Tetrahedron Letters 51 (2010) 1648–1650

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Relative substituent position on the strength of π–π stacking interactions

Benjamin W. Gung [a,*], Bright U. Emenike [a], Celeste N. Alverez [a], John Rakovan [b], Kristin Kirschbaum [c], Nirbhay Jain [c]

[a] Department of Chemistry and Biochemistry, Miami University, Oxford, OH 45056, United States
[b] Department of Geology, Miami University, Oxford, OH 45056, United States
[c] Department of Chemistry, University of Toledo, Toledo, OH 43606, United States

ARTICLE INFO

Article history:
Received 14 October 2009
Revised 16 December 2009
Accepted 17 December 2009
Available online 24 December 2009

ABSTRACT

It was observed that the relative position of the arene substituents has a profound influence on the strength of π–π stacking in the 9-benzyl-substituted triptycene system. A new series of model compounds (**3a–i**) capable of revealing quantitatively π–π stacking interactions was studied. This series of compounds (**3a–i**) has an *ortho*-substituted methyl group in one of the two interacting arenes and the *syn*/*anti* ratios were determined and compared to a series previously studied compounds (**4a–i**) that have a *para* methyl group on the corresponding arene. A greater than 50% increase in the strength of π–π stacking interactions was observed with the methyl group in the *ortho* position comparing to that in the *para* position. No difference in π–π stacking interactions was observed when the other aromatic ring was a pentafluorobenzoate group.

Noncovalent interactions play an increasingly important role in modern chemical research.[1–3] The concept of π-stacking interactions has been used in a wide ranging field of science including materials science,[4] template-directed synthesis,[5] and enzyme design.[6] Currently there is a strong interest to understand the origins and the mechanism of substituent effects in π–π stacking interactions.[7–9]

It has been reported that a direct interaction between the aromatic ring hydrogens and the substituents themselves may influence the magnitude of arene–arene interaction.[10] Theoretical studies also corroborated this observation using benzene dimers with multiple substituents. The substituent effects were found to be nearly additive in sandwich configurations, which would not be consistent with the traditional model of aromatic substituent effects.[8] More recently, computational studies by Wheeler and Houk directly challenged the conventional concept of substituent effects.[7] Their study suggests that substituents interact directly with another aromatic ring, rather than through the polarization of the arene. According to this study, the traditional concept of π–π interactions tuned by substituents through electron-withdrawing or electron-donating to the aromatic rings is flawed and should be corrected by direct interactions between the substituents and the unsubstituted ring. In this Letter, we report experimental observations which show that the relative position of the arene substituents has a strong influence on π–π stacking strength, thus appears to suggest a direct interaction between a substituent and another aromatic ring.

The 1,9-disubstituted triptycene system has proven to be a valuable tool in our examination of arene–arene interactions, **1** (Fig. 1).[11–13] The rotation of the C(9) benzyl group around the C_{sp3}–C_{sp3} bond gives rise to three rotational minima: one *anti* and two *syn* conformations. In each of these three conformations, the C(9) phenyl ring is fit snugly between the rigid triptycene skeleton aromatic rings, but has no forced contact. The rotation around the C(9)–benzyl carbon bond in **1** is hindered by the triptycene

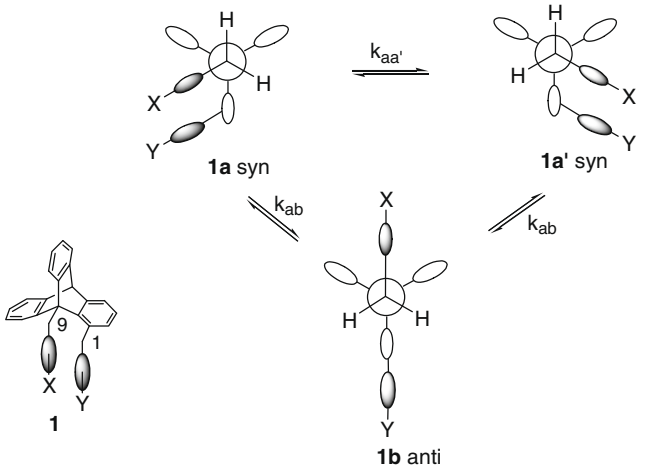


Figure 1. Sketches illustrating the *syn* and *anti* conformational isomers derived from 1,9-di-substituted triptycene derivative, **1** (the sketch is a modified version of the drawing by Oki).[14]

