Supramolecular Interactions

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Molecular Torsion Balances: Evidence for Favorable Orthogonal Dipolar Interactions Between Organic Fluorine and Amide Groups**

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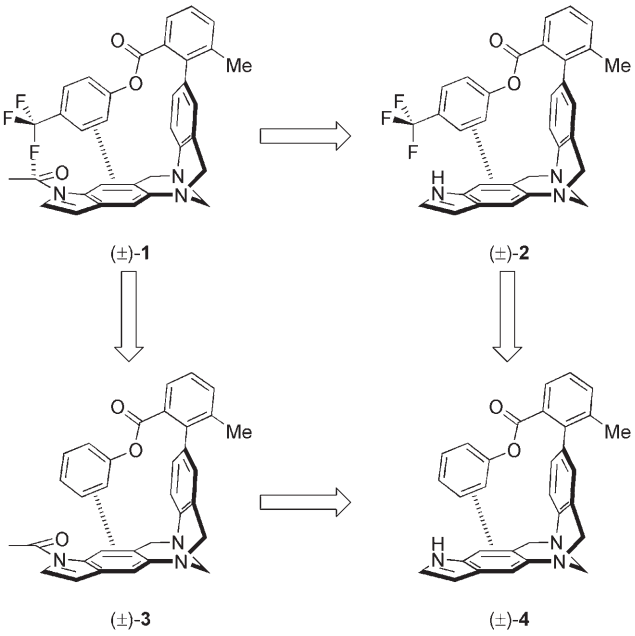
Dedicated to Professor David Reinhoudt on the occasion of his 65th birthday

Dipolar interactions are omnipresent in chemistry and biology.[1] It is theorized that owing to steric constraints, bond dipoles prefer an orthogonal alignment at closest contact distance. The observation of an apparently attractive orthogonal C–F···C=O interaction between a backbone C=O of the serine protease thrombin and the C_{aryl}–F dipole of a bound inhibitor initiated our program to determine experimentally the energetics of such interactions.[2] The expected weakness prevented any attempts at their energetic quantification by studying a bimolecular protein–ligand or even well-defined host–guest complexes. Therefore, we relied on a monomolecular system, the molecular torsion balance, introduced by Wilcox et al.,[3] which enables the quantification of weak interactions with a greater accuracy than with a comparable bimolecular system. Using a chemical double-mutant cycle approach, popularized by Hunter et al.,[4] we showed that the orthogonal interaction between an aryl-CF_3 group and a secondary CH_3CONH-aryl group in apolar solvents was energetically favorable, with a free enthalpy contribution of $\Delta\Delta G = -1.05 \pm 0.25$ kJ mol^{-1} in $CDCl_3$ and -0.85 ± 0.25 kJ mol^{-1} in C_6D_6.[5] However, a number of serious uncertainties remained after this first study: 1) The validity of the chemical double-mutant cycle could be questioned since the changes in substitution, made to extract the energetics of the dipolar interactions, were substantially perturbing the primary edge-to-face aromatic interactions in the molecular torsion balance (see below).[6] 2) The dipolar momentum of a freely rotating CF_3 group is not oriented along a single C–F bond but is aligned along the CF_3–C bond, thereby poorly reproducing the orthogonal interaction geometry observed at short C–F···C=O distances. 3) It could not be precluded that the interaction free enthalpy initially reported arises from a weak, but geometrically possible $N_{arylamide}$–H···F–C hydrogen-bond-like interaction. Herein, we present two new sets of molecular torsion balances in which the Tröger base scaffold, bearing the rotor, has been extended to an indole moiety. In two newly designed double-mutant cycles, the concerns addressed above are overcome and we give final proof for the existence of an attractive noncovalent dipolar C_{sp^2}–F···C=O interaction in a broader range of solvents.[7]

In the first set of new molecular torsion balances, the CF_3 group on the edge component used in the earlier system was maintained, while an acetylated indole moiety ensures the in-plane orientation of the interacting acetamido group which no longer features an N–H fragment. The envisioned double-mutant cycle resulting from this modification is shown in Scheme 1. Equation (1) provides the incremental free interaction enthalpy between the CF_3 and the acetamido carbonyl group.

$$\Delta\Delta G_{CF_3\cdots C=O} = \Delta G_{(\pm)\text{-}\mathbf{1}} - \Delta G_{(\pm)\text{-}\mathbf{2}} - \Delta G_{(\pm)\text{-}\mathbf{3}} + \Delta G_{(\pm)\text{-}\mathbf{4}} \quad (1)$$



Scheme 1. Double-mutant cycle of indole-extended molecular torsion balances for the determination of the interaction free enthalpy between a CF_3 and an acetamide group. The change from (±)-**2** to (±)-**4** takes into account how the effect of substitution alters the edge-to-face aromatic–aromatic interaction which is the primary force behind the folding of the molecule.

