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Molecular Torsion Balance for Weak Molecular Recognition Forces. Effects of "Tilted-T" Edge-to-Face Aromatic Interactions on Conformational Selection and Solid-State Structure[1]

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In the solid state, proximate benzenoid rings are often found in an edge-to-face orientation and the gas-phase benzene dimer favors a T-shaped geometry.[2,3] These observations have stimulated interest in "edge-to-face aromatic interactions". Following Burley and Petsko's influential paper,[4] observations of edge-to-face orientations have increased and this interaction between aromatic rings has been cited as a structure-determining factor in many examples of molecular recognition.[5] A recent paper concluded that such phenomena are now known to play an important role in protein folding and molecular recognition.[6] Is this so?

Edge-to-face interactions are most often explained as an electrostatic phenomenon arising from interaction of the electric fields surrounding benzenoid rings.[3,7] Theoretical calculations suggest that this electrostatic interaction is small compared to dispersion forces.[8] Jorgensen and Severance's electrostatic model for benzene (a Coulomb plus Lennard-Jones approach) predicts that a "tilted-T" geometry is favored with an optimum centroid–centroid distance at 5 Å. Most of the attractive force is provided by London dispersion forces.[9]

Conformational isomerism can provide a sensitive probe of weak molecular forces.[10] We reasoned that a molecule that had two gently restricted conformational states, only one of which had a well-defined aryl–aryl interaction, would allow an experimental probe of aryl–aryl interaction energies and allow them to be compared with other interactions. The molecule would act as a simple torsion balance. The restoring force would be entropic, and deviations from the 1:1 ratio of states would reveal any intramolecular forces. Direct NMR observation of the relative populations of each state can provide needed data for testing theoretical models of edge-to-face interactions.

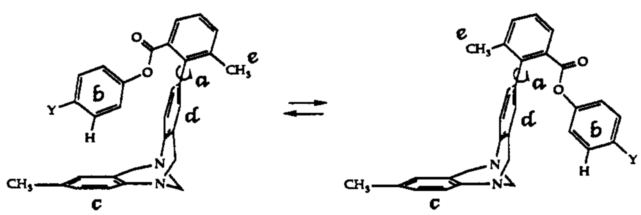
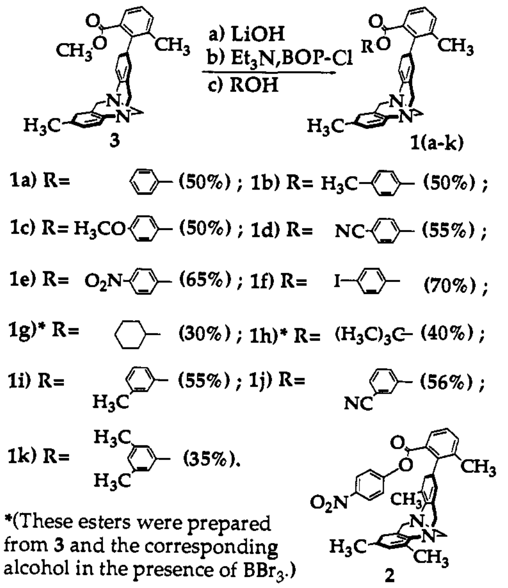


Figure 1. Conformational states for aryl esters **1a-f**. Rotation about bond α is slow ($E_a \approx 16$ kcal/mol at 298 K). Separate NMR peaks are observed for each state.[15]

Scheme I



*(These esters were prepared from **3** and the corresponding alcohol in the presence of BBr_3.)

We synthesized esters **1a-k**, **2**, and **3** (Scheme 1). Each ester has two conformations that interconvert by slow rotation. For the folded conformation (left hand, Figure 1), ring b lies over ring c and is oriented in a tilted-T position relative to that ring. In the unfolded conformation, the interaction with ring c is remote. (Both conformations include an interaction between rings b and d, so this interaction should not perturb the relative populations.) Methyl ester **3** shows no preference for either state, so long-range effects that might contribute to conformer selection and confound our data analysis are insignificant.

