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#### **Stacking Interactions**

Guest Editor: Pavel Hobza

#### Editorial

<u>Stacking interactions</u> Phys. Chem. Chem. Phys., 2008, **10**, 2581 DOI: <u>10.1039/b805489b</u>

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# Through-space interactions between parallel-offset arenes at the van der Waals distance: 1,8-diarylbiphenylene syntheses, structure and QM computations<sup>†</sup>

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Received 2nd January 2008, Accepted 19th March 2008 First published as an Advance Article on the web 16th April 2008 DOI: 10.1039/b800031j

A model for studying polar– $\pi$  interactions between arenes spaced at van der Waals distances is developed on the basis of *peri*-diarylbiphenylenes. A set of 1,8-diarylbiphenylenes is synthesized comprising two Hammett series, one with reference to mesityl ring interactions and the other with reference to pentafluorophenyl ring interactions. X-Ray crystal structures of several derivatives are determined. Barriers to rotation of the probe aryl ring are derived from dynamic NMR data and show a trend for the mesityl reference series ( $\Delta G^{\neq} vs. \sigma^{\circ}$ ). The model is also used as a test for comparison of modern density functional methods, including B3LYP, M06-2X and BMK functionals; dispersive effects are seen to be an important factor in the proper theoretical treatment of arene interactions.

#### Introduction

Through-space polar $-\pi$  interactions between aromatic rings continue to be invoked as important structural determinants in a variety of natural and synthetic molecules.<sup>1</sup> They have been implicated as influencing the three-dimensional structures of important biomacromolecules such as proteins and nucleic acids.<sup>2</sup> These interactions have also been extensively exploited in the design of new drugs,3 in the formation of supramolecular adducts and new materials<sup>4</sup> and in attempts to predetermine crystal structures.<sup>5</sup> Because dissecting the elementary component effects of systems like drug-receptor complexes is prone to difficulties, much of the basis for claims of polar- $\pi$ involvement comes from parallels drawn from the statistical analysis of protein structures, computational estimates or physical organic model systems. Finding a model system in which the rings were at an optimal distance has been elusive. The 1 and 8 (peri) positions of biphenylene point in parallel directions and sit 3.7 Å apart, which matches well with the conventional 3.6-3.8 Å interplanar spacing observed for co-

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Interacting arenes can adopt a continuum of different relative orientations, which can be crudely classified by three general classes (Fig. 2): parallel-stack (PS), parallel-offset (PO), and edge-to-face (EF).<sup>6</sup> In the PS disposition the surface contact is larger than in the other cases and, accordingly, the interaction between the aromatic systems is at its maximum. On passing to the PO and EF arrangements, the strength of the interaction decreases proportionally to the decreasing contact area, to the point that the importance of the EF interaction has sometimes been questioned.<sup>7</sup>

Several experimental studies on model systems have been devoted to elucidating the nature and the relative importance of the phenomena determining the aryl-aryl interaction.<sup>8</sup> One interpretation of these studies leads to the conclusion that dispersive forces dominate the interaction which is then modulated by simple and induced dipolar effects (the so-called polar– $\pi$  effect).<sup>9</sup> Such a model is further supported by extensive theoretical work predicting the repulsive nature of the PS disposition and the attractive nature of both the PO and EF ones.<sup>10</sup> This combined view of experiments and theory also allows one to understand the nature of a variety of arene–arene interactions in very different systems.<sup>1,2</sup>

Being aware of the fact that polar effects depend critically on the distance between the interacting dipoles, the biphenylene model, in which the arenes are located at a distance



Fig. 1 Geometry of (peri) 1,8-biphenylenes

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† Electronic supplementary information (ESI) available: Coordinates of the primary computed structures and details of the synthesis of 3d and 3e. CCDC reference numbers 678682 & 679270–679272. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b800031j



Fig. 2 Three classes of arene-arene interaction.

approximating the van der Waals (vdW) contact distance, helps to refine our understanding of the polar– $\pi$  contribution to arene–arene interactions. By synthesizing compounds comparable to the *peri*-substituted naphthalene derivatives employed in previous studies<sup>9</sup> and performing related X-ray, NMR and computational investigations, one obtains a broader view of the geometric factors influencing the polar– $\pi$  effect, on which the design of molecules whose functions and properties ostensibly depend on the interactions between aromatic systems can be based.

