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Effect of Diazocine Bridgehead Modification on the Folding of the Wilcox Molecular Torsion Balance: A View from a Different Angle

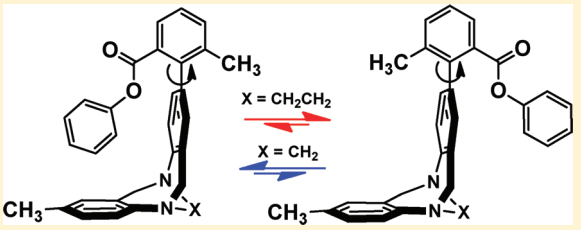
Brijesh Bhayana[†] and Mark R. Ams*[,‡]

[‡]Department of Chemistry, Allegheny College, 520 North Main Street, Meadville, Pennsylvania 16335-3902, United States

[†]Wellman Center for Photomedicine, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, United States

Supporting Information

ABSTRACT: Replacing the *methano* (NCH_2N) bridgehead with an *ethano* (NCH_2CH_2N) bridgehead affects the conformational equilibrium of the Wilcox molecular torsion balance. With a NCH_2CH_2N bridgehead, the phenyl and the cyclohexyl esters prefer the out conformation, whereas with the NCH_2N bridgehead, they were found to prefer the folded conformation.



The Wilcox torsion balance was introduced nearly two decades ago as a tool for measuring weak edge-to-face aromatic interactions that would normally be difficult to quantify.[1] Such interactions are ubiquitous in chemistry and biology and are involved in wide-ranging phenomena such as protein folding, DNA replication, chiral discrimination, stereoselective synthesis, molecular recognition, self-assembly, crystal packing, and metal coordination to name a few.[2] An elegant feature of the torsion balance is its simple design, consisting of a gently rotating functionalized phenyl ring mounted on a V-shaped rigid framework of Tröger's base. The two ortho-substituents on the phenyl ring provide a rotational barrier high enough for two atropisomers to be observed distinctly by NMR spectroscopy at room temperature. It was found that the folded (in) conformation in which the ester resides above the arene was preferred over the out conformation by a free energy difference of 0.2−0.8 kcal/mol, and that electron-withdrawing or -donating substituents on the bottom arene had little effect on the folding ratio. These observations were originally thought to be consistent with the predominantly dispersive nature of the CH−π interactions, but subsequent studies have shown that the trends in folding behavior of these molecules can also be explained by a delicate balance of solvent and electrostatic interactions.[3]

An architectural feature common to the torsion balances reported to date is the *methano* (NCH_2N) bridgehead, which imposes an almost T-shaped geometry between the ester CH bonds and the bottom arene. Despite the general rigidity, the dihedral angle between the planes of the two aromatic rings of the Tröger's base have been observed to vary from 86° to 104° in X-ray crystal structures of various analogues.[4] Interestingly, both crystal-structure data and geometry-optimization studies show a significant decrease, up to 20° in some cases, in the dihedral angle when an *ethano* bridgehead is used instead (Figure 1).[5]

On the basis of this observation, we surmised that a torsion balance with an ethanodibenzodiazocine framework will have a shorter CH−π interaction distance and its folding ratio could provide valuable information on how this interaction scales with distance. Herein, we describe the folding behavior of a new molecular torsion balance that contains a bridgehead modification from methyl to ethyl (Figure 2).

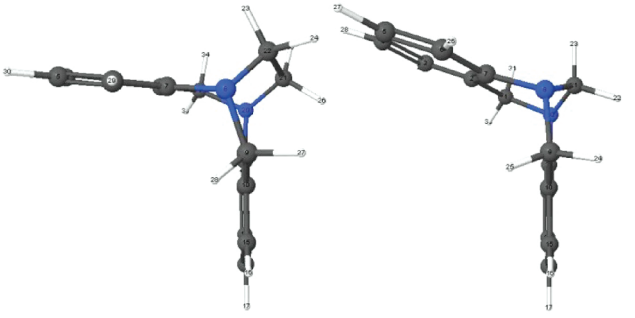


Figure 1. Gaussian geometry optimization predictions of *ethano* (left) and *methano* (right) strapped Tröger's base.

