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Unexpected Substituent Effects in Offset $\pi-\pi$ Stacked Interactions in Water

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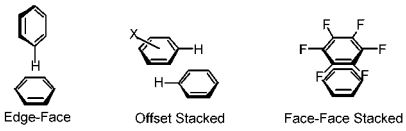
Aromatic interactions are common motifs in biomolecular structure and molecular recognition.[1−3] However, despite their frequent occurrence, there is no unifying picture of the factors that contribute to the interaction, which include electrostatic (quadrapole−quadrapole and quadrapole−dipole, and dipole−dipole),[4] hydrophobic,[2a,5] and van der Waals interactions.[2a,4d] This is complicated by the fact that aromatic rings interact in several different conformations, each of which is favored by a different combination of forces.[1] These conformations include the edge−face interaction for two unsubstituted benzene rings, the offset stacked conformation for substituted aromatic rings, and the face-face stacked geometry for the interaction of benzene with perfluorobenzene. The offset stacked geometry is the most common geometry for aromatic interactions, but the least well studied. To clarify the factors that influence offset stacking, we have undertaken a quantitative study of substituent effects on this interaction in aqueous solution. We have found that the magnitude of the offset stacked interaction is dependent on the orientation of the rings, and it appears that a direct interaction between the ring hydrogens and the substituents themselves may significantly influence the magnitude of the interaction.



As a model system for offset stacking interactions, we investigated meta- and para-substituted *N*-benzyl-2-(2-fluorophenyl)-pyridinium bromides of the type **1**, which stack in the offset conformation in the solid state.[6] The single methylene linker between the **B** and **C** rings prohibits edge−face interactions. The pyridinium ring provides water solubility and the ortho-fluoro group was incorporated to desymmetrize ring **A**, making H_a and H_b diastereotopic. The relative strengths of the stacking interactions with various substituents, X, were determined by measuring rate constants for restricted rotation around the biaryl bond in which the stacking interaction between rings **A** and **C** must be disrupted in the transition state. The rotational barrier was determined by dynamic NMR through simulation of the line-broadened spectra of H_a and H_b in D_2O.[7] Because the substituent, X, does not interact with the **A** or **B** ring in the transition state either through space or via conjugation, changes in the rotational barrier can be attributed solely to changes in the ground-state interaction.

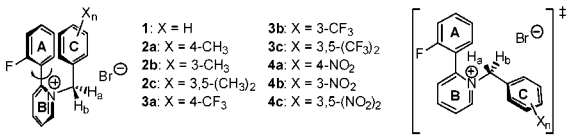


Table 1. Rotational Barriers (kcal/mol) of Substituted Benzyl Pyridinium Bromides in Water[a]

compd	X	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{(X-H)}$	$\Delta\Delta G^{\ddagger}_{(m-p)}$
1	H	16.81	−	−
2a	4-CH_3	16.80	−0.01	−
2b	3-CH_3	16.86	0.05	0.06
2c	3,5-$(CH_3)_2$	16.88	0.07	−
3a	4-CF_3	16.87	0.06	−
3b	3-CF_3	17.17	0.36	0.30
3c	3,5-$(CF_3)_2$	17.47	0.66	−
4a	4-NO_2	16.91	0.1	−
4b	3-NO_2	17.13	0.32	0.22
4c	3,5-$(NO_2)_2$	17.32	0.51	−

[a] Energies were measured at 332 K as described in the text. Propagation of errors gives an uncertainty of less than ±0.04 kcal/mol.[7]

Inspection of the rotational barriers in Table 1 indicates that there is a small substituent effect on offset stacking in which electron-withdrawing groups increase the magnitude of the rotational barrier, and that it is larger for meta-substituents than para-substituents.[8] Comparison of the electrostatic potential surfaces of compounds **1** (X = H) and **4a** (X = 4-NO_2) suggests that the higher barrier found with electron-withdrawing groups in the para position is due to the reduced electron density on the face of the **C** ring relative to compound **1** (Figure 1).[9] Reduction in the electron density on the face of one ring has been shown to decrease the repulsive component resulting from interaction of the π-clouds in the face-face stacked conformation.[4b] The effect is significantly smaller in the offset-stacked conformation, presumably due to the reduced interaction of the π-clouds in this geometry.

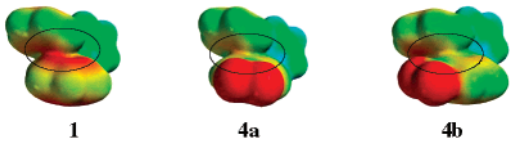


Figure 1. Ab initio electrostatic potential calculations of **1**, **4a**, and **4b** indicating the interactions of the faces of the **A** (top) and **C** (bottom) rings.[9]

The larger rotational barrier observed for the meta-substituents relative to the para-substituents cannot be explained by changes in the electron density on the face of the rings alone. For example, compound **4b** (X = 3-NO_2) has a similar degree of electron density on the face of the **C** ring as compound **4a** (Figure 1), but the rotational barrier for **4b** is 0.22 kcal/mol higher in energy than that of **4a**. Modeling studies indicate that an oxygen on the *m*-nitro group is in close proximity to H_d of the **A** ring in compound **4b**, suggesting that there may be an attractive electrostatic interaction between the edge hydrogen ($\delta+$) and oxygen ($\delta-$) of the nitro group that is not possible in **1** or **4a** (Figure 2), and that this may contribute to the higher rotational barrier for **4b** relative to **4a**.