#### **Results and discussion**

#### peri-Substituted biphenylene as model system

In designing the model system a strong influence came from previous work on 1,8-diaryInaphthalenes of general formula 1 and 2. A PS disposition of the arenes was expected, albeit with a larger aryl-aryl separation at the ipso positions, and an almost parallel as opposed to a splayed conformation. Two series of compounds were targeted, 3 and 4. The "reference" aryl rings were chosen as mesityl and pentafluorophenyl for  $\delta$ - and  $\delta$ + centered rings, respectively. This designation comes from analogy to the quadrupolar nature of mesitylene and hexafluorobenzene. These reference aryl rings bear ortho and ortho' substituents, which additionally support a locked-orthogonal conformation between the reference ring and the biphenyene scaffold. The variable or probe ring is either mono-ortho or -meta substituted to provide the necessary symmetry breaking in the static ground state while providing a dynamic symmetry that renders sites on the reference ring equivalent during rapid flipping of the probe ring. With this model a systematic study of the effect of electronic substituents on the arene interaction using variable temperature (VT) NMR is readily accessible.

#### Synthesis of series 3 and 4

In accordance with this model, 1,8-diarylbiphenylenes **3a–f** and **4a–c** were synthesized as depicted in Scheme 1. The synthesis of both series started from 1,8-dibromobiphenylene, **5**. In series **3**, Suzuki coupling of **5** with mesitylboronic acid produced a common intermediate 1-bromo-8-mesitylbiphenylene **6**, in which the reference mesityl ring was installed in 43% yield. From **6**, a second Suzuki coupling with the respective 4-X-substituted-2-tolyl boronic acid produced **3a** (X = OMe, 74%), **3b** (X = H, 70%), **3c** (X = Cl, 60%), **3d** (X = CN, 50%) and **3e** (X = F, 77%). Demethylation of **3a** with boron tribromide in dichloromethane produced **3f** (X = OH, 93%).

In series **4**, it was necessary to create three independent monocoupled intermediates, **7a–c**, *via* Stille coupling of **5** with the appropriate 4-X-substituted-3-tolyl trimethylstannane. Each of these intermediates was then subjected to standard



Ullmann coupling with pentafluoroiodobenzene to produce 4a (X = OMe), 4b (X = H), and 4c (X = Cl) in paltry overall yields of 6, 13 and 5% respectively.



Scheme 1 (a)  $Pd(PPh_3)_4$ ; (b)  $Pd(PPh_3)_4$ ; (c)  $Pd_2$ (dibenzylidene acetone)<sub>3</sub>; (d) Cu-bronze; (e) BBr<sub>3</sub>.

#### Structural studies

Crystals of 3b-e (X = H, Cl, CN, F) suitable for X-ray crystal analysis<sup>†</sup> were obtained and subjected to diffraction analysis. A pseudo- $C_2$  symmetry axis can be defined by consideration of the canted orientation of both rings. The disorder in the structure of 3e reflects this pseudo symmetry in that the molecules pack such that a crystallographic average  $C_2$  axis is manifested. There is also some concern about the *R* factor for the structure of **3b** (R = 0.16). Taken as a single structure, the quality would be far lower than one wishes, but in the context of a series of derivatives and the various computational studies (see below), these additional structures provide corroborative evidence of a common conformational motif in which the probe ring's ortho-methyl group is proximal and pointing toward the reference ring. A further consideration in favor of retaining these data is that no abnormal geometrical parameters result from the refinement (Table 1).<sup>11</sup>

The structures **3b**–e were analyzed for their relative separation of reference and probe rings by considering the following carbon-to-carbon distances: (a) biphenylene positions 1-to-8; (b) arene ring positions *ipso*-to-*ipso*; (c) arene ring positions *para*-to-*para*. The planar separation of the rings could also be estimated by the orthogonal distance from the *ipso*- and *para*carbons of the reference ring to the mean plane of the probe ring ( $ip_{\perp}$ ) and ( $pr_{\perp}$ ), respectively. The suitability of biphenylene as a scaffold for holding the rings at a relatively unstrained distance was gauged by the 8-1-*ipso*<sub>reference ring</sub> ( $\alpha$ ) and 1-8-*ipso*<sub>probe ring</sub> ( $\beta$ ) angles. Ideally they should be around 90° if no distortion of the bond vectors takes place. An assessment of the preference for PS *vs.* PO orientation comes from the ring

