Molecular Balances

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Direct Experimental Evidence for Halogen–Aryl π Interactions in Solution from Molecular Torsion Balances

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Abstract: *We dissected halogen–aryl π interactions experimentally using a bicyclic N-arylimide based molecular torsion balances system, which is based on the influence of the nonbonded interaction on the equilibria between folded and unfolded states. Through comparison of balances modulated by higher halogens with fluorine balances, we determined the magnitude of the halogen–aryl π interactions in our unimolecular systems to be larger than −5.0 kJ mol^{-1}, which is comparable with the magnitude estimated in the biomolecular systems. Our study provides direct experimental evidence of halogen–aryl π interactions in solution, which until now have only been revealed in the solid state and evaluated theoretically by quantum-mechanical calculations.*

Halogen–aryl π interactions have received increasing attention with respect to molecular recognition in chemical and biological systems, as a large number of studies have shown that nonbonding halogen interactions contribute significantly to high binding affinity in rational drug design and lead optimization.[1] For a long time, however, only steric and lipophilic contributions of halogens were considered in ligand binding. The situation changed when different theoretical investigations revealed that higher halogen atoms (Cl, Br, and I) could form an attractive interaction with electronegative regions as a result of the anisotropic charge distribution along the C–X axis, the σ hole, whereas there is no such anisotropy in the valence-shell charge concentration of fluorine.[2] Although various theoretical investigations provided a good basis for understanding halogen–aryl π interactions, there is still no direct experimental evidence for such interactions in solution, because in the proteinaceous environment a multitude of contacts and synergistic interactions in protein–ligand complexes renders the situation highly complex; in particular, free-energy changes in protein–ligand systems are often governed by entropic contributions, such as solvent effects.[3] Nevertheless, direct experimental evidence and determination of the magnitude of halogen–aryl π interactions in solution is essential for any rational approach to drug design and would provide an experimental basis for predictions and theoretical calculations.

In this study, we aimed to dissect the halogen–aryl π interactions experimentally by using molecular torsion balances, which are based on the influence of the nonbonding interactions on the equilibria between folded and unfolded states in a unimolecular system.[4] Molecular balances have proven to be a reliable model system to quantify weak noncovalent interactions, since this unimolecular system has minimal entropic penalty associated with the intermolecular association, and no other perturbations influence the overall stability.[5] We adopted herein *N*-aryl imide based balances, which were originally proposed by Shimizu and co-workers and have been used to determine different nonbonding interactions, such as CH–π, CD–π, cation–π, π–π, and metal–π interactions.[6]

To verify the formation of the halogen–aryl π interactions, we synthesized three *N*-aryl imide based balances with increasing size of the aromatic shelf, which was benzene in **1**, phenanthrene in **2**, and pyrene in **3**. Each balance was modulated with different halogen atoms (F, Cl, Br, and I) at the *ortho* position of the *N*-aryl group (Scheme 1). Despite the fact that the observed free energy ΔG decomposes into an enthalpic interaction term and an entropic contribution, we expected higher halogens to form attractive interactions with the aromatic π faces in balances **1**–**3**, whereas fluorine does not engage in such interactions because of its generally highly electronegative character and very low polarizability.[2d,3b,7] Ethylene balances **4** served as reference balances, as both van der Waals and electrostatic interactions between halogens and aromatic π faces are absent.

Determination of the conformations of both folded and unfolded states in solution is challenging by X-ray crystallography. Quite often only the crystal structure of the unfolded conformation could be established.[6b] In this investigation, we