* Corresponding author. Tel.: +1 513 529 2813; fax: +1 513 529 5715.
E-mail address: gungbw@muohio.edu (B.W. Gung).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.095

scaffold. When the rotation becomes sufficiently slow at below rt, the ^{1}H NMR signals for the *syn* and *anti* conformations of compound **1** decoalesce, with the former an *AB* quartet and the latter a singlet (see Supplementary data). The benzyl CH_2 group serves as an effective conformational reporter. A statistical 2:1 *syn*/*anti* ratio is expected when there is no interaction between the C(1) and the C(9) groups. Because the triptycene scaffold provides an otherwise identical environment for the *syn* and *anti* conformations, the *syn*/*anti* ratio represents the degree of preference for the interactions between the C1 and the C9 groups. In this study, we compare the *syn*/*anti* ratios on *ortho*-substituted benzene at the C(9) position (**3**) and the corresponding *para*-substituted model compounds (**4**).

The new series of triptycene compounds (**3a–3i**) were synthesized using the procedures similar to our previously reported methods.[11–13,23] Crystal structures for compounds **3a** and **3e** were obtained, and X-ray structure analysis shows the parallel-displaced stacking conformation (i.e., *syn* conformation) is also preferred in the solid state (Fig. 2). The X-ray structures of model compounds **3a** and **3e** displayed an inter-arene distance of ~3.5 Å and a vertical displacement of ~1.2 Å. This is consistent with our previous studies using the triptycene-derived models, which showed a similar parallel displaced conformation. While the model compounds used to study π stacking interactions such as **4a–4i** did not show clear signals for the *syn* and *anti* isomers until −40 °C, distinct *AB* quartet for compounds **3a–3i** could be observed at −10 °C (Fig. 3). The *ortho* methyl substitution is believed to further raise the rotational barrier around the C–C bond linking the bridgehead C(9) and the benzyl group because a greater steric congestion is encountered when the *ortho* methyl-substituted benzyl group rotates pass the triptycene blades in the rotational transition states. This makes model compound **3** series more convenient conformational reporters in the experimental measurements.

The experimentally observed *syn*/*anti* ratios for compounds **3a–i** and **4a–i** and the corresponding free energies (calculated using the equation: $\Delta G = -RT\ln K_{eq} = -RT\ln(\text{ratio of } 1/2{\cdot}syn/anti)$) are compiled in Table 1. Electron-withdrawing groups increase the *syn*/*anti* ratios for both series. The *ortho*-methyl model compounds **3a–3i** universally favour the *syn* conformation, even with electron-donating groups on the C(1) benzoate group (**3a–c**). This is in contrast to what was observed for model compounds **4a–c**, which prefer the *anti* conformation.[13] In addition, all the compounds in the model **3** series show a greater preference for the stacked (*syn*) conformation except for the pentafluorobenzoate derivative, **3i**, which shows the same *syn*/*anti* ratio as compound **4i**.

For the triptycene model system, the preference for the *syn*/stacked conformation is either due to attractive interactions in the *syn* conformation and/or repulsions in the *anti* conformation.

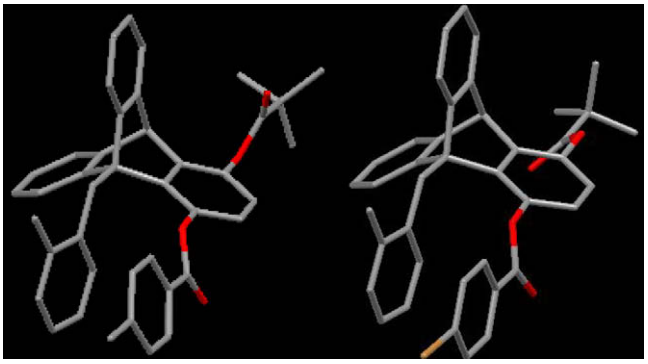


Figure 2. X-ray structures of compounds **3a** and **3e** displayed as stick models. The structure shows a *syn* conformation with a parallel π-stacking arrangement between the C(9) arene and the C(1) benzoate group. The inter-arene distance is ~3.5 Å and the vertical displacement is ~1.2 Å.