Table 1 Geometry of reference and probe-ring orientations



3b = H3d = CN3e = F3c = ClGeometric parameters Exptl Exptl Exptl Exptl 3.797(5) 3.796(4) a/Á 3.80(1)3.773(6) b/Å3.89(1)3.815(6) 3.824(4)3.812(5)c/A3.84(1)3.776(6) 3.795(4)3.715(5)  $\alpha/^{\circ}$ 90.7(4) 90.3(2) 89.5(1) 90.3(1)  $\beta/c$ 92.3(4) 91.2(3) 91.6(1) 90.3(1) 65.8(3)  $\phi/^{\circ}$ 61.0(9) 62.1(6) 65.2(3) 65.8(3)  $\varphi$ 65.1(9)59.2(7) 64.1(3)0.99(8) 2.4(1)3.0(2)3.7(1)Y 3.498(2) 3.595(6) 3.456(4) 3.544(2) $ip_{\perp}$  $\hat{p}r_{\perp}^{+a'}/\text{\AA}$ 3.607(7) 3.481(4)3.483(3) 3.490(3)

<sup>*a*</sup>  $ip_{\perp}$  and  $pr_{\perp}$  = orthogonal distance from *ipso*- or *para*-carbon of reference ring to mean plane of probe ring respectively; *R* factor for **3b** is large (0.16); structure for **3e** is 2-fold disordered.

torsion angles ( $\phi$ ) and ( $\phi$ ) in combination with the out-ofplane twisting described by the dihedral *para*<sub>reference ring</sub>-1-8-*para*<sub>probe ring</sub> angle ( $\chi$ ). One could argue that there should be a substantial conjugation component between the individual arene rings and the biphenylene scaffold. This effect has been considered and found to be relatively small compared to the steric effects.

All four structures have relatively similar geometries. Distances *a*, *b* and *c* cluster around an average value of 3.80  $\pm$  0.04 Å, with  $ip_{\perp}$  and  $pr_{\perp}$  distances around 3.52  $\pm$  0.06 Å. Overall, the rings appear close to parallel. The average of angles  $\alpha$  and  $\beta$  fall very close to the ideal 90° (avg. = 90.78  $\pm$  0.90°), indicating little strain. The ring torsions  $\phi$  and  $\varphi$  average 63.5  $\pm$  2.4°, favoring a PO over PS geometry, and the average  $\chi$  value close to zero (avg. = 2.5  $\pm$  1.1°) supports little out-of-plane twisting of the biphenylene. Overall, it seems clear that this model adopts a strain-free PO aryl–aryl orientation in the ground state.

#### **Computational studies**

The conformational analyses of 3a-c and 4a-c described in this study, including structural and orbital arrangements as well as property calculations, were carried out using the Gaussian98<sup>12</sup> and GAMESS<sup>13</sup> software packages. Structural computations of all compounds were performed using density functional methods (DFT) as well as MP2.14 The B3LYP method employed Becke's 3 parameter functional<sup>15</sup> with nonlocal correlation provided by the Lee-Yang-Parr expression<sup>16,17</sup> with local and nonlocal terms, the new M06-2X functional<sup>18</sup> of Zhao and Truhlar, and the BMK functional of Boese and Martin.<sup>19</sup> Dunning's correlation-consistent basis set, cc-pVDZ, a [3s2p1d] contraction of a (9s4p1d) primitive set, was employed.<sup>20</sup> Full geometry optimizations were performed and uniquely characterized via second-derivative (Hessian) analysis to determine the number of imaginary frequencies (0 = minima; 1 = transition state) and zero-point contributions. Molecular-orbital and electrostatic-contour plots, used as an aid in the analysis of results, were generated and depicted using the programs 3D-PLTORB<sup>21</sup> and QMView.22

