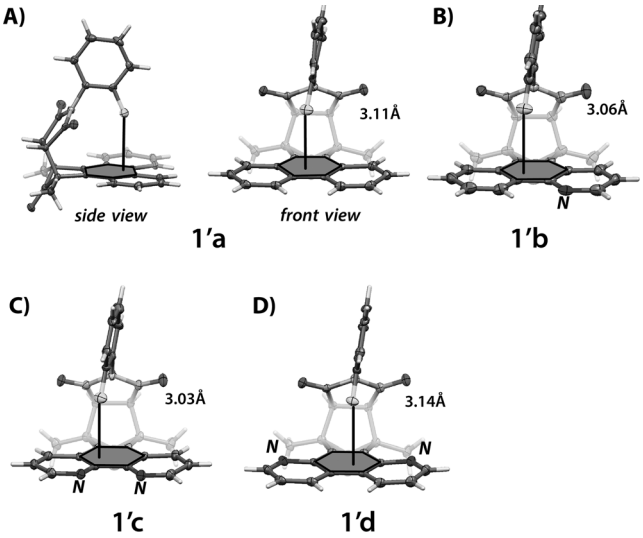

Figure 2. X-ray crystal structures of the folded fluorine-substituted balance analogues **1′a** (A), **1′b** (B), **1′c** (C), and **1′d** (D). The intramolecular distances between the fluorine atoms and the aromatic planes are highlighted (black lines).

tional predictions of the F–π interaction between CH_3F and various arenes.[22] For example, CH_3F has been predicted to form a slightly repulsive interaction with benzene but a strongly attractive interaction with hexafluorobenzene.

The electrostatic nature of the F–π interaction was evident from comparison with the molecular balances **2a**–**2d**, which formed intramolecular CH–π interactions[17a,b,d] that have only a minor electrostatic component[23] (Figure 1). In contrast to the F–π molecular balances **1a**–**1d**, compounds **2a**–**2d** showed little variation across the same set of isomeric aromatic surfaces, providing support for the dominant electrostatic component of the F–π interactions in **1**. Comparison of the folding energies of molecular balances **1** and **2** provides confirmation of the attractive and stabilizing nature of the F–π interactions. With a non-heterocyclic aromatic surface (**1a** vs. **2a**), the F–π interaction was slightly destabilizing ($\Delta\Delta G = +0.3$ kcal mol^{-1}) compared to the CH–π interaction. However, with cationic aromatic surfaces (**1b**·H$^+$–**1d**·H$^+$ vs. **2b**·H$^+$–**2d**·H$^+$), the F–π interactions became significantly more stabilizing ($\Delta\Delta G = -1.5$ kcal mol^{-1}) than the CH–π interactions.

Next, the F–π interactions were characterized by X-ray crystallography.[24] Molecular balances **1a**–**1d** did not consistently crystallize in the folded conformer. However, analogues **1′a**–**1′d** without the 5-methyl group crystallized as mixtures of the folded and unfolded conformers.[25] Solution studies confirmed that **1′a**–**1′d** displayed analogous folding energy trends as **1a**–**1d** (Figure S2). In the crystal structures of **1′a**–**1′d**, the F atoms were positioned over the central rings of the aromatic shelves (Figure 2). The short atom-to-plane distances (3.0–3.1 Å) are consistent with previous reports on F–π interactions.[10d,14a,b]

To investigate the possible role of dipole–dipole interactions in the F–π interactions, the folding energies of fluorine-substituted molecular balances with isomeric 4,7- (**1c**) and 1,10-phenanthroline (**1d**) shelves were compared. These heterocyclic shelves have similar electrostatic potentials (see below) but have opposing dipoles relative to the C–F bond (Figure S13). The solution folding energies of **1c** and **1d** were nearly identical (± 0.02 kcal mol^{-1}). Similarly, the protonated versions (**1c**·H$^+$ and **1d**·H$^+$) had very similar folding energies. These results suggest that the stabilizing F–π interactions were not due to dipole–dipole interactions. A possible reason is the nearly perpendicular geometry of the C–F bond relative to the aromatic surface in the crystal structure (Figures 2). This perpendicular F–π geometry is similar to that observed by Diederich and co-workers between a C–F bond and a carbonyl π-system.[11]

Next, the hypothesis that the F–π interaction involves attraction between the partial negative charge (δ^-) on F and electropositive heterocyclic and cationic surfaces was explored.[6,22] The folding energies of **1** were correlated with the calculated electrostatic potentials (ESPs) of the seven aromatic shelves (Figure 3). ESPs have been successfully applied to study the electrostatic component of many noncovalent aromatic interactions.[26] ESP values of an aromatic surface are strongly correlated with the Hammett σ parameter but have the advantage that they can be applied to heterocyclic and charged aromatic surfaces. The ESP values at the central ring of the aromatic shelves (**a**–**d**, **b**·H$^+$, **c**·H$^+$, and **d**·H$^+$) were calculated at the B3LYP/6-31G* level of theory using the truncated versions capped with methyl groups. An excellent linear correlation was found between the ESP values and the folding energies of **1** (Figure 3). Separate trends were observed for the neutral and cationic aromatic shelves owing to their drastically different ESPs. ESP analysis also accurately predicted the similar folding energies of the isomeric compounds **1c** and **1d** as well as **1c**·H$^+$ and **1d**·H$^+$.