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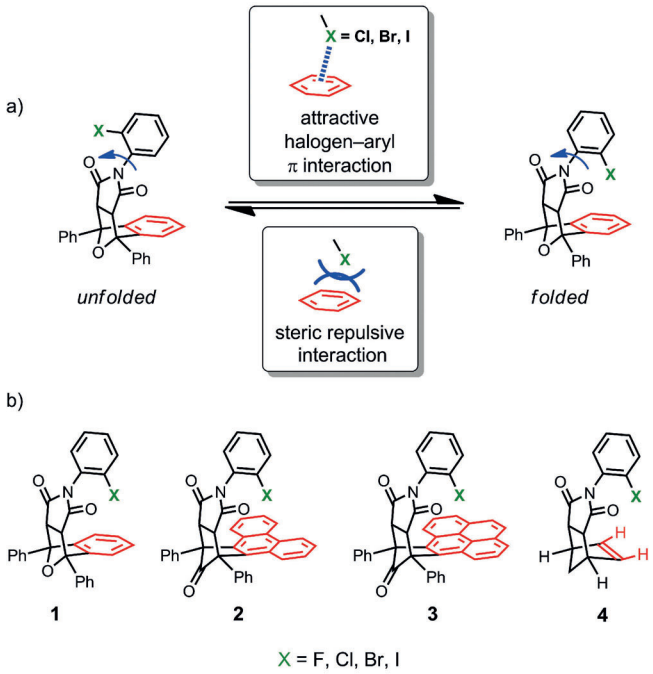

Scheme 1. a) Conformational equilibrium of the unfolded and folded states of the molecular torsion balances used for determining the nonbonding halogen aromatic interactions. b) Molecular balances **1**–**4** with a benzene, phenanthrene, pyrene, and ethylene shelf, respectively.

decided to take advantage of the method based on residual dipolar coupling (RDC) to study both conformations, as the RDC is a powerful NMR parameter that provides long-range structural information on internuclear vector orientation.[8] RDC-enhanced NMR spectroscopy has emerged as an important technique for the determination of the conformation and relative configuration of structurally challenging systems.[9] In this study, we aligned **1-Cl** in a cross-linked polyacrylamide-based (PH) gel[10] and obtained eight $^1D_{CH}$ values for each state (folded and unfolded). The excellent fit between theoretically predicted RDCs for the conformations calculated by DFT computations and the experimental values ($Q = 0.12$ for both folded and unfolded states) confirmed the quality of the DFT-computed structures and allowed us to employ them as well as structures of other balances in the energy calculations (Figure 1; see also Table S4 in the Supporting Information).

For the folded state of **1-Cl**, the distance between the halogen atom and the arene shelf is 3.3 Å (Figure 1 b), which is slightly lower than the value of 3.5 Å at which the minimum distance of the Cl–aryl π interaction was previously established by MP2 calculations.[1d] Distances of 3.5–3.7 Å between the halogen and the centroid of the aromatic ring were determined in a series of factor Xa ligand complexes (PDB: 2BQW, 4A7I, 2BOH, 2BMG), which were used extensively as model systems to characterize the halogen–aryl π interactions in the proteinaceous environment (Figure 1 c).[11]

The free-energy difference between the observed folded and unfolded states was determined from the ratio of the corresponding rotamer peaks in the ^{1}H NMR spectrum, as the transition between the two conformations was slow enough

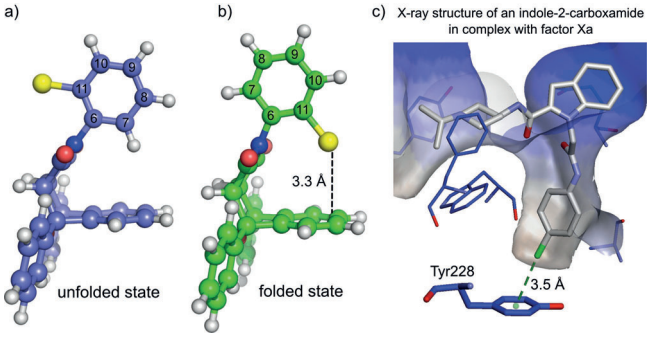

Figure 1. a, b) Conformations of the unfolded and folded states of **1-Cl**, as determined by quantum-mechanical calculations and RDC-based NMR spectroscopy (Cl atom: yellow). c) X-ray crystallographic structure of an indole-2-carboxyamide in complex with human factor Xa (PDB: 2BQW) showing the Cl–aryl π interaction observed in the biological system.[11]

that separate peaks could be observed for both states. The unfolded rotamer could be readily identified by the upfield shift of the *ortho* hydrogen atom H-7 (numbering shown in Figure 1 and Figure S1 of the Supporting Information) of the halobenzene ring as a result of the ring-current effect of the aromatic shelf. Furthermore, we computed the energy differences of folded and unfolded conformers by DFT calculations at the M06-2X/cc-pVDZ level of theory,[12] which was also used for geometry optimization (for iodinated compounds, see the Supporting Information; see Figure S5–S12 for optimized structures of all balances). Overall, the computed energy differences between folded and unfolded conformers are in a good agreement with the experimental ΔG_{fold} values for all balances **1**–**3** (Table 1), which suggests an overall low entropic contribution to the conformational equilibria in the balances with arene shelves.