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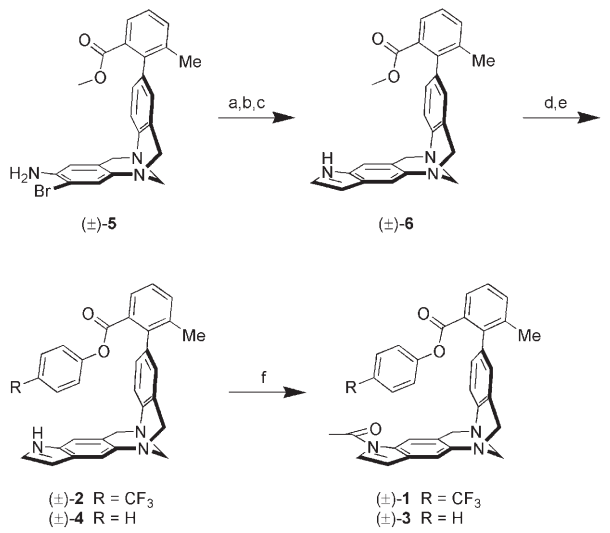
Supporting information for this article (synthesis and characterization of compounds (±)-**1** to (±)-**4**, ^{1}H, ^{19}F NOESY experiments of (±)-**1** and (±)-**7**, X-ray crystal structure data of molecules (±)-**3**, (±)-**8**, and (±)-**10**, error analysis of the physical data) is available on the WWW under http://www.angewandte.org or from the author.

The four molecules (±)-**1** to (±)-**4** were all synthesized starting from the common precursor (±)-**5** (Scheme 2, see the Supporting Information). Compound (±)-**5** was prepared in a newly developed 15-step synthesis starting from commercially



Scheme 2. Synthesis of (±)-**1** to (±)-**4**. a) Ac_2O, CH_2Cl_2, 0°C–24°C, 98%. b) $Me_3SiC{\equiv}CH$, CuI, $[Pd(PPh_3)_4]$, Et_3N, 75°C, 99%. c) nBu_4NF, THF, 70°C, 92%. d) LiOH, $MeOH/H_2O$, 50°C, 91%. e) Phenol or 4-(trifluoromethyl)phenol, BOP, Et_3N, CH_2Cl_2, 24°C, 72–83%. f) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 24°C, 57–72%. BOP = benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate, DMAP = 4-*N*,*N*-dimethylaminopyridine.

available materials.[8] Acetylation of the amino group and Sonogashira cross-coupling of the bromide with Me_3Si-C≡CH led to an intermediate that underwent thermal cyclization to indole (±)-**6** under rather mild conditions in excellent yield.[9] Deprotection of the methyl ester and subsequent esterification with 4-(trifluoromethyl)phenol or phenol led to target molecules (±)-**2** and (±)-**4**. Acetylation of (±)-**2** and (±)-**4** provided (±)-**1** and (±)-**3**, respectively, in satisfying yields.

The structure of the molecular torsion balances with the extended indole scaffold was confirmed by X-ray crystallography. Comparison of the crystal structure of (±)-**3** (see Figure 1 and the Supporting Information) with structures of torsion balances previously reported by Wilcox and our group only shows slight deviations from the expected geometry.[10] The phenyl ester is not exactly centered on the indole moiety, therefore the H atom on C34 (the CF_3-substituted position in (±)-**1**) resides at a distance of 3.84 Å and an angle of $\alpha_{H\cdots C=O} = 103°$ over C37 of the acetamide group.