Support for the presence of an interaction between a ring hydrogen and the nitro substituent in **4b** comes from ^{1}H NMR

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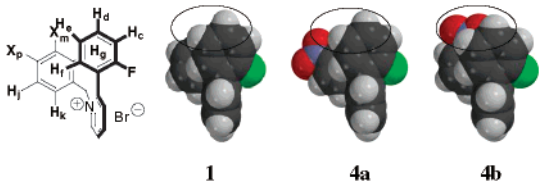
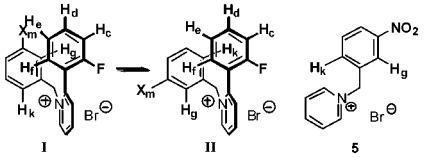


Figure 2. Space-filling models of **1**, **4a**, and **4b** indicating the interaction of H_d on ring **A** (front) with the substituent on ring **C** (back).

chemical shift data. If interaction of H_d with the nitro group in **4b** does indeed increase the stability of the offset stacked geometry, conformation **I** should be favored over conformation **II** (Scheme 1). We compared the chemical shifts of H_g and H_k on the **C** ring of **4b** to a control compound, **5**, in which the **A** ring is missing. The relative upfield shifts of H_g and H_k should reflect the relative populations of **I** and **II**. Both H_g and H_k in compound **4b** are upfield shifted relative to the ortho hydrogens in compound **5**, but H_g is upfield shifted by about 0.1 ppm more than is H_k, indicating that **I** is in fact the lower energy conformation.[10]

Scheme 1. Possible Conformations for Meta-Substituted Compounds



The difference in barriers of **3a** (X = 4-CF_3) and **3b** (X = 3-CF_3) shows the same trend as for the *m*- and *p*-nitro-substituted compounds. As with the 3-NO_2 group, modeling studies indicate a close contact between the CF_3 group and H_d and H_e of the **A** ring in **3b** (Figure 3) that is not possible in **3a**. Because fluorine is poorly solvated by water, the larger interaction with the CF_3 group may also be due to the hydrophobic effect. However, no significant difference between the rotational barriers is observed for the *p*- and *m*-methyl compounds **2a** (X = 4-CH_3) and **2b** (X = 3-CH_3), despite the fact that the 3-CH_3 group is also in close proximity to the edge of the **A** ring. This suggests that the hydrophobic effect alone cannot explain the difference in rotational barriers of compounds **3a** and **3b**.

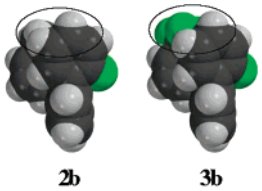


Figure 3. Space-filling models of **2b** and **3b** indicating the interaction of H_d and H_e on ring **A** (front) with the substituent on ring **C** (back).

Because the meta-substituted compounds are in rapid conformational equilibrium, the magnitude of the rotational barrier reflects the relative ground-state populations of **I** and **II**. If the interaction of the meta-substituent with the ring is important, as proposed, then the rotational barrier should be higher for a compound with two meta-substituents. This is in fact what was found with compounds **3c** and **4c**. For example, the rotational barrier for compound **3b** (*X* = 3-CF_3) is 0.36 kcal/mol greater than that for compound **1** (X = H), and the barrier for **3c** (X = 3,5-$(CF_3)_2$) is 0.66 kcal/mol greater than that for compound **1**. In contrast, as for **2b** (X = 3-CH_3), compound **2c** (X = 3,5-$(CH_3)_2$) showed a negligible increase in rotational barrier.

In summary, our results indicate that the orientation of two stacked rings can have a significant effect on the magnitude of the interactions.[11] Although variations in interaction strength are small, these variations can have a considerable effect in the context of a protein, in which many of such weak interactions are involved. The variation in the magnitude of the stacking interaction with the meta-substituents in this system appears to be due in part to direct interaction of the edge hydrogens of one ring with electronegative substituents on the other ring. This may have implications for stacking of other substituted rings such as the DNA bases. The generality of these findings is currently under investigation.

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Supporting Information Available: Synthesis, characterization, and kinetic measurements of reported compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Spectra were simulated using the program *g*NMR version 3.6.5 (Adept Scientific). Each rate constant was measured at least twice, with an error of less than 5%. The temperature was calibrated before and after each spectrum based on the temperature dependence of ethylene glycol chemical shifts, with an uncertainty of ±0.2 K, resulting in an uncertainty of less than ±0.04 kcal/mol. The spectra were found to be independent of concentration under the conditions studied, indicating that no aggregation was occurring. The chemical shifts of H_a and H_b were found to be independent of temperature.

(8) Similar energy differences have been observed for edge−face interactions and the interactions of heteroaromatic rings. See: Kim, E.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192−11193. McKay, S. L.; Haponstall, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 1244−45.

(9) Electrostatic potential surfaces were generated by mapping 6-311G* electrostatic potentials onto surfaces of molecular electron density using Spartan (Wavefunction, Inc, Irvine, CA). The potential energy range is 50−125 kcal/mol for all surfaces shown. Red indicates areas of greater electron density and blue indicates areas of less electron density.

(10) The sum of the upfield shifts of H_g and H_k (1.25 ppm) agrees well with the value of 1.24 ppm calculated from the crystal structure of *N*-benzyl-2−phenylpyridinium bromide,[6] suggesting that the rings spend a significant proportion of their time in the offset stacked conformation in solution. See: Pople, J. A. *J. Chem. Phys.* **1956**, *24*, 1111.

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