Polarizability and vdW effects constitute a large portion of just about all intermolecular interactions. The PS and PO interaction between arenes certainly follows this rule. Recently, several new computational methods have been developed to account for such vdW effects within DFT computations. Systems like **3a–c** and **4a–c** provide an excellent testbed for these new computational methods. Specifically, the M06-2X and BMK functionals were compared against the classical B3LYP functional.<sup>‡</sup>

Two ground-state conformations were found, corresponding to a slight canting of the aryl groups such that the methyl of the probe ring is either *endo* (pointing over the reference ring) or *exo* (pointing outside the reference ring). In both series all derivatives are predicted to adopt the *endo* conformation with a preference of between 2 to 5 kJ mol<sup>-1</sup>. This prediction

 $<sup>\</sup>ddagger$  In light of the results found here, a more complete analysis of the theoretical methods for the treatment of  $\pi$  systems by the various DFT methods could be warranted as part of a follow-on project.

is consistent with the crystallographic forms found in studies of the **3** series. Thus, subsequent comparisons use the *endo* isomer.

Whereas the general geometric predictions of bond lengths and angles are similar for all three methods, an analysis of the long-range parameters that describe the inter-arene interactions reveal a distinctly better performance by BMK for predicting the geometry in series **3**. Ten geometric parameters were used to describe the nature of the inter-arene interaction in the X-ray crystallographic structures† (*cf.* Table 1). Each of these was also derived from the **3a–c** structures computed with the M06-2X, BMK and B3LYP functionals. For the critical interplanar stacking distance ( $ip_{\perp}$ ) predicted values increase from 3.3 to 3.6 to 4.0 Å for M06-2X, BMK and B3LYP respectively—only BMK approaches the experimentally observed 3.6 Å (Fig. 3).

With regard to the angle  $(\alpha, \beta)$  and torsion  $(\phi, \varphi, \chi)$  parameters, the comparison between experiment and DFT method again clearly favors BMK. Deviation from the experimental values is largest for B3LYP, followed by M06-2X, and then BMK which provides the best prediction. From the nature of the distortion, it appears that M06-2X overestimates the attraction between the arenes and ends up with a tighter PO geometry. In contrast, B3LYP underestimates the attraction between the arenes, likely because of its known inability to handle vdW attractions. The result is PO geometrical predictions in which the arenes are splayed apart and the biphenylene scaffold is substantially distorted. Following this analysis we continue our discussion of geometry using the BMK predicted values (Fig. 4).

Looking at the interplanar distances  $ip_{\perp}$  and  $pr_{\perp}$ , BMK computations predict an average value of  $3.51 \pm 0.05$  Å for the **3** series, which is spot on with that found crystallographically. Across the series **3a**, **3b** and **3c**, the interplanar distances  $ip_{\perp}$  ( $pr_{\perp}$ ) are relatively constant, 3.52 (3.50), 3.50 (3.64) and 3.46 (3.41) respectively. A minor trend toward shorter distances is seen for  $ip_{\perp}$  consistent with a stronger interaction between the



Fig. 3 Comparison of crystallographic (red) inter-arene distances in Å with M06-2X (blue), BMK (yellow) and B3LYP (green) DFT predictions.



**Fig. 4** Deviation of M06-2X (blue), BMK (yellow) and B3LYP (green) DFT predictions from crystallographically measured angles  $(\alpha, \beta)$  and torsions  $(\phi, \phi, \chi)$ .

rings as a function of greater donor strength; however, this trend is extremely small and it would be dangerous to overinterpret it.

The general computed geometry of the **3** series nicely agrees with that found crystallographically. Overall, the rings appear close to parallel. The average of angles  $\alpha$  and  $\beta$  fall very close to the ideal 90° (avg. = 90.42 ± 0.63°), slightly smaller than that observed crystallographically (avg. = 90.78 ± 0.90°). The ring torsions  $\phi$  and  $\phi$  average 62.9 ± 2.1°, favoring a PO over PS geometry and the average  $\chi$  value close to zero (avg. 3.1 ± 2.2°). On the whole, the BMK functional seems to do an excellent job in reproducing the crystallographic geometry.