As shown in Scheme 1, the weighting of the steric repulsive interaction and the attractive halogen–aryl π interaction determines the population ratio of folded and unfolded states. The experimental and theoretically calculated ΔG_{fold} values (Table 1) are positive for all aromatic balances, thus indicating that repulsive steric energy between the halogen atom and the aromatic shelf is dominant over other interactions. To dissect the halogen–aryl π interaction from other energy contributors, we compared the ΔG_{fold} values of higher-halogen balances with the fluorine balances, as theoretically no significant fluorine–aryl interaction is expected.[2d,3b,7]. The ΔG_{fold} values of the arene-shelf balances modulated with fluorine and higher halogens were first plotted within each series against the van der Waals (vdW) radius (F: 1.47 Å, Cl: 1.75 Å, Br: 1.85 Å, I: 1.98 Å).[13] Interestingly, we found that in the whole aromatic series (balances **1**–**3**) the ΔG_{fold} value increased nearly linearly from chlorine to iodine ($R > 0.98$), whereas the values for the fluorine balances deviated significantly from the line (Figure 2 a–c). This result strongly suggests that different interactions are involved in fluorine and higher-halogen balances.

By using the linear regression of the ΔG_{fold} values obtained for higher-halogen balances, we extrapolated the ΔG_{fold} values for fluorine (denoted as $\Delta G_{fold,pred->F}$) under the assumption that fluorine balances share the same interaction

Table 1: Comparison of the folded/unfolded ratios at 288 K in $CDCl_3$, experimentally determined ΔG_{fold} values, and computed ΔE_{fold} values (from DFT calculations) for the balances with different aromatic shelves and halogens.[a]

Balance		K_{eq}[b]	$\Delta G_{fold,\,exp}$ [kJ mol^{-1}]	$\Delta E_{fold,\,calc}$ [kJ mol^{-1}]
1 (benzene)	**F**	0.265	3.2	3.2
	Cl	0.087	5.8	5.3
	Br	0.037	7.9	6.7
	I	0.007	11.8	12.6
2 (phenanthrene)	**F**	0.340	2.6	4.1
	Cl	0.469	1.8	1.6
	Br	0.295	2.9	0.4
	I	0.130	4.9	4.8
3 (pyrene)	**F**	0.410	2.1	3.7
	Cl	0.532	1.5	1.3
	Br	0.346	2.5	0.9
	I	0.141	4.7	3.8
4 (ethylene)	**F**	1.267	−0.6	−4.6
	Cl	0.644	1.1	1.7
	Br	0.412	2.1	1.3
	I	0.191	4.0	4.2

[a] For error analysis, see Table S1 in the Supporting Information. [b] The folded/unfolded ratio was determined by integration of ^{1}H NMR signals for both states.

characteristics as the higher-halogen balances. Considerably lower predicted $\Delta G_{fold,pred->F}$ values than the experimentally determined values were found for all arene-shelf balances with fluorine, thus suggesting a contribution of attractive halogen–aryl interactions that results in an overall decrease in ΔG_{fold} in higher-halogen balances. The difference between the predicted $\Delta G_{fold,pred->F}$ value and experimental the ΔG_{fold} value for fluorine, denoted as $\Delta\Delta G'$, can be considered as an approximate measure for the magnitude of the halogen–aryl π interactions. The calculated $\Delta\Delta G'$ values are highly consistent in all arene-shelf balances: −4.8 kJ mol^{-1} in benzene **1**, −4.7 kJ mol^{-1} in phenanthrene **2**, and −5.1 kJ mol^{-1} in pyrene **3** (Figure 2a–c). Additionally, we excluded the possibility that our observations rely on solvent effects by measuring phenanthrene balances **2** in acetonitrile, which resulted in an even larger $\Delta\Delta G'$ value of −6.5 kJ mol^{-1} (see Figure S13).