Since the interconversion between the rotational conformers (atropisomers) in (±)-**1** to (±)-**4** is slow on the ^{1}H NMR spectroscopy timescale ($\Delta G^{\neq} \geq 67\ kJ\,mol^{-1}$ at 298 K), two separate signals for the aromatic methyl group of the rotor can be observed (see the Supporting Information).[3a] ^{1}H,^{19}F NOESY experiments demonstrate the expected proximity of the CF_3 group and the CH_3CO moiety in the folded conformation of (±)-**1** (see the Supporting Information). The ^{1}H NMR spectra were line-fitted to Lorentz functions and integrated to determine the

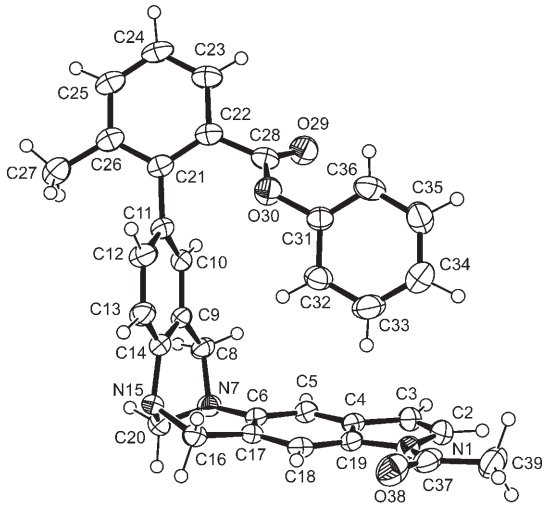


Figure 1. ORTEP plot of (±)-**3**. Thermal ellipsoids at 203 K are set at 50% probability.

folding equilibrium of the two rotamers.[11] The resulting folding free enthalpies ΔG are summarized in Table 1 for five different solvents. Applying the double-mutant cycle approach and Equation (1) provides the incremental free enthalpies $\Delta\Delta G_{CF_3\cdots C=O}$ for the interaction between the

Table 1: Folding free enthalpies for compounds (±)-**1** to (±)-**10**.

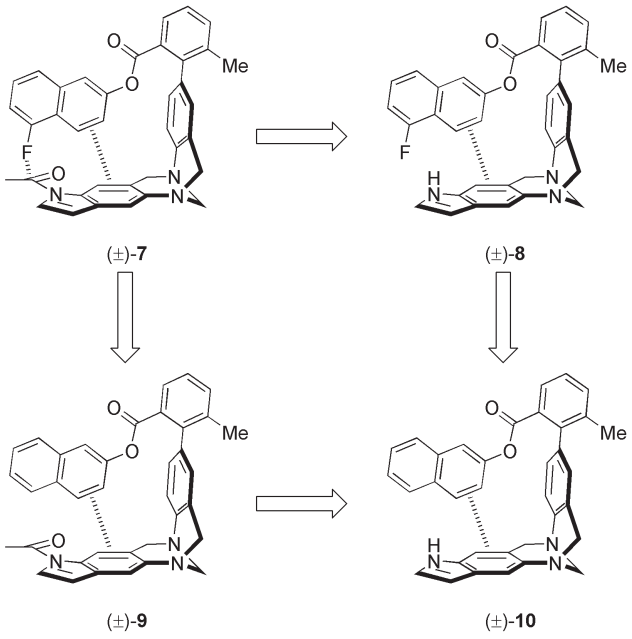
Compound	ΔG [kJ mol^{-1}][a]				
	$CDCl_3$	C_6D_6	CD_2Cl_2	CD_3OD	$C_2D_2Cl_4$
(±)-**1**	−3.54	−4.59	−2.92	−3.80	−3.00
(±)-**2**	−3.36	−4.36	−2.78	−3.09	−2.62
(±)-**3**	−0.90	−1.36	−1.16	−2.62	−0.25
(±)-**4**	−1.03	−1.91	−1.20	−2.33	−0.68
(±)-**7**	−1.41	−1.60	−1.18	n.s.[b]	−1.08
(±)-**8**	−1.33	−1.31	−0.95	n.s.[b]	−0.78
(±)-**9**	−0.55	−0.76	−0.78	n.s.[b]	−0.18
(±)-**10**	−1.06	−1.67	−1.05	n.s.[b]	−0.62

[a] Determined by integration of the line-fitted (100% Lorentz functions) ^{1}H NMR (500 MHz) spectra of 10 mM solutions at 298 K recorded on a Bruker AMX-500 spectrometer. Uncertainty: ±0.12 kJ mol^{-1}. For an error analysis see the Supporting Information. [b] n.s. = not soluble.