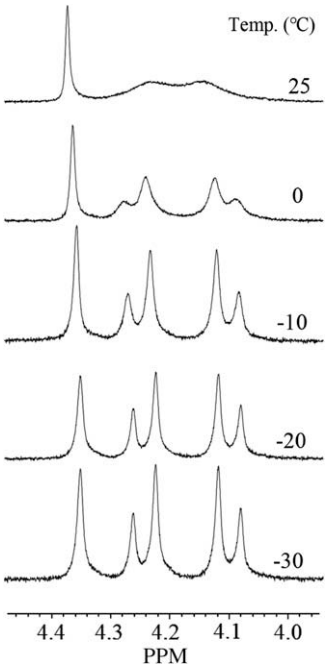
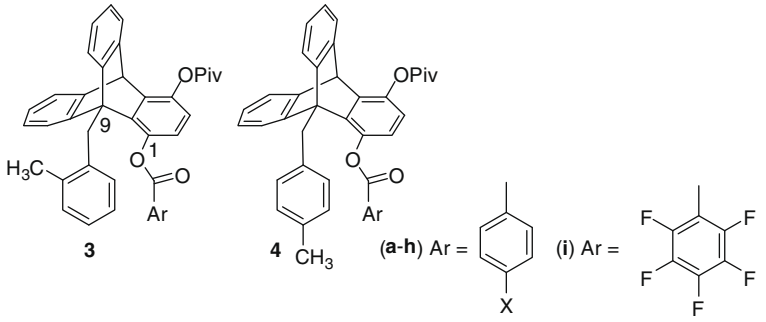


Figure 3. Temperature dependent ^{1}H NMR (300 MHz) signals for the C(9) benzyl protons of model compound **3a**.

When the methyl substituent on the C(9) benzyl group is moved from the *para* position to the *ortho* position, either the attractions increased in the *syn* conformation or the repulsions increased in the *anti* conformation. The fact that model compounds **3i** and **4i** have the same preference for the *syn* conformation seems to support the notion that there is an increase in attractive interactions in the *syn* conformation. Both compounds **3i** and **4i** have the pentafluorobenzoate group at C(1). Because a pentafluorobenzoate group at C(1) sees no difference where the methyl group's position is on the C(9) benzene ring, the difference in π-stacking interactions in the mono-substituted benzoate compounds (**3a–h** and **4a–h**) should be due to the relative positions of the substituents in the *syn* conformation. This conclusion points to the importance of the relative positions of the arene substituents on the strength of π–π stacking interactions. Because there is no apparent steric effect involved, the importance of the relative positions of the arene substituents lends support to the notion of direct interactions between substituents and the other aromatic ring.[7,15]

Other factors to consider include local dipoles of the substituents and dispersion forces involving the substituents and the aromatic ring. Benzene and hexafluorobenzene are known to have opposite, large and permanent quadrupole moments.[16,17] These facts led to the description of aromatic rings as polar groups for studies related to π–π interactions, and cation–π interactions.[18–20] However, when the aromatic ring is disubstituted, local dipoles of the substituents should become more important in the interactions with other aromatic rings. Model compounds **3** series can be considered to have a 1,2-disubstituted aromatic ring at C(9) considering the triptycene scaffold as a substituent. Similarly, model compounds **4** series can be considered to have the corresponding 1,4-disubstituted aromatic ring at C(9). Both series have 1,4-disubstituted benzoates at C(1) to assume a parallel displaced conformation with the C(9) aromatic ring. It could be argued that because both the substituents on the C(9) arene are electron-donating groups, 1,2-disubstitution should lead to a more polarized aromatic ring (**3**) than the more symmetrical 1,4-disubstituted compounds (**4**), and consequently a stronger interaction with the other aromatic ring. This line of analysis would support the traditional theory of substituent effects. However, we

Table 1
Relative position effect of the aromatic ring substituent on ratios of *syn*/*anti* isomers for arene–arene interactions (experiments were performed in $CDCl_3$)



X = Me (**a**), MeO (**b**), H (**c**), F (**d**), Br (**e**), I (**f**), CN (**g**), NO_2 (**h**)

Entry	Ar	*syn*/*anti* ratio (−50 °C)		$\Delta G_{anti\rightarrow syn}$ in $CDCl_3$[a] (kcal/mol)		$\Delta\Delta G$
		3	**4**[b]	**3**	**4**	
1	4-MeC_6H_4	3.4	1.3	−0.24	0.19	0.43
2	4-$MeOC_6H_4$	3.5	1.4	−0.26	0.16	0.42
3	C_6H_5	4.1	1.6	−0.32	0.10	0.42
4	4-FC_6H_4	5.9	2.5	−0.48	−0.10	0.38
5	4-BrC_6H_4	6.6	na	−0.53	na	na
6	4-IC_6H_4	6.2	3.3	−0.50	−0.22	0.28
7	4-NCC_6H_4	10.7	6.4	−0.75	−0.52	0.23
8	4-$NO_2C_6H_4$	13.4	6.7	−0.84	−0.54	0.30
9	F_5C_6[c]	14.4	14.4	−1.0	−1.0	0

[a] Errors are estimated at ±0.05 kcal/mol (from an average of two runs).
[b] Ref. 13.
[c] Determined at −15 °C.

currently favour the hypothesis proposed by Wheeler and Houk, that is, substituents interact directly with the other aromatic ring.[7,15] Therefore, the position of the substituent on the aromatic ring is important with regard to π–π stacking interactions.

