Substituent effects on the aromatic edge-to-face interaction†‡

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Substituent effects on the folding equilibrium of molecular torsion balances are rationalised on the basis of changes in the electrostatic interactions, the exchange repulsion, and the dispersive contributions to the interaction free enthalpy.

Aromatic edge-to-face interactions are ubiquitous in structural chemistry and biology.[1–4] While investigations on model systems have much contributed to the energetic quantification of these C–H···π contacts,[5,6a,b] the nature of the interactions, and in particular their modulation by substituent and solvent effects, remains the subject of controversial experimental and theoretical study.[7–9]

Our attention was drawn to the study of aromatic edge-to-face interactions during the energetic quantification of orthogonal dipolar C–F···C=O interactions[10] using molecular torsion balances initially introduced by Wilcox and co-workers.[6] For systems bearing a 4-(trifluoromethyl)phenyl ester moiety as an edge component (Fig. 1), Hof *et al*. observed a strong linear free energy relationship in C_6D_6 between the folding free enthalpy (*i.e*. the measure of the strength of the aromatic–aromatic interaction) and the Hammett constants σ_{meta} of substituents on the face aromatic ring, suggesting a substantial contribution of electrostatic interactions to the driving force for folding.[10] In agreement with recent theoretical treatments[7–9] electron-donating substituents on the face component strengthen the edge-to-face interaction while electron-accepting substituents weaken it. In contrast, previous experiments in $CDCl_3$ by Wilcox and co-workers on a closely related system bearing a phenyl ester (Fig. 1) had shown no effects of face substituents on the folding free enthalpy. This led these researchers to conclude, that aromatic edge-to-face interactions are dominated by dispersion rather than electrostatic forces.[6a,b]

The apparent discrepancy between the two sets of experiments led Cockroft and Hunter to a theoretical treatment,[11] by applying a purely electrostatic solute–solvent model.[12] According to this model, in the case of the torsion balances bearing a phenyl ester moiety measured in $CDCl_3$, the substituent effect on the face aromatic ring is washed out by desolvation. In contrast, the interaction of the torsion balances bearing an electron-accepting CF_3 group on the edge aromatic ring studied in C_6D_6 is dominated by an electrostatic term. The authors concluded that the apolar solvent C_6D_6 cannot compete with the 4-(trifluoromethyl)phenyl ester for the binding to the face aromatic ring. Since both model systems had been measured in differing solvents and under differing conditions, we decided to repeat the experiments for the two sets of torsion balances in both C_6D_6 and in $CDCl_3$ in order to attain reliable and conclusive data for the folding equilibria.

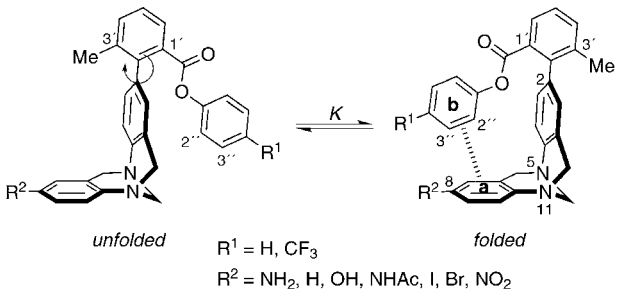

Fig. 1 Schematic representation of the folding equilibrium of the molecular torsion balances used to determine the interaction free enthalpy for the edge-to-face C–H···π contact between aromatic rings **a** and **b**.

A set of 14 molecular torsion balances bearing a phenyl or a 4-(trifluoromethyl)phenyl ester as the edge component and a series of electron-donating and electron-accepting substituents on the face aromatic ring was synthesised according to literature procedures.[6c,10] Atropisomerism around a biaryl-type single bond allows the system to adopt a well-defined folded conformation featuring an edge-to-face interaction between aromatic rings **a** and **b** or a less ordered unfolded conformation bearing essentially no stabilising interaction (Fig. 1). The difference in free enthalpy ΔG between both conformers can be directly attributed to the strength of the C–H···π contact. The relative population of both states in solution can be monitored by ^{1}H NMR spectroscopy at slow conformer exchange, by integration of the signal of the methyl group adjacent to C3′ in the two states. The folding equilibrium constants K of the torsion balances (±)-**1** to (±)-**14** as 10 mM solutions in C_6D_6 and $CDCl_3$ were determined at 298 K (see Fig. S1–S4 in the ESI‡). The respective folding free enthalpies ΔG are summarised in Table 1. For a better understanding of the substituent effects on the folding equilibrium, the entire series of torsion balances was examined using a free energy relationship between the individual folding free enthalpy ΔG and the Hammett constant σ_{meta} for the substituent R^2 (Fig. 2).[10,13]

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Table 1 Folding free enthalpy for torsion balances (±)-**1** to (±)-**14** (for the position of R^1 and R^2, see Fig. 1)