appended dipoles. In apolar solvents, such as C_6D_6 ($-0.78 \pm 0.25\ kJ\,mol^{-1}$) and $C_2D_2Cl_4$ ($-0.82 \pm 0.25\ kJ\,mol^{-1}$), the interaction is strongest, consistent with the previously reported values.[5] In smaller dipolar chlorinated solvents, such as $CDCl_3$ ($-0.31 \pm 0.25\ kJ\,mol^{-1}$) and CD_2Cl_2 ($-0.18 \pm 0.25\ kJ\,mol^{-1}$), the interaction is substantially weaker. We attribute this to competing solvation of the extended Tröger base structure, with the positively polarized hydrogen atoms of solvent molecules interacting with the electron-rich indole moiety, thereby shifting the equilibrium in favor of the unfolded conformation. In the polar solvent CD_3OD ($-0.43 \pm 0.25\ kJ\,mol^{-1}$), we observe a stronger interaction energy than in the previously reported system. In polar protic solvents, the indole-based torsion balances apparently are less solvated than the previously reported, CH_3CONH-bearing systems, which feature a strong hydrogen-bond donor.[5]

Analysis of the thermodynamic data in Table 1 reveals that the acetylation of the indole nitrogen atom ((±)-**4**→(±)-**3**) causes a small unfavorable change in the folding free enthalpy of +0.04 to +0.55 kJ mol^{-1} in benzene and the chlorinated solvents. In the case of CD_3OD, an inverse effect is observed (−0.29 kJ mol^{-1}). The change in folding free enthalpy for the substitution of the edge component with a CF_3 group ((±)-**4**→(±)-**2**) instead is much larger (−0.76 to −2.45 kJ mol^{-1}) and similar to the first system reported.[5] This large change raises questions regarding the validity of the double-mutant cycle.[6] The application of the double-mutant cycle is restricted to systems that can be separated into independent subsystems. Only then can the total free enthalpy ΔG be expressed as a sum of its components, one of them being the dipolar interaction. The substantial energetic change upon moving from (±)-**4** to (±)-**2**, however, shows a strong perturbation of the primary edge-to-face interaction. The acidification of the edge protons of the phenyl ester by the CF_3 group in (±)-**2** causes a stronger primary edge-to-face aromatic–aromatic C–H···π interaction, showing that both interactions are strongly cooperative and cannot be regarded as independent subsystems. Therefore, the validity of this double-mutant cycle is limited.

In an attempt to better meet the requirements for a valid double-mutant cycle, we developed the model system shown in Scheme 3. The four target molecules (±)-**7** to (±)-**10** were synthesized along the route shown in Scheme 2.[8] Incorporation of a 5-fluoronaphth-2-yl ester in (±)-**7** allows for an orthogonal dipolar interaction since the local dipole moment is oriented along the C–F bond. Control compounds (±)-**9** and (±)-**10** bear an unsubstituted naphth-2-yl ester. X-ray crystal-structure analyses of (±)-**8** and (±)-**10** (Figure 2) reveal only negligible structural changes upon mutating



Scheme 3. Double-mutant cycle for the determination of the interaction free enthalpy between a C_{sp^2}–F bond dipole and an acetamide group.