X-ray crystallography confirmed edge-to-face interactions for the folded isomers. Crystal structures of *p*-nitrophenyl esters **1e** and **2** revealed that, in the solid state, rings b and c have a theoretically near-perfect tilted-T relationship. For **1e** and **2** the relevant centroid–centroid distances are 4.95 and 5.09 Å, respectively (Figure 2).

What is interesting here is the energetic cost of "denaturing" this folded state, and the influence of substituents and solvents on this energy change. The in:out ratios were determined in solution by 300-MHz ^{1}H-NMR spectroscopy at 298 K (Table 1). The folded isomer was identified readily because the proton meta to the C–O bond in ring b was shifted upfield in this conformer. Phenyl ester **1a** is characteristic of the general trend: the folded state is preferred, in this case by a ratio of 3:2, or $\Delta G^\circ_{\mathrm{fold}} = -0.24$ kcal/mol. A *p*-methyl group perturbs this equilibrium slightly (ester **1b**, $\Delta G^\circ_{\mathrm{fold}} = -0.37$), but the electron-donating *p*-methoxy group has no effect on the equilibrium, despite its effect on the electric field surrounding ring b.[11] The electron-withdrawing groups (*p*-cyano and *p*-nitro, **1d** and **1e**, Table 1) affect the ratio more than a methyl group ($\Delta G^\circ_{\mathrm{fold}} = -0.65$ kcal/mol). Electron-withdrawing substituents change the polarizability of ring b as well as the local electric field and so affect dispersion forces as well as electrostatic forces. We prepared the *p*-iodophenyl ester **1f**. It shows an enhanced preference for the folded state, favoring by 3:1 the folded conformation, just as did the *p*-nitrophenyl ester, so the stabilization of the folded state is not induced solely by strongly electron withdrawing groups.

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(11) For example, AM1 single point calculations (MM3 optimized structures) give dipole moments of 1.4 D for phenyl acetate versus 1.5 and 2.1 D for the two conformers of *p*-methoxyphenyl acetate.

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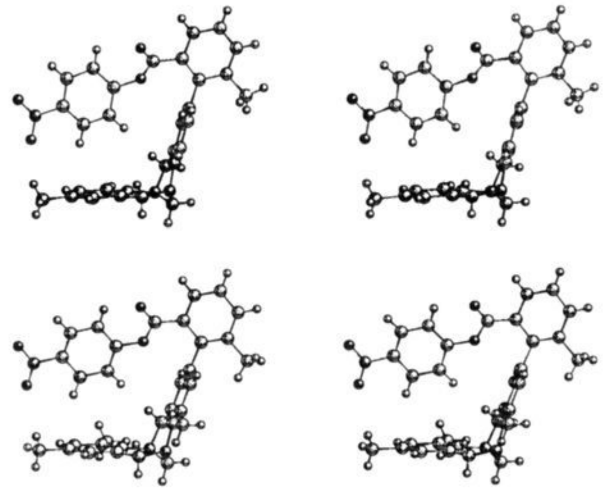

Figure 2. Stereoviews of the crystallographically determined solid-state structures of esters **1e** (top) and **2** (bottom).

It is especially enlightening to see that a preference for the folded state is *not* unique to aryl esters. The cyclohexyl ester **1g** favors the folded state more than the phenyl ester. The *tert*-butyl ester **1h** favors the folded state by 4:1, a preference greater than that shown by *any* aryl ester. Although the edge-to-face orientation of rings b and c is directly observable in the solid state, the influence of this edge-to-face interaction on the dynamic equilibrium involving folding of the molecule is not more important than cyclohexyl–aryl interactions or *tert*-butyl–aryl interactions.

The dielectric effect of the solvent should modulate intramolecular electrostatic interactions. Furthermore, if the dipole moments of the two states differ, their relative free energies can be a direct consequence of solvation energies.[12] However, solvent has a negligible effect on the observed ratios. The observed in:out ratio for the phenyl ester **1a** was unchanged in $CDCl_3$, CD_3NO_2, d_6-DMSO, C_6D_6, and CCl_4. Solvent size and shape can also affect solvation energies for molecules, especially those that have concave surfaces.[13] The phenyl ester in:out ratio was unchanged in tetrachloroethylene or in tetrachloroethane.