In summary, we have demonstrated the importance of the relative positions of the arene substituents on π–π stacking. It is currently not clear whether the increased preference for the *syn* conformation in the series of model compounds **3** is due to a direct interaction of the substituent with the other arene or through the polarization of the aromatic ring. Regardless of the origin of the enhancement in π–stacking interactions, the present findings have broad implications considering the use of substituted aromatic amino acid analogues in the characterization of ligand binding sites.[21,22] Although studies of substituent effects in π–π stacking have been reported, few studies have focused on the relative positions of the substituents. Studies with additional substituents of different electronic properties are currently underway in our laboratories.

Acknowledgements

Financial support from the National Institutes of Health (GM069441) is gratefully acknowledged. B.W.G. thanks the CFR of Miami University for a summer stipend.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.095.

References and notes

1. Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: New York, 1995.
2. Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.
3. Cerny, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2007**, *9*, 5291–5303.
4. McNeil, A. J.; Muller, P.; Whitten, J. E.; Swager, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 12426–12427.
5. Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643–1663.
6. Rothlisberger, D.; Khersonsky, O.; Wollacott, A. M.; Jiang, L.; DeChancie, J.; Betker, J.; Gallaher, J. L.; Althoff, E. A.; Zanghellini, A.; Dym, O.; Albeck, S.; Houk, K. N.; Tawfik, D. S.; Baker, D. *Nature* **2008**, *453*, 190–194.
7. Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10854.
8. Ringer, A. L.; Sinnokrot, M. O.; Lively, R. P.; Sherrill, C. D. *Chem. Eur. J.* **2006**, *12*, 3821–3828.
9. Gung, B. W.; Zou, Y.; Xu, Z. G.; Amicangelo, J. C.; Irwin, D. G.; Ma, S. Q.; Zhou, H. C. *J. Org. Chem.* **2008**, *73*, 689–693.
10. Rashkin, M. J.; Waters, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 1860–1861.
11. Gung, B. W.; Wekesa, F.; Barnes, C. L. *J. Org. Chem.* **2008**, *73*, 1803–1808.
12. Gung, B. W.; Patel, M.; Xue, X. W. *J. Org. Chem.* **2005**, *70*, 10532–10537.
13. Gung, B. W.; Xue, X. W.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 3641–3644.
14. Oki, M. *Acc. Chem. Res.* **1990**, *23*, 351–356.
15. Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 3126.
16. Dennis, G. R.; Ritchie, G. L. D. *J. Phys. Chem.* **1991**, *95*, 656–660.
17. Williams, J. H. *Acc. Chem. Res.* **1993**, *26*, 593–598.
18. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.
19. Muller-Dethlefs, K.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143–167.
20. Mecozzi, S.; West, A. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566–10571.
21. Dougherty, D. A. *Chem. Rev.* **2008**, *108*, 1642–1653.
22. Dougherty, D. A. *J. Org. Chem.* **2008**, *73*, 3667–3673.
23. *A representative benzoylation procedure and selected data for compound* **3a**: To a solution of the triptycene precursor (0.1 mmol) in dry dichloromethane (4 ml) was added pyridine (0.5 ml) at 0 °C under N_2. DMAP (0.01 mmol) and *p*-methyl benzoyl chloride (0.15 mmol) were subsequently added. The reaction mixture was stirred and monitored by TLC till all starting materials have disappeared. The reaction was quenched with 15 ml of water and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic phase was washed with 15 ml of satd $NaHCO_3$ and 20 ml of brine. The solution was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give the desired triptycene model compound (**3a**) as a solid.
A white solid, mp 220–222 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 1.61 (9H, d, J = 13 Hz), 2.12 (3H, s), 2.46 (3H, s), 4.02–4.47 (2H, s, br), 5.59 (1H, s), 6.69–7.45 (15H, m). ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 19.67, 21.76, 27.54, 32.73, 39.49, 48.72, 51.93, 120.08, 121.56, 123.67, 124.73, 125.37, 125.54, 125.58, 125.91, 126.09, 128.58, 129.43, 129.47, 129.97, 130.13, 130.74, 136.23, 136.55, 140.19, 143.11, 144.01, 144.14, 164.74, 176.56. IR (neat): 3065, 3022, 2912, 1749, 1732, 1474. HRMS calcd for $C_{41}H_{36}O_4$ + Na, 615.2511. Found 615.2516.