Several new torsion balances bearing the NCH_2CH_2N bridgehead were synthesized via Suzuki-coupling (Scheme 1), and their corresponding folding ratios measured by ^{1}H NMR spectroscopy.[5,6]

The folding ratios revealed an interesting trend. The folding energies (ΔG_{ethyl}°) for the *ethano*-bridged torsion balances (methyl, isopropyl and *tert*-butyl) were close to the values observed for the corresponding *methano*-bridged torsion balances ($\Delta G_{methyl}^{\circ}$). Although the differences between the folding energies ($\Delta\Delta G^{\circ} = \Delta G_{ethyl}^{\circ} - \Delta G_{methyl}^{\circ}$, ~0.1 kcal/mol) in the methano vs ethano balances are small for these esters, the results do not automatically imply that the CH−π interaction was unaltered. This is because the conformational equilibrium is

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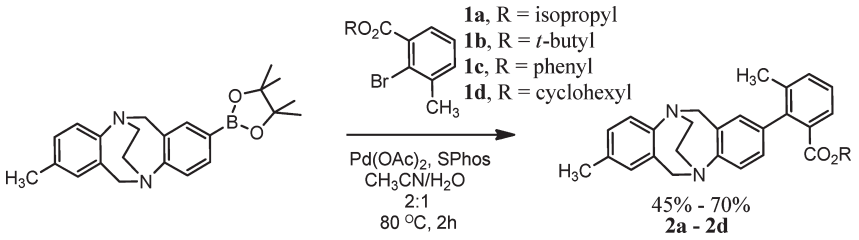
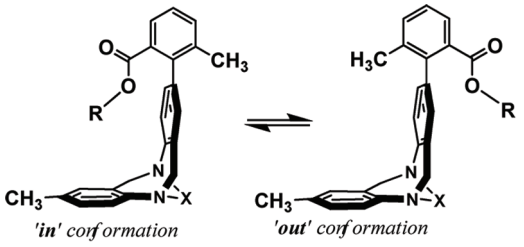
Scheme 1





Entry	R	$\Delta G_m°$ (X = CH_2)[a]	$\Delta G_e°$ (X = CH_2CH_2)	$\Delta(\Delta G°)$ (=$\Delta G_e°$-$\Delta G_m°$)
1	$CH(CH_3)_2$	-0.44	-0.61	-0.17
2	$C(CH_3)_3$	-0.82	-0.75	+0.07
3	C_6H_{11}	-0.37	*+0.07*	+0.44
4	C_6H_5	-0.24	*+0.16*	+0.40

Figure 2. Folding ratios of *methano*- and *ethano*-bridged torsion balances (kcal/mol, in $CDCl_3$ at 298K, ± 10%). [a]Reported by Wilcox in reference 1a,b.

determined by the overall sum of many different individual energetic contributions such as those arising from dispersion interactions, electronic, steric, and solvation effects. An increase in the attractive CH−π component accompanied with a corresponding increase in repulsive interactions (such as steric effects) can also result in a small $\Delta\Delta G°$. Chemical calculations can shed more light on how individual energetic contributions are affected by bridgehead modification. Therefore, these results may be of interest to computational chemists.

The conformational equilibria of the phenyl and cyclohexyl esters are more intriguing. For these balances, the $\Delta\Delta G°$ is much larger (~0.4 kcal/mol) and in favor of the out conformation. Since these esters have a more extended contact area with the bottom arene compared to the isopropyl and *tert*-butyl esters, a bigger $\Delta\Delta G°$ may be expected. A preference for the out conformation suggests that steric repulsions dominate over the attractive interactions. The solid state structures of the phenyl ester torsion balances by Wilcox show a close contact distance between the meta hydrogen atom on the ester ring (A in Figure 3) and the bottom arene. In our study, the replacement of the *methano* bridgehead with an *ethano* bridgehead could decrease the interaction distance and therefore increase steric repulsions in this region. The end result is a denatured balance that avoids the steric clash.

