ORGANIC
LETTERS

1999
Vol. 1, No. 13
2049−2051

Theoretical Studies of the Wilcox Molecular Torsion Balance. Is the Edge-to-Face Aromatic Interaction Important?

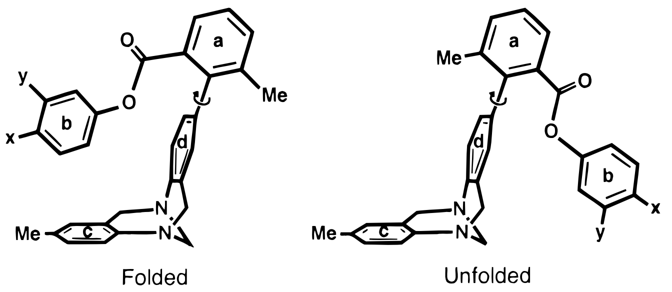
Kensuke Nakamura[†] **and K. N. Houk***[,‡]

Department of Chemistry and Biochemistry, University of California, Los Angeles, 405
Hilgard Avenue, Los Angeles, California 90095-1569, and Institute for Medicinal
Molecular Design, 5-24-5 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

houk@ucla.chem.edu

Received September 7, 1999

ABSTRACT



Molecular mechanics calculations with several different force fields and the GB/SA solvation model were carried out for the molecular torsion balance developed by Wilcox et al. to investigate the intramolecular nonbonded interactions between two aromatic rings. The preference is found to arise from a balance between intramolecular van der Waals interactions and solvation effects, with the latter favoring the unfolded conformation.

Nonbonded interactions between aromatic groups have attracted considerable attention in the past few years.[1] There are two limiting interaction modes, so-called “face-to-face”-(parallel) and “edge-to-face”(perpendicular), between two aromatic rings. While the face-to-face interaction is often thought to lead to “π-stacking” interactions, there is now much experimental evidence for edge-to-face structures in solid and gas phases. The edge-to-face aromatic interaction is proposed to be essential in many biologically important processes, such as protein folding and ligand−receptor interactions.[2] The intermolecular interactions between aromatic systems are interesting from a computational point of view, as well, mainly because of the difficulty in reproducing the liquid properties of benzene and other aromatic solutions.[3]

Wilcox et al. recently developed a unique molecular device to analyze the nonbonded intramolecular interactions between two aromatic rings.[4] The abstract illustrates the structures of these molecules in two conformations. There are two distinct conformational states called “folded” and “unfolded”. They are rotational isomers around the biphenyl linkage between the a and d rings. Aromatic−aromatic interactions between the b and d rings are present in both folded and

---

[†] Institute for Medicinal Molecular Design; nakamura@immd.co.jp.
[‡] University of California, Los Angeles.

(1) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. Singh, J.; Thornton, J. M. Chem. Phys. **1975**, *63*, 1419. Blundell, T.; Singh, J.; Thornton, J.; Burley, S. K.; Petsko, G. A. *Science* **1986**, *234*, 1005.

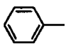
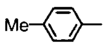
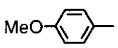
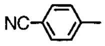
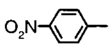
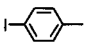
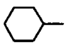
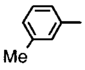
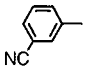
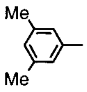
(2) Cox, E. G.; Cruikshank, D. W. J.; Smith, J. A. C. *Proc. R. Soc. London* **1958**, *A247*, 1. Janda, K. C.; Hemminger, J. C.; Winn, J. S.; Novick, S. E.; Harris, S. J.; Klemperer, W. J. *J. Chem. Phys.* **1975**, *63*, 1419.

(3) Jorgensen, W. L.; Severance, D. L. J. *J. Am. Chem. Soc.* **1990**, *112*, 4768.

(4) (a) Paliwal, S.; Geib, S.; Wilcox, C. S.; *J. Am. Chem. Soc.* **1994**, *116*, 6, 4497. (b) Kim, E.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192.

10.1021/ol991019d CCC: $18.00

Table 1. Relative Energies between Folded and Unfolded Conformational States (AMBER*, MM2*, MM3*, and MMFF with Macromodel Gas Phase and GB/SA Solvation Model Calculations (Chloroform)). Computed Facing Angle between c and b Rings in Each Folded Optimized Structure (Defined in Figure 1) Is Located under Each Energy Difference

ester	R	exp.	AMBER*		MM2*		MM3*		MMFF	
			gas	solv.	gas	solv.	gas	solv.	gas	solv.
1a		-0.24	-1.60 75°	-0.50 85°	-2.05 5°	-0.77 70°	-2.79 45°	-0.90 80°	-2.68 60°	-0.46 70°
1b		-0.37	-3.29 0°	-0.78 5°	-2.73 15°	-0.95 75°	-2.95 50°	-0.98 55°	-2.93 60°	-0.48 70°
1c		-0.24	-2.93 0°	-0.77 90°	-2.63 50°	-1.53 75°	0.03 0°	-1.12 10°	-4.74 65°	-0.60 70°
1d		-0.65	-4.01 15°	-1.32 15°	-2.61 10°	-0.74 60°	-2.51 5°	-1.29 50°	-2.06 45°	-0.77 80°
1e[a]		-0.65							-1.87 40°	-0.90 80°
1f		-0.65	-2.86 -40°	-0.82 90°	-2.98 -30°	-1.04 -40°	-3.76 15°	-1.49 60°	-3.24 40°	-0.78 70°
1g		-0.37	-0.83	-0.75	-2.35	-0.62	-2.67	-1.13	-2.87	-0.38
1h		-0.82	-1.69	-0.73	-2.14	-0.82	-1.84	-0.95	-2.86	-0.38
1i		0.00	-1.77 85°	-0.68 85°	-2.16 40°	-0.76 45°	-2.32 40°	-0.81 45°	-3.15 60°	-0.37 75°
1j		-0.24	-4.09 90°	-1.56 85°	-2.01 40°	-0.68 45°	-2.91 45°	-0.62 50°	-3.05 60°	-0.58 75°
1k		0.37	-3.14 0°	-1.33 0°	-3.61 0°	-1.63 5°	-2.87 5°	-0.44 5°	-1.93 45°	0.43 50°

a. Force field parameters were not available for the nitro group with MM2*, MM3* and AMBER*.

unfolded conformations, but interactions between the b and c rings only exist in the folded conformation. The relative population of each conformation can be used as a measure of the intramolecular interaction between b and c.