It is highly interesting that the ΔG_{fold} values of higher-halogen balances show a linear relationship with the atomic radius. In particular, when the ΔG_{fold} value of benzene balance **1** was subtracted from those of **2** and **3**, the $\Delta\Delta G_{fold}$ values decreased linearly from fluorine to iodine for both balance pairs (see Figure S14). The linear relationship between the free-energy changes contributed by steric effects and vdW radii was established by Taft and Charton in the 1952 and 1975.[14] The linear correlation observed in our system between the ΔG value and the vdW radius can thus be considered as a measure of repulsive energy. Nevertheless, previous theoretical calculations suggested an increasing trend of attractive halogen–aryl π interactions when going from chlorine to iodine.[15] Consequently, it is possible that the ΔG values associated with the attractive halogen–aryl π interactions decrease linearly with the atomic size, or their relationship has only a small nonlinear term. Hence, we deduce that the magnitude of halogen–aryl π interactions for the higher-halogen balances is larger than the $\Delta\Delta G'$ values derived as described above, as the $\Delta\Delta G'$ values were predicted for fluorine balances on the assumption that the fluorine balances exhibit the same linear relationship as the higher-halogen balances.

To further corroborate the significance of the halogen–aryl π interactions observed in the arene-shelf balances, we plotted the ΔG_{fold} values of ethylene balances modulated with fluorine and higher halogens against the vdW radius (Figure 2d). Ethylene balances **4** were chosen in this case as reference balances, as both van der Waals and halogen–aryl interactions are supposed to be absent owing to the lack of an aromatic π face. Indeed, with a $\Delta\Delta G'$ value of −2.0 kJ mol^{-1}, we observed a considerably smaller difference between the predicted $\Delta G_{fold,pred->F}$ value and the experimentally determined value. Inter-

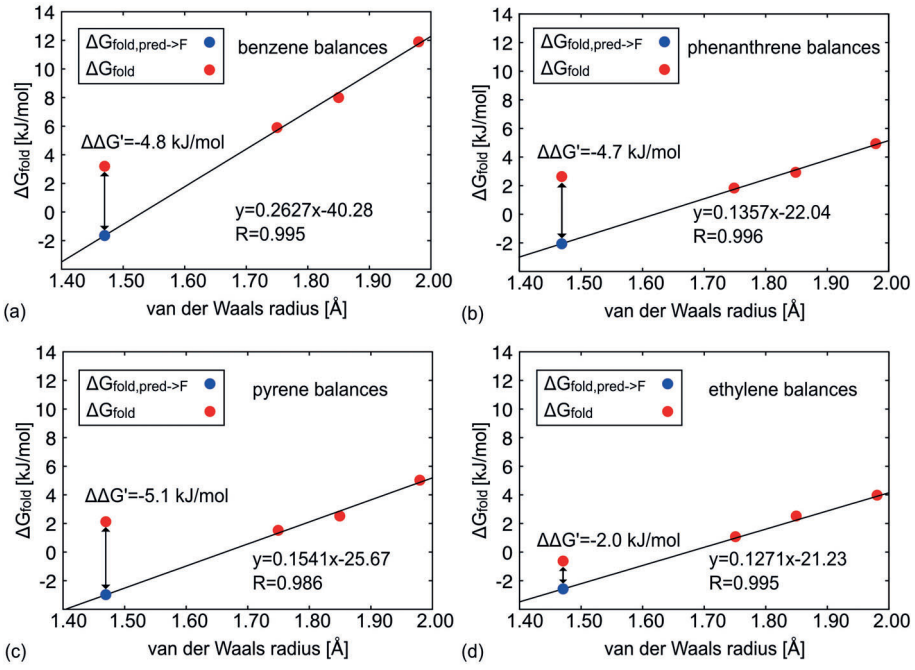

Figure 2. Correlation plots of the experimental ΔG_{fold} value against the vdW radius for a) benzene balance **1**, b) phenanthrene balance **2**, c) pyrene balance **3**, and d) ethylene balance **4**. From the linear fits obtained for the higher-halogen balances, values were predicted for the corresponding fluorine balances (depicted in blue).