In conclusion, our data suggest that replacing the *methano* bridgehead with an *ethano* bridgehead in the Wilcox torsion balance leads to a decrease in the ester−arene interaction distance. We believe that like previously, the data from this study will be of value to researchers interested in modeling weak interactions and solvation effects.[7] The torsion balance has been used by Diederich to study nonbonding interactions such as the

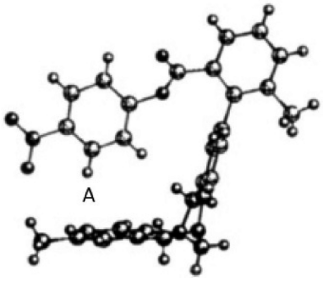


Figure 3. Solid-state structure of a phenyl-ester torsion balance reported by Wilcox and co-workers (reprinted with permission from ref 1a; copyright 1994, American Chemical Society).

orthoganol dipolar interaction between amide carbonyls and an amide−CF_3 interaction (see ref 3). A bridgehead modification in such studies can be a useful tool for altering the interaction distance.

EXPERIMENTAL SECTION

All reagents were purchased from commercial suppliers and used without further purification. ^1H and ^{13}C spectra were recorded on a 300 MHz NMR spectrometer. The spectra are referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm). The ^{13}C spectra are referenced to $CDCl_3$ (δ = 77.0 ppm). The coupling constants are reported in hertz (Hz). Thin layer chromatography was performed on silica gel 60 F_{254} plates. The pinacolatoboronate ester of ethanodibenzodiazocine was synthesized by using known procedures.[5]

Representative Procedure for the Suzuki-Coupling Reaction. A 6 mL screw cap glass vial equipped with a magnetic stir bar and a plastic screw cap with Teflon septum was charged with *tert*-butyl 2-bromo-3-methylbenzoate (27.0 mg, 0.1 mmol), 2-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,12-dihydro-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine (37.0 mg, 0.10 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and dicyclohexyl(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine (SPhos, 4.1 mg, 0.01 mmol). After these additions, the vial was purged with argon and 0.2 mL of acetonitrile (HPLC grade), then 0.1 mL of 2.0 M K_2CO_3 was added to it with a syringe. The reaction mixture was then stirred at 80 °C for 2 h and cooled to room temperature, then the reaction solution was layered on a TLC plate. Purification by using prep TLC (ethyl acetate:hexanes, 1:3) provided the desired product **2b** (21 mg, 48% yield) as a thick light yellow oil.

NMR Characterization. Isopropyl 3-methyl-2-(8-methyl-6,12-dihydro-5,11-ethanodibenzo[*b*,*f*][1,5]diazocin-2-yl)benzoate (**2a**): ^1H NMR δ 7.55−7.50 (m, 1H), 7.33−7.2 (m, 2H), 7.12−7.05 (m, 1H), 7.0−6.95 (m, 1H), 6.93−6.8 (m, 2H), 6.75−6.65 (m, 2H), 4.89−4.35 (m, 5H), 3.66−3.50 (m, 4H), 2.16 (s, br, 3H), 2.04/1.85 (s, 3H, *2.8/1*), 0.96/0.33 (d, *J* = 6.2 Hz, 3H, *1/2.8*), 0.94/0.27 (d, *J* = 6.2 Hz, 3H, *1/2.8*). ^{13}C NMR δ 168.9, 149.0, 147.6, 147.5, 140.2, 137.1, 136.8, 136.6, 136.2, 134.1, 133.9, 133.0, 132.9, 132.5, 132.3, 129.2, 128.8, 128.0, 127.86, 127.83, 127.6, 127.5, 127.4, 127.0, 126.9, 126.4, 124.6, 68.1, 59.18, 59.12,

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55.0, 54.9, 54.8, 54.7, 21.38, 21.31, 20.7, 20.6, 20.47, 20.43. HRMS *m/e* calcd for $C_{28}H_{30}N_2O_2$ 426.2307, found 426.2322.