The amounts of the two possible conformers in solution were measured for various substituted systems;[4] the corresponding free energies are listed in the third column of Table 1. R refers to the ester substituent. The X-ray crystallography of the **1e** showed the edge-to-face contact of the b and c rings in the folded conformation. Interestingly, cyclohexyl and *tert*-butyl groups show as much preference for the folded form as substituted aromatic rings. Most aromatic groups show a preference for the folded conformation except for mono- and di-*m*-methyl-substituted phenyl systems **1i** and **1k**.

We carried out force field calculations on these systems using Macromodel[5] with AMBER*,[6] MM2*[7] MM3*,[8] and MMFF.[9] Solvation in chloroform was calculated with the GB/SA model available in the program.[10]

For various substituted torsion balance molecules, the relative energies of folded and unfolded conformations were calculated and are listed in Table 1. In gas-phase calculations,

---

(5) Still, W. C.; *Macromodel, Version 4.5*; Department of Chemistry, Columbia University; New York, 1994. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M. Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, 440.

(6) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S., Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

(7) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

(8) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

(9) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

(10) Still, W. C.; Tempczyk, R. C.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.

all but one case show a preference for the folded conformation. The preference is always overestimated by 1−3 kcal/mol compared to experimental observation. This is due to the favorable intramolecular van der Waals contacts. In the liquid phase, the relative instability of the unfolded conformation can be compensated by the interaction with solvent molecules.

Inclusion of solvation effect provides an impressive improvement of the agreement between experimental and calculated energies. An overestimation of 0.2−0.5 kcal/mol for the stability of the folded conformation compared with experimental results is still observed. Otherwise, the agreement with experimental values is good and reproduces the trends for *para*-substituted aromatic molecules (**1a**−**1f**).

The importance of edge-to-face interaction is brought into question by these results. Table 1 lists the facing angle in the folded conformation, defined in Figure 1, for each optimized structure. With the AMBER* force field, **1a**, **1c**, and **1f** have nearly 90° facing angles corresponding to the edge-to-face interaction. **1b** and **1d** have nearly face-to-face orientations. Other force fields also give optimized structures with face-to-face orientations. Overall, the calculation suggested the small energetic preference of the folded conformation regardless of the relative orientation of two aromatic rings.

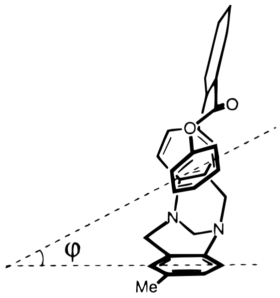


Figure 1. Facing angle definition.

Analysis of the energy components provided further insights. The difference between folded and unfolded conformations in the gas phase mostly comes from the difference between intramolecular van der Waals terms. With GB/SA solvation model calculations, the relative intramolecular interactions are the same as those for gas-phase calculations, but the solvation term favors the unfolded conformation. The preference for the unfolded structure in the solvation term comes from the cavity and solute−solvent van der Waals term, which is a product of the solvent accessible surface area (SA) of solute and a parameter. The solute−solvent polar interaction (GB) term shows no significant differences, which is consistent with the indifference of the preference to the solvent variation in the experiment.

Folded conformations are preferred in the gas phase because of larger intramolecular van der Waals contacts. The preference decreases in solution, because the unfolded conformation has a larger surface area and larger stabilizing interactions with the solvent. The folded conformer has a smaller surface area, regardless of whether it exists in the edge-to-face or the face-to-face conformation.

Wilcox observed no preference with **1i** and the unfolded preference for **1k**. He concluded that the shift toward the unfolded conformation by the *meta*-substituents is due to the loss of a rotational degree of freedom.

A simple MMFF calculation has reproduced the slight preference shift from **1b** to **1i** (0.09kcal/mol) and the preference reversal from **1i** to **1k**. We consider the effect of *meta*-substituents to be steric rather than entropic. We consider that the source of the shift in preference is as follows. The first *m*-methyl group on ring b can have a moderate vdW interaction with ring d in the *unfolded* conformation, and the presence of second *m*-methyl group clearly hinders the stability of the folded conformation through its bulkiness. The much smaller preference shift by *m*-cyano groups supports this hypothesis.

The X-ray crystal structure of **1e** provides clear evidence of the existence of the edge-to-face interaction in the solid state. However, the edge-to-face orientation between two aromatic groups may not always be preferred. The interaction between two groups can be mostly described as a balance between van der Waals contact between them and solute−solvent interactions.

The fact that we are able to reproduce the preference for the folded conformation with *tert*-butyl and cyclohexyl groups is in good agreement with Wilcox's conclusion. It is more likely that the observed preference for folded conformations is due to the dispersion forces rather than a particular electrostatic interactions such as "edge-to-face" aromatic interactions.

Acknowledgment. We are grateful to Professor Craig Wilcox for suggesting this project and to Grigory Vayner for helpful comments. We thank the National Science Foundation and National Institutes of General Medical Sciences, National Institutes of Health, for financial support of this research.

OL991019D