A similar analysis on the 4 series predicts closer interplanar contacts (avg.  $ip_{\perp}$  and  $pr_{\perp} = 3.34 \pm 0.11$  Å). No general trend in the average interplanar distances as a function of structure is present, the  $pr_{\perp}$  values increase from 3.34 to 3.42 to 3.49 Å for **4a**, **4b** and **4c** respectively, whereas the  $ip_{\perp}$  values decrease from 3.37 to 3.23 to 3.19 Å, indicative of a simple tilting of the ring orientation about a common average interplane separation. One might have expected opposing trends for the **3** and **4** series where the reference rings have opposite core polarity ( $\delta + vs$ ,  $\delta -$ ); however, the effects here are extremely small, and vdW and polarizability effects could easily swamp out polar– $\pi$  effects.

A further caveat on inferring unique supramolecular  $\pi$  effects from the 4 series comes from the analysis of its other average structural features. While the rings still seem to be more or less parallel and  $\alpha$  and  $\beta$  angles sit close to the ideal 90° (avg. = 89.30 ± 0.57°), the ring torsions  $\phi$  and  $\phi$  average 50.1 ± 2.0° and the  $\chi$  value extends to greater than 10° (avg. 12.4 ± 0.6°) indicating stronger conjugation interactions between the aryl rings and the biphenylene scaffold as well as stronger out-of-plane distortions due to steric repulsion between the probe and reference rings. In the absence of any crystallographic data for the 4 series, the BMK predictions are interpreted here at face value.

#### Dynamic VT NMR studies

Having established crystallographically and computationally that the PO conformation is preferred in the series **3** and **4**, one can probe the through-space polar– $\pi$  interaction by studying the barrier to rotation of the probe ring as a function of *para* substitution ( $\sigma^{\circ}$ ).<sup>23</sup> For series **3** with a  $\delta$ – reference ring one should expect lower barriers for electron donating groups (X = EDG), and higher barriers for electron withdrawing groups (X = EWG). In contrast, for series **4** a similar substitution should lead to the opposite effect on the barrier. The absolute value of the slope of the plot gauges the strength of the interaction, and the sign of the slope indicates the nature of the reference ring ( $\delta$ + *vs*.  $\delta$ –). In previous studies of series **1** and **2**, the observed slopes were  $15 \pm 2$  kJ mol<sup>-1</sup>  $\sigma^{\circ}$  (**1** R = H);  $5 \pm 2$  kJ mol<sup>-1</sup>  $\sigma^{\circ}$  (**1** R = Me) and  $-4 \pm 2$  kJ mol<sup>-1</sup>  $\sigma^{\circ}$  (**2**) respectively.<sup>9</sup>

<sup>1</sup>H-NMR spectra of **3a–f** in CDCl<sub>2</sub>F showed a single signal for the *ortho* methyls of the mesityl ring at room temperature. This observation is consistent with rapid rotation around the biphenylene–aryl bond on the NMR timescale. Upon cooling the samples, however, the signals split into well-separated singlets ( $\Delta\delta$  in Hz = 77, 123, 87, 160, 145 and 103 for **3a–f** respectively), thus showing restricted rotation. By line-shape analysis the  $\Delta G^{\neq}$  in kJ mol<sup>-1</sup> for the rotation around the bond connecting the biphenylene scaffold to the 2-tolyl ring was determined to be 39.3 (198 K), 40.6 (208 K), 42.2 (213 K), 42.6 (220 K), 44.2 (227 K) and 39.9 (203 K) for **3a–f** respectively.

A plot of  $\Delta G^{\neq} vs$ . the  $\sigma^{\circ}$  values for the X substituents showed a simple correlation between the variation of the barrier and the EDG or EWG nature of the substituent (Fig. 5). The observed trend is consistent with the polar- $\pi$ interpretation. In this context the through-space interaction between PO arenes of similar polarity is electrostatically repulsive. Accordingly, when the reference ring is  $\delta$ - and the probe ring is made more electron-rich by the presence of an



**Fig. 5** Free energies of activation in kJ mol<sup>-1</sup> for **3a–f** and **4a–c** plotted against  $\sigma^{\circ,23}$  Triangles represent **3a–f**; diamonds represent **4a–c**. Red is derived from BMK computations; blue is derived from VT NMR experiments. (*x*-Axis errors come from Taft's estimate that  $\sigma^{\circ}$  values are transferable  $\pm 0.03 \sigma$  units;<sup>23</sup> *y*-axis errors come primarily from errors in  $T_{\text{coalescence-}}$ )