tert-Butyl 3-methyl-2-(8-methyl-6,12-dihydro-5,11-ethanodibenzo[*b*,*f*][1,5]diazocin-2-yl)benzoate (**2b**): ^{1}H NMR δ 7.5−7.4 (m, 1H), 7.35−7.17 (m, 2H), 7.15−7.11 (m, 1H), 7.0−6.95 (m, 1H), 6.9−6.8 (m, 2H), 6.75−6.65 (m, 2H), 4.68−4.35 (m, 4H), 3.68−3.50 (m, 4H), 2.18 (s, br, 3H), 2.03/1.86 (s, 3H, *3.6/1*), 1.19/0.67 (s, 9H, *1/3.6*). ^{13}C NMR δ 168.6, 148.9, 147.6, 139.9, 136.9, 136.7, 136.3, 136.2, 134.2, 134.1, 131.9, 129.0, 128.6, 128.2, 128.1, 128.03, 127.8, 127.4, 126.9, 126.2, 80.8, 80.6, 59.18, 59.12, 54.99, 54.95, 27.57, 27.0, 20.6, 20.3. HRMS *m/e* calcd for $C_{29}H_{32}N_2O_2$ 440.2464, found 440.2453.

Phenyl 3-methyl-2-(8-methyl-6,12-dihydro-5,11-ethanodibenzo[*b*,*f*][1,5]diazocin-2-yl)benzoate (**2c**): ^{1}H NMR δ 7.72/7.65 (d, *J* = 7.0 Hz, 1H, *1.3/1*), 7.5−6.7 (m, 12H), 6.26 (m, 1H), 4.68−4.2 (m, 4H), 3.77−3.50 (m, 4H), 2.18 (s, br, 3H), 2.1/1.9 (s, 3H, *1.3/1*). ^{13}C NMR δ 166.8, 150.1, 148.7, 146.9, 140.6, 136.8, 135.9, 135.7, 133.3, 132.7, 132.5, 131.0, 128.6, 128.3, 128.2, 127.3, 127.2, 127.0, 126.49, 126.45, 125.0, 124.5, 120.7, 120.4, 58.6, 58.4, 54.4, 54.2, 20.3, 20.1, 19.7. HRMS *m/e* calcd for $C_{31}H_{28}N_2O_2$ 460.2151, found 460.2137.

Cyclohexyl 3-methyl-2-(8-methyl-6,12-dihydro-5,11-ethanodibenzo-[*b*,*f*][1,5]diazocin-2-yl)benzoate (**2d**): ^{1}H NMR δ 7.56/7.49 (d, *J* = 6.6 Hz, 1H, *1.14/1*), 7.3−7.2 (m, 2H), 7.12−7.08 (m, 1H), 6.99−6.8 (m, 3H), 6.75−6.6 (m, 2H), 4.7−4.3 (m, 5H), 3.77−3.50 (m, 4H), 2.18 (s, br, 3H), 2.04/1.83 (s, 3H, *1.13/1*), 1.6−0.3 (m, 10H). ^{13}C NMR δ 168.6, 148.9, 147.5, 140.5, 140.1, 137.17, 137.12, 136.6, 136.5, 136.4, 136.3, 136.2, 133.9, 132.9, 132.4, 132.2, 129.19, 129.15, 128.8, 128.7, 128.5, 127.99, 127.92, 127.91, 127.8, 127.7, 127.6, 127.5, 127.49, 127.44, 127.3, 126.8, 126.6, 126.3, 73.0, 72.9, 59.2, 59.1, 59.04, 59.02, 58.9, 55.1, 55.0, 54.9, 54.8, 54.76, 31.1, 30.5, 30.3, 25.3, 25.2, 23.6, 23.3, 23.1, 20.3. HRMS *m/e* calcd for $C_{31}H_{34}N_2O_2$ 466.2620, found 466.2622.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: mams@allegheny.edu.

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