				ΔG/kJ mol^{-1}[b]	
	R^1	R^2	σ_{meta}[a]	C_6D_6	$CDCl_3$
(±)-**1**	CF_3	NH_2	−0.160	−3.91	−2.65
(±)-**2**	CF_3	H	0.000	−3.47	−2.41
(±)-**3**	CF_3	OH	0.121	−3.46	−2.31
(±)-**4**	CF_3	NHAc	0.210	−3.74	−2.74
(±)-**5**	CF_3	I	0.352	−1.52	−0.61
(±)-**6**	CF_3	Br	0.391	−1.89	−1.01
(±)-**7**	CF_3	NO_2	0.710	−0.19	−0.47
(±)-**8**	H	NH_2	−0.160	−1.95	−0.89
(±)-**9**	H	H	0.000	−1.56	−1.00
(±)-**10**	H	OH	0.121	−1.61	−1.04
(±)-**11**	H	NHAc	0.210	−1.36	−0.35
(±)-**12**	H	I	0.352	−2.11	−1.37
(±)-**13**	H	Br	0.391	−2.01	−1.41
(±)-**14**	H	NO_2	0.710	−1.28	−0.96

[a] Hammett substituent constants based on the ionisation of substituted benzoic acid.[13] [b] Determined by integration of the line-fitted (100% Lorentz function) ^{1}H NMR spectra of 10 mM solutions at 298 K. Uncertainty: ±0.12 kJ mol^{-1}.

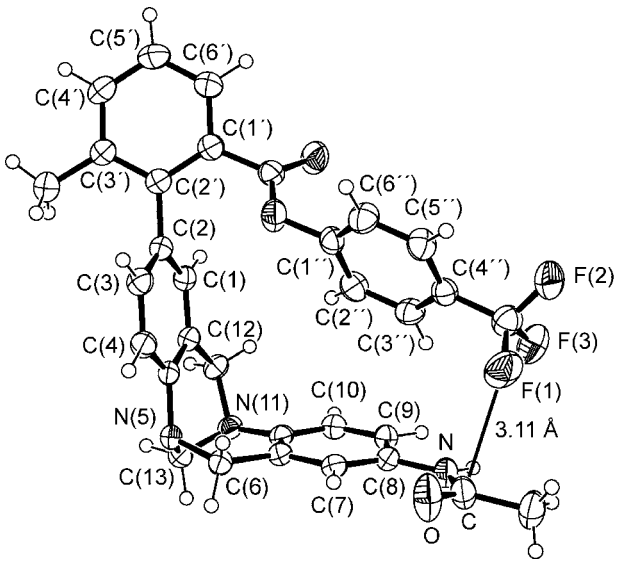

Fig. 3 ORTEP plot of (*R*,*R*)-**4**. Thermal ellipsoids at 223 K are shown at the 50% probability level.

In both C_6D_6 and $CDCl_3$, the folding free enthalpy of the 4-(trifluoromethyl)phenyl torsion balances (±)-**1** to (±)-**7** follows a steep linear slope (m = 4.6 ± 0.8 and m = 3.9 ± 0.8, respectively), consistent with the expected behaviour for an interaction strongly modulated by an electrostatic term. The folding free enthalpy of the torsion balances bearing a phenyl ester ((±)-**8** to (±)-**14**), however, is essentially independent of the substitution pattern on the face aromatic ring both in C_6D_6 and $CDCl_3$ (m = 0.3 ± 0.5 and m = −0.3 ± 0.5, respectively). The sole significant deviation from linearity can be observed for the torsion balances bearing an acetamide substituent on the face aromatic ring. In the process of this work we were able to obtain crystals of (±)-**4** suitable for X-ray analysis (Fig. 3). The orthogonal dipolar C–F···C=O interaction (d = 3.11 Å) between the appended functional groups, previously studied by Hof *et al.*,[10] shifts the equilibrium towards the folded conformation. On the basis of the electrostatic solute–solvent model employed by Cockroft and Hunter,[11] the polar solvent $CDCl_3$ should compete with the edge aromatic ring for the binding to the Tröger base cleft in the torsion balances (±)-**1** to (±)-**7**. Even though the individual folding free enthalpies decrease (~1 kJ mol^{-1}) upon going from C_6D_6 to $CDCl_3$, the correlation of ΔG with the Hammett constant σ_{meta} is effectively unperturbed within the experimental error. The data implies that the solvent effect acts equally on the torsion balances bearing a 4-(trifluoromethyl)phenyl or a phenyl ester. The discrepancy regarding the magnitude of substituent effects on the folding equilibrium cannot be rationalised by invoking solute–solvent interactions.