EDG substituent (as in **3a**) the ground state is destabilized (higher in energy) and the barrier is lower. On the contrary, introduction of an EWG substituent (as in **3c**) leads to a less destabilized ground state (lower in energy) and to a higher barrier. The slope ( $\rho$ ) for the plot of  $\Delta G^{\neq} vs$ . the  $\sigma^{\circ}$  for series **3** (*ca.* 6.2  $\pm$  2 kJ mol<sup>-1</sup>  $\sigma^{\circ-1}$ ) is smaller than that observed for series **1** when R = H and about the same as when R = Me.<sup>9</sup>

One might be concerned as to what extent these variances come from changes in the inter-ring interactions vs. simple conjugation as in substituted biphenyls. The variance due to conjugation effects in the barrier to biphenyl rotations is, however, much smaller than seen here and should bend both ends of the series to lower barriers due to stabilization of the transition state. This effect is discussed in more detail in ref. 9*a*.

As in the <sup>1</sup>H spectra of series **3a–f**, <sup>19</sup>F-NMR spectra of **4a–c** in CDCl<sub>2</sub>F showed single signals for the *meta*-fluorine atoms at room temperature, consistently with rapid rotation around the biphenylene–aryl bond on the NMR timescale. Upon cooling the samples, the signals split into separated singlets ( $\Delta \delta = 0.51, 0.20$  and 0.66 ppm for **4a**, **4b** and **4c** respectively), thus showing restricted rotation. By line-shape analysis the  $\Delta G^{\neq}$  values for the rotation around the bond connecting the biphenylene scaffold to the probe ring were determined to be 31.3 (167 K), 30.6 (157 K) and 30.9 kJ mol<sup>-1</sup> (166.5 K) for **4a**, **4b** and **4c** respectively. Thus, the coalescence temperatures and the rotational barriers were considerably lower for **4a–c** than for **3a–f**. More importantly, the overall variation was extremely small (0.7 kJ mol<sup>-1</sup>) and the trend was not in full agreement with the polar– $\pi$  interpretation of the interaction.

As already observed for compounds of series 2, the inverted polarity of the perfluorinated ring should lead to a more stabilized ground state (higher barrier) when the probe ring is made more electron-rich by the introduction of an EDG substituent as the MeO group in 4a; by the same token, the barrier should decrease on passing to the H-substituted compound 4b and further decrease in the case of the Cl-substituted adduct 4c; clearly this is not the case, the barrier for 4b being lower than that of 4a and 4c as assessed by VT-NMR experiments. In contrast, the barrier for 4b is predicted to be higher than that of 4a and 4c when the BMK DFT data are considered. Overall it is safest to say that all these barriers lie within experimental error of one another and no simple trend can be identified or rationalized.

A fundamental difference between series 2 and 4 is the distance between the aryl groups and their specific geometry. In series 2 the aryl groups were bound to the *peri* positions of naphthalene and the *ipso* positions were much closer to each other (*ca.* 2.9 Å) than the *para* positions (>4.0 Å). The interaction was intimate and specific at the *ipso* positions, with a distinctly splayed orientation of the rings. In series 4, the aryl groups are calculated to be more uniformly parallel (see geometry discussion above). Despite the parallel relationship between the aryl groups it was noted above that the aryl-to-biphenylene torsion angle is significantly smaller than in other systems studied and a substantial out-of-plane twisting of the *peri* positions is predicted to occur. These more distorted geometries point to the possibility that factors other than arene–arene interactions are at play.



**Fig. 6** Comparison of barrier energies in kJ mol<sup>-1</sup> measured by VT-NMR (red) with M06-2X (blue), BMK (yellow) and B3LYP (green) DFT predictions.

Among these, one factor that may play a role in these systems derives from the special character of aromatic fluorides. Although the polarity of the carbon(sp<sup>2</sup>)-fluorine bond is  $\delta$  + on carbon, a substantial  $\alpha$ -effect on the  $\pi$  electrons keeps the ionization potential in polyfluoroaromatics relatively constant compared to their parent hydrocarbons. Additionally, although many discussions consider the "quadrupolar" moment of the aryl rings, at such short distances interactions among the individual point charges determine the actual interaction energy. The *para* substituent on the probe ring must play an influential role such that chlorine–fluorine (**4c**) and oxygen–fluorine (**4a**) through-space interactions could complicate the analysis.