The dibenzodiazocine structure is useful here because it provides order, yet it is flexible enough to allow the hinge angle (the angle formed by extension of the least-squares planes of rings c and d, Figure 1) to adjust to accommodate a good contact distance.[14] This hinge angle can be made larger by adding methyl groups to the unsubstituted sites ortho to the dibenzodiazocine nitrogen atoms.[14,15] If in ester **1e** the folded conformer was strained due to too-close contacts between rings b and c, then adding methyl groups to those positions would result in an increased preference for the "in" isomer. This methylated molecule was prepared (**2**, Scheme 1), and the hinge angle was observed to increase (Figure 2), but the extra methyl groups do not change the in:out ratio.

Table 1. Experimental Folding Energies for Esters **1a–k**, **2**, and **3**

ester	% folded[a]	$\Delta G°$ (±10%)[b]	ester	% folded[a]	$\Delta G°$ (±10%)[b]
1a	60	–0.24	**1g**	65	–0.37
1b	65	–0.37	**1h**	80	–0.82
1c	60	–0.24	**1i**	50	0.00
1d	75	–0.65	**1j**	60	–0.24
1e	75	–0.65	**1k**	35	0.37
1f	75	–0.65	**2**	75	–0.65
			3	50	0.00

[a] Mole percent of solute in the folded state as determined by NMR spectroscopy in $CDCl_3$ at 298 K. Numbers represent average of several determinations and have been rounded off to nearest 5%. [b] Kilocalories/mole.

Another line of reasoning also supports the idea of an edge-to-face folded state in solution. Suppose the folded state is favored due to a *stacking* interaction between rings b and c (Figure 1). In that case adding a methyl group to the meta position of ring b should have little or no effect. On the other hand, if the edge-to-face orientation is dominant, then a meta substiuent would lead to an enhanced preference for the unfolded conformer. The internal rotational entropy contribution of the meta-substituted ring would make the folded conformer less favorable by a factor of $RT \ln 2$ by increasing by a factor of 2 the rotational states available for the unfolded isomer.[16,17] In fact, in both cases (**1i** and **1j**) the single meta substituent induced a shift toward the unfolded state equal to a free energy change of $RT \ln 2$ (0.4 kcal/mol). Two meta substituents (**1k**) lead, not surprisingly, to a preference for the unfolded state.

These esters are the first examples of molecules that have crystallographically observed edge-to-face interactions and also, in solution, have two easily quantified folding states. They provide a simple model of denaturation processes that would disrupt aryl edge-to-face contacts. The data in Table 1 should prove valuable for testing theoretical and empirical models for edge-to-face interactions. Theory suggests that the preference for edge-to-face orientation in the solid state is due to electrostatic forces. In this experiment these are found to be weak interactions, affecting conformational energies by about 0.5 kcal/mol at 298 K.[18] We expect that many functional groups will be found to interact to this extent with the electric fields presented by aromatic molecular substructures, and that other pairs of polar functional groups will have interaction energies equal to or greater than the edge-to-face aryl interaction. The experimental approach outlined here can help to quantify functional group interactions, and such experiments are underway. The notion that edge-to-face interactions are "important" is a matter for individual interpretation, but given these results, which show cyclohexyl, phenyl, and *tert*-butyl esters to have similar affinities for the face of an aryl ring, a circumspect approach is warranted.

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Supplementary Material Available: NMR spectra for esters **1a-k**, **2**, and **3** details of crystallographic reports for **1e** and **2** (33 pages); listing of observed and calculated structure factors (32 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) This is a maximum effect and would be expected only if edge-to-face orientations are dominant for the folded state. If the folded state allowed many equally energetic relative orientations, fewer than half of these would be precluded by the meta substituent and the effect would be less than $RT \ln 2$.

(18) The question of the relative roles of permanent field effects and London dispersion forces in such interactions is worth further consideration.