Recent high-level computational analyses unanimously agree that the dispersion energy provides for the largest contribution to the edge-to-face interaction. The substituent effects may be attributed to a modulation of the electrostatic contribution to the interaction energy.[7–9] The findings by Wilcox and co-workers,[6a,b] Hof *et al.*[10] and those of the present investigation can be explained on the basis of the results of these calculations. In accordance with

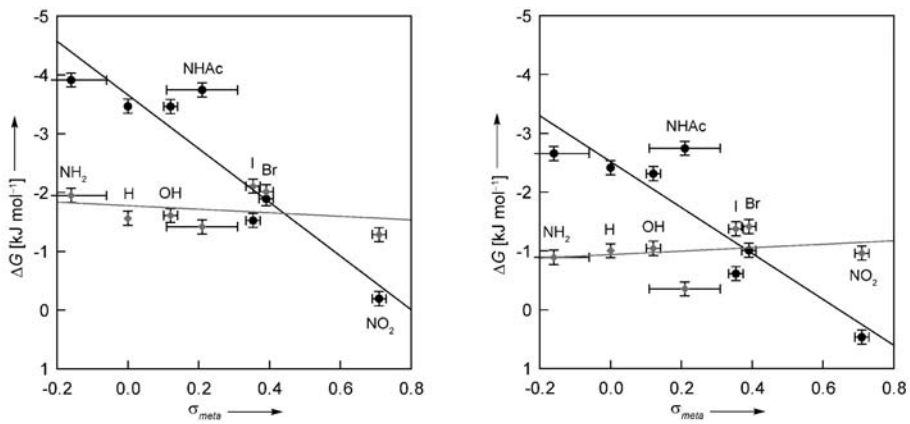

Fig. 2 Experimental folding free enthalpies of molecular torsion balances in C_6D_6 (left) and $CDCl_3$ (right) at 298 K plotted against the Hammett parameter σ_{meta} of the respective substituents R^2.[13] Color code: grey: R^1 = H; black: R^1 = CF_3.

Lee *et al.*, the interaction total energy E_{tot} between two substituted aromatic rings can be estimated as the sum of increments:[9]

$$E_{tot} = E_{es} + E_{ind} + E_{exch} + E_{disp} + \delta_{int}$$

with E_{es} being the electrostatic contribution, E_{ind} the energy stemming from inductive effects, E_{exch} the exchange repulsion energy, E_{disp} the dispersion energy and δ_{int} the induction and exchange terms of higher order. In order to assess the effect an electron-accepting or an electron-donating group on the face component has on the interaction total energy, the individual perturbations of E_{es}, E_{ind}, E_{exch}, E_{disp} and δ_{int} induced by the substituent have to be accounted for. Functional groups on the aromatic ring **a** induce only minor changes in E_{ind}, E_{disp} and δ_{int}. The substituent effect on the interaction total energy E_{tot} can thus solely be attributed to significant variations of the electrostatic component E_{es} and the exchange repulsion term E_{exch}. The latter, a direct consequence of the Pauli principle,[14] results from the repulsion of electrons with parallel spins and is reflected in the distance dependence (r^{-12}) of the repulsive term in the Lennard-Jones potential. Even though the importance of E_{exch} for the discussion of attractive interactions between neutral closed-shell molecules is well accepted in the theoretical community,[15–17] it is frequently underestimated in the interpretation of experimental results.[18]

The electrostatic component E_{es} to the folding equilibrium of both the Wilcox and the Hof torsion balances increases upon enhancing the electron-donating character of the functional group appended to the face aromatic ring. Yet, in the case of the torsion balances bearing an electron-rich phenyl ester moiety, the change in E_{es} is counterbalanced by an increase in the exchange repulsion term E_{exch}, reflected in a small slope (grey lines) in the linear free energy correlations in Fig. 2. The electrostatic contribution E_{es} to the edge-to-face interaction in the Hof torsion balances instead, is not only modulated by the substituents on the face component, but is amplified by a cooperative effect of the electron-accepting CF_3 group on the aromatic ring **b**. Moreover, the introduction of the electron-deficient 4-(trifluoromethyl)phenyl ester induces a decrease of the exchange repulsion term. E_{exch} no longer compensates the increase in the electrostatic term induced by the electron-donating substituents on the face aromatic ring **a**. Accordingly, the correlation of the folding free enthalpy of the Hof torsion balances (black lines in Fig. 2) with the Hammett constants σ_{meta} of the substituents on the edge component shows a steep slope both in C_6D_6 and $CDCl_3$.

The revelation from this analysis is, that even though the dispersion interaction is dominating the total interaction energy, the substituent effects on the folding equilibrium of the torsion balances are reflected by the counterbalancing modulation of the electrostatic and the exchange repulsion terms. In the case of the Wilcox torsion balances the electrostatic component to the edge-to-face interaction is effectively compensated by E_{exch}. The 4-(trifluoromethyl)phenyl ester inherent to the Hof torsion balances instead cooperatively strengthens E_{es}, while the Pauli exchange repulsion decreases due to the reduced electron density of the edge component. The substituent effects on the folding equilibrium of torsion balances both in C_6D_6 and $CDCl_3$ can only be rationalised on the basis of dispersion interactions and the counterbalancing effects of electrostatic and exchange repulsion forces contributing to the total interaction free enthalpy.

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