To test that the BMK function was the best choice for predicting energies as well as geometries, the barriers for **3a–c** were determined using the M06-2X, BMK and B3LYP functionals. The extreme overestimation of the barriers by M06-2X is striking, in line with the suppositions made by inspection of the geometries that the inter-arene attractions were overestimated. Although B3LYP predictions were more reasonable than M06-2X, only BMK-computed data fell within 1 kJ mol<sup>-1</sup> for the three systems (**3a–c**) studied by all three methods (Fig. 6). Over the full series **3a–f**, BMK-computed data displayed a root mean deviation within 1 kJ mol<sup>-1</sup> between predicted and experimental values; the largest deviations (1.5 kJ mol<sup>-1</sup>) were found for **3e** and **3f**.

#### Conclusions

Series **3a–f** and **4a–c** provide a model system for the systematic investigation of the polar– $\pi$  interaction between arenes in a PO geometry and at vdW distance between the rings. The sensitivity to substituents is reduced in these *peri*-substituted biphenylene-based models compared to the previously studied naphthalene systems, a major difference being the proximity and orientation of the rings. X-Ray crystallographic data<sup>†</sup> demonstrate that members of the **3** series adopt the structures expected from the model design and that barriers for **3a–f** follow the expected trend, albeit with a very slight variation in the barriers. Series **3a–f** and **4a–c** further serve as excellent test systems for computational methods, specifically for determining the geometry and energetics of **3a–f**. DFT functionals M06-2X, BMK and B3LYP were all implemented at the basis set cc-pVDZ. The BMK functional was found to provide superior results for predicting geometry and barriers to rotation when compared to experiment. Overall, the substituentmodified polar– $\pi$  effect is seen to be rather weak for rings not in intimate contact. The observation and modeling of a preferred PO geometry still supports the idea that polar– $\pi$ effects destabilize the PS geometry. Complications in the interaction of perfluoroarene-containing derivatives indicate that in this case secondary effects play a stronger role than previously considered. In all such systems the vdW dispersive and other polarizability effects must be considered.

#### Experimental

**General.** <sup>1</sup>H-NMR spectra were recorded at 300 or 500 MHz in CDCl<sub>3</sub>, and were referenced to tetramethylsilane (TMS) at 0.00 ppm; peak assignments were based on direct and longrange C–H correlations as well as on two-dimensional experiments. <sup>13</sup>C-NMR spectra were recorded at 75 or 125 MHz and were referenced to 77.0 ppm in CDCl<sub>3</sub>. <sup>19</sup>F-NMR spectra were recorded at 470 MHz in CDCl<sub>2</sub>F as solvent and were referenced to hexafluorobenzene at –163.00 ppm. Commercially available reagents were used as purchased; solvents were dried following standard purification procedures. Non-commercial boronic acids and trimethylstannane derivatives were prepared according to standard described procedures.

1-Bromo-8-(2,4,6-trimethylphenyl)biphenylene (6). To a degassed 9:1 DME-water solution (20 mL) kept under argon, mesitylboronic acid (2.46 g, 15 mmol), 1,8-dibromobiphenylene (3.10 g, 10 mmol),<sup>22,24</sup> barium hydroxide monohydrate (2.84 g, 15 mmol) and tetrakis(triphenylphosphine)palladium (0.347 g, 0.3 mmol) were added and the mixture was refluxed for 18 h. Water (10 mL) was then added to the cooled mixture and this was extracted three times with diethylether  $(3 \times 20)$ mL). The combined organic phases were washed with water, then with brine, and dried over magnesium sulfate. The solvent was removed under vacuum and the crude product was purified by flash-column chromatography using hexane as eluant. The product was a pale-yellow, very thick oil (1.5 g, 43%). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 6.90 (2H, s), 6.87–6.58 (6H, m), 2.31 (3H, s), 2.15 (6H, s); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): *δ* 152.9, 151.4, 149.7, 147.8, 136.9, 136.4, 134.6, 131.9, 131.8, 131.2, 129.7, 129.1, 127.7, 116.3, 115.7, 110.1, 21.0, 20.6; HRMS (EI+) m/z calcd for (M+) C<sub>21</sub>H<sub>17</sub>Br: 348.0514 and 350.0493; found: 348.0525 and 350.0492.