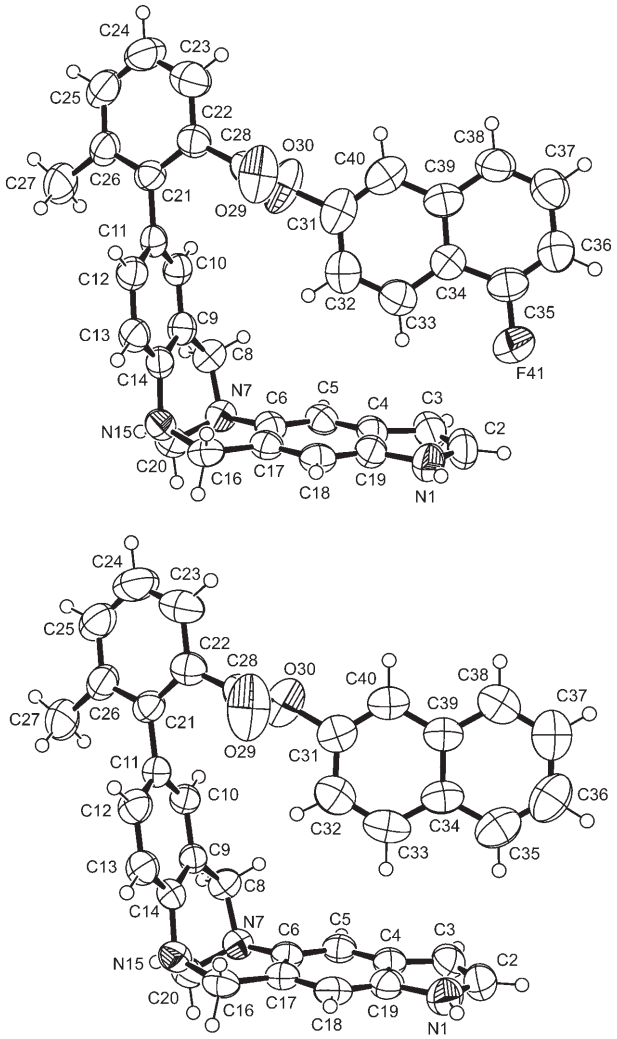


Figure 2. Top: ORTEP plot of (±)-**8**. Thermal ellipsoids at 233 K are set at 50% probability. Bottom: ORTEP plot of (±)-**10**, arbitrary numbering. Thermal ellipsoids at 298 K are set at 50% probability.

naphth-2-yl ester (±)-**10** to 5-fluoronaphth-2-yl ester (±)-**8**. In particular, no additional primary C–H···π interaction of the proton on C35 of the naphthyl fragment in (±)-**10** with the indole system is possible. ^{1}H, ^{19}F NOESY experiments demonstrate the expected proximity of the fluorine atom and the CH_3 group of the acetamide in the folded conformation of (±)-**7** (see the Supporting Information).

The resulting folding free enthalpies are summarized in Table 1 for four of the previously used solvents. Adapting Equation (1) to the second double-mutant cycle provides the free interaction enthalpy for a truly orthogonal interaction between a C_{sp^2}–F and a C=O dipole. In the apolar solvents C_6D_6 (−1.21 ± 0.25 kJ mol^{-1}) and $C_2D_2Cl_4$ (−0.74 ± 0.25 kJ mol^{-1}), the interaction is strongest while the interaction free enthalpy in the dipolar solvents $CDCl_3$ (−0.59 ± 0.25 kJ mol^{-1}) and CD_2Cl_2 (−0.49 ± 0.25 kJ mol^{-1}), which, as discussed above, compete by favorable solvation of the indole moiety in the unfolded conformer, only amounts to half of the magnitude. The difference in free enthalpy between the

solvents $CDCl_3$ and CD_2Cl_2 of 0.10 kJ mol^{-1} correlates with the difference in dipole moment.

The data in Table 1 shows that acetylation of the indole N–H ((±)-**10**→(±)-**9**) is accompanied by a small (+0.27 to +0.91 kJ mol^{-1}) unfavorable change in folding free enthalpy, consistent with the observations in the first double-mutant cycle. The mutation of a naphth-2-yl to a 5-flouronaphth-2-yl ((±)-**10**→(±)-**8**) instead is almost neutral in energy (−0.27 to +0.36 kJ mol^{-1})—as expected from the analysis of the X-ray crystal structures—and certainly meets the criteria for the validity of a double-mutant cycle.

In summary, we have presented the design, synthesis, and evaluation of two novel, indole-extended molecular torsion balances giving final proof for the existence of attractive orthogonal dipolar interactions between a C_{sp^2}–F bond and an amide carbonyl group. The measured interaction free enthalpies in nonpolar solvents lie in the range of −0.8 to −1.2 kJ mol^{-1}. Furthermore we have shown that the restrictions imposed on the validity of a double-mutant cycle approach can be met by a careful design of the model system combined with a thorough analysis of the influence of substituent effects on the energetic contributions to the folding equilibrium. Attractive orthogonal dipolar interactions clearly represent a new promising tool to enhance the stability of protein–ligand interactions in medicinal chemistry and to assemble supramolecular architectures.

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[8] All compounds were fully characterized by melting points, ^{1}H and ^{13}C NMR spectroscopy, IR, MS, and high-resolution MS. The preparation of (±)-**1**–(±)-**4** starting from (±)-**5** is described in full detail in the Supporting Information; the synthesis of (±)-**5** and the new molecular torsion balances (±)-**7**–(±)-**10** will be part of a future full paper, that also addresses the solvent influences discussed in Ref. [7].
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[10] The X-ray crystal structures of three previously reported torsion balances can be found in the Cambridge Structural Database: PIWYAV,[3a] PIWYEZ,[3a] and WAFLOF.[5] To date we have not been able to obtain crystals of (±)-**1** and (±)-**7** suitable for X-ray analysis.
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