The F–π stability trends in **1** were compared with other halogen–π interactions using the Cl, Br, and I molecular balances **3**–**5** (Figure 4).[14a,b] All of the halogen balances showed similar trends with stronger stabilizing interactions for electron-poorer aromatic surfaces.[27] However, the trend was steeper for F–π balance **1**, which is consistent with the more negative atomic charge on the F atom.[28] Further support for the strongly stabilizing nature of the F–π interaction in **1** was provided by a similarly steep trend for

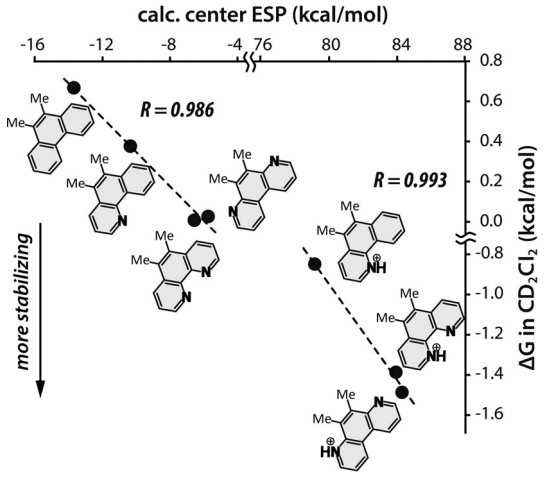

Figure 3. Correlation between the solution folding energies (in CD_2Cl_2) of the fluorine-substituted balances **1a**–**1d** and **1b**·H^+–**1d**·H^+ and the calculated center ESP values of truncated versions of the aromatic shelves (**a**–**d**, **b**·H^+, **c**·H^+, and **d**·H^+).

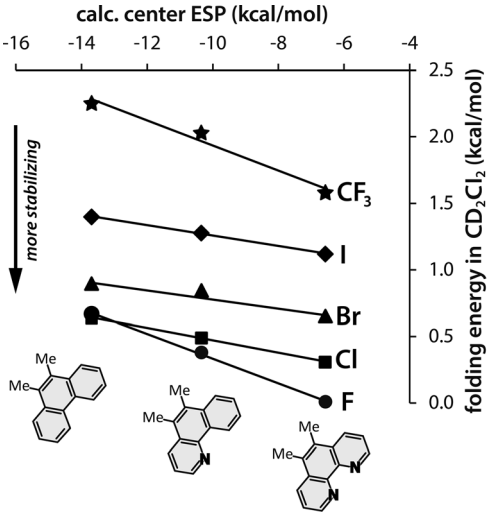

Figure 4. Correlation of the solution folding energies (in CD_2Cl_2) of the molecular balances **1** and **3**–**5** with F, Cl, Br, I and CF_3 arms with the calculated ESP values of the aromatic surfaces.

CF_3 balance **6**. The steep trend of **6** is even more remarkable as the electrostatic F–π interaction must overcome the steric repulsion of the large CF_3 group, which is evident from its least favorable (most positive) folding energies.

In conclusion, analysis of the six series of molecular balances **1**–**6** (37 in total) has confirmed the ability of fluorine atoms and fluorine-containing groups to form stabilizing interactions with electron-poor aromatic surfaces. These F–π interactions are consistent with an attractive electrostatic interaction between an electronegative fluorine atom and electron-deficient heterocyclic and cationic aromatic surfaces. The F–π interactions are clearly different to other types of halogen bond interactions.[29] For example, the halogen–π interaction was strongest for the most electronegative fluorine atom. In contrast, halogen bond interactions involving lone pairs or sigma holes are the strongest with the most polarizable and least electronegative halogen atoms. In this respect, the F–π interaction in **1** appears to be similar to an anion–π-type interaction.[30] We recognize that the terminology "F–π" is a convenient description of the interacting groups but not an accurate description of the underlying basis of the interaction. Further studies are currently underway to quantify the dispersion, solvophobic, and steric components of these F–π interactions.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: electrostatic interactions · fluorine · F–π interactions · supramolecular chemistry · π interactions

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[20] The singly protonated molecular balances (**1b**·H^+, **1c**·H^+, and **1d**·H^+) were prepared in situ by dissolving the corresponding heterocyclic molecular balances in 10 % (v/v) CF_3CO_2D/CD_2Cl_2 solution. The efficacy of this procedure was demonstrated by the TFA titration experiments detailed in the Supporting Information.

[21] The procedure for measuring the ratio of folded to unfolded conformers in solution is detailed in the Supporting Information.

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[24] CCDC 1538758 – 1538766 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[25] A good correlation was observed between the solid-state and solution folded/unfolded ratios of **1′a**–**1′d** (Figure S1).

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[27] Complete ESP correlation analysis of five halogen-substituted molecular balances (**1** and **3**–**6**) with five types of aromatic shelves (**a**–**d**, **b**·H^+, **c**·H^+, and **d**·H^+) is provided in the Supporting Information (Figure S3).

[28] Additional crystallographic analysis suggested that the different correlation slopes among halogen-arm balances were less likely to be due to changes in the halogen–π geometry (Figure S4).

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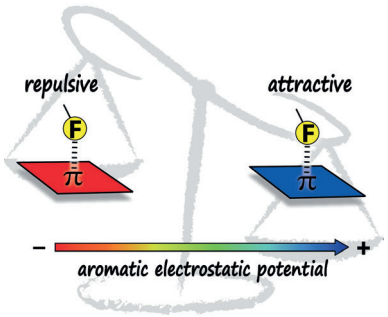

Attractive fluorine: The F–π interaction between a fluorine substituent and an aromatic surface was measured by using a series of molecular balances. This interaction was found to be slightly repulsive with electron-rich surfaces but strongly attractive with electron-poor and cationic surfaces.