estingly, although the C–F axis was not directed towards the ethylene π surface in the ethylene balance (see Figures S11 and S12), a small $\Delta\Delta G'$ value, which was attributed to the halogen–π interactions between higher halogens and the π surface in ethylene, could still be identified. Furthermore, we found that the magnitude of the halogen–aryl interactions in all three aromatic balances were highly consistent, although the σ holes along the C–X bond are in a more favorable perpendicular geometry with respect to the aromatic π faces in the phenanthrene and pyrene balances as compared to the benzene balances. On the basis of these two observations, we hypothesize that halogen–aryl π interactions are less directional than suggested by most theoretical investigations,[15b,c] possibly as a result of additional induced polarization of the halogen atom owing to contact with the electron-rich π system, as suggested previously by DFT calculations.[16] Furthermore, this finding is in good agreement with previous surveys on protein databases showing that halogen–aryl π interactions exhibit only a certain degree of directionality in the biomolecular system.[1c,11a]

Although it is impossible to directly determine the halogen–aryl interactions in biological systems, comparison of the affinities (K_i or IC_{50}) of halogenated and nonhalogenated inhibitors toward an identical protein provides an indirect measure of halogen–aryl interactions in protein environments. In our previous study with fXa inhibitors, the addition of chlorine to the ligand structure led to an estimated change in the free energy of binding ($\Delta\Delta G$) of −10.5 and −8.5 kJ mol^{-1} in the indole-2-carboxamide and 3-oxybenzamide series, respectively.[11a] In contrast, a fluorine atom at the same position had a significantly lower effect, with an $\Delta\Delta G$ value of only −3 kJ mol^{-1}. The difference in $\Delta\Delta G$ between chlorine- and fluorine-substituted ligands, −7.5 and −5.0 kJ mol^{-1} for the indole-2-carboxamide and 3-oxybenzamide series, respectively, can be considered as approximate measures of halogen–aryl interactions in the fXa protein–ligand system. In our current study, we determined the magnitude of halogen–aryl interactions in the unimolecular systems to be larger than −5.0 kJ mol^{-1}, which is in good agreement with the experimentally estimated values in the fXa systems.

In conclusion, we employed *N*-aryl imide based molecular torsion balances to probe halogen–aryl interactions experimentally. These interactions are difficult to assess in a proteinaceous environment. The comparison of higher-halogen-containing balances with fluorine-containing reference balances revealed a clear attractive contribution of the halogen–aryl π interactions in solution. Until now these effects had only been inferred from crystallographic evidence and theoretically evaluated by quantum-mechanical calculations. We estimated the magnitude of the halogen–aryl π interactions in our unimolecular systems to be larger than −5.0 kJ mol^{-1}. Our study provides an experimental basis for theoretical investigations of halogen–aryl π interactions and further enabled us to directly compare the magnitude of such interactions with estimated values from affinity measurements of protein–ligand systems.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: halogen bonding · halogen–aryl π interactions · molecular balances · molecular recognition · residual dipolar coupling

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Communications

Molecular Balances

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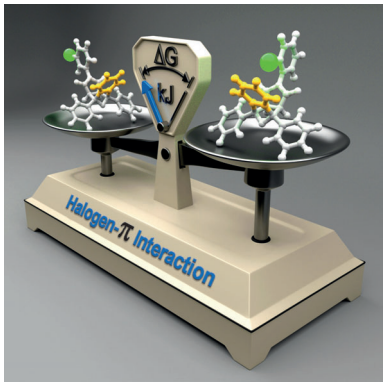
Direct Experimental Evidence for Halogen–Aryl π Interactions in Solution from Molecular Torsion Balances



Weighty evidence: Molecular torsion balances containing an *N*-aryl imide and an additional aromatic moiety provided direct experimental evidence for halogen–aryl π interactions in solution (see picture). The magnitude of the halogen–aryl π interactions in the unimolecular systems described herein are found to be larger than $-5.0\ kJ\ mol^{-1}$.