**1-Mesityl-8-(4-methoxy-2-methylphenyl)biphenylene** (3a). This product was prepared by the coupling procedure described above from **6** (0.349 g, 1 mmol) and 4-methoxy-2-methylphenylboronic acid (0.250 g, 1.5 mmol). Purification involved flash chromatography with hexane as the eluant. The product was a yellow solid (74% yield), mp 184–186 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.80–6.64 (5H, m), 6.59 (1H, d, J = 8.5 Hz), 6.51 (1H, d. J = 8.5 Hz), 6.49 (2H, s), 6.31 (1H, dd, J = 8.5, 2.5 Hz), 6.28 (1H, d, J = 2.5 Hz), 3.74 (3H, s), 2.20 (3H, s), 1.93 (3H, s), 1.90 (6H, s); <sup>13</sup>C-NMR (125 MHz,

 $\begin{array}{l} {\rm CDCl}_3)\,\delta\,158.7,\,151.1,\,151.0,\,150.1,\,136.5,\,136.3,\,135.3,\,134.3,\\ 132.2,\,131.1,\,130.8,\,130.4,\,130.0,\,129.1,\,128.2,\,128.1,\,127.6,\\ 115.6,\,115.5,\,115.4,\,114.6,\,110.0,\,54.8,\,20.7,\,20.3,\,20.0;\,{\rm HRMS}\\ {\rm (EI+)}\,\,m/z\,\,{\rm calcd}\,\,\,{\rm for}\,\,\,({\rm M+})\,\,{\rm C}_{29}{\rm H}_{26}{\rm O};\,\,390.1984;\,\,{\rm found};\\ 390.1973.\end{array}$ 

**1-MesityI-8-(2-methylphenyl)biphenylene (3b).** This product was prepared by the coupling procedure described above from **6** (0.349 g, 1 mmol) and 2-methylphenylboronic acid (0.205 g, 1.5 mmol). Purification involved flash chromatography with hexane as the eluant. The product was a yellow solid (yield 70%), mp 92–95 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.68–6.44 (12H, m), 2.15 (3H, s), 1.90 (3H, s), 1.85 (6H, s); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  151.1, 151.0, 150.1, 149.8, 137.4, 136.4, 135.0, 134.9, 134.1, 132.4. 131.3, 130.8, 130.2, 129.1, 128.2, 128.0, 127.7, 126.4, 124.9, 115.7, 115.6, 115.5, 20.8, 20.3, 19.8; HRMS (EI + ) *m/z* calcd for (M + ) C<sub>28</sub>H<sub>24</sub>: 360.1878; found: 360.1875.

**1-Mesityl-8-(4-chloro-2-methylphenyl)biphenylene (3c).** This product was prepared by the coupling procedure described above from **6** (0.349 g, 1 mmol) and 4-chloro-2-methylphenylboronic acid (0.256 g, 1.5mmol). Purification involved flash chromatography with hexane as the eluant. The product was a pale-yellow solid (yield 60%), mp 154–155 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.81–6.51 (11H, m), 2.28 (3H, s), 1.92 (3H, s), 1.88 (6H, s); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  151.1, 151.0, 149.9, 149.7, 137.3, 136.9, 135.9, 135.2, 134.1, 132.7, 131.3, 131.1, 130.9, 129.8, 129.3, 128.9, 128.4, 128.3, 127.7, 124.8, 115.9, 115.7, 21.0, 20.4, 19.9; HRMS (EI+) *m/z* calcd for (M+) C<sub>28</sub>H<sub>23</sub>Cl: 394.1488; found: 394.1498.

1-Mesityl-8-(4-nitrilo-2-methylphenyl)biphenylene (3d). This product was developed starting from 3c (0.130 g, 0.329 mmol) and CuCN (0.295, 0.329 mmol) dissolved in HMPA, then the mixture is heated to 225 °C under inert atmosphere for 2.5 h. It is then cooled and a solution of NaCN is added. The product extracted from the mixture was washed successively with H<sub>2</sub>O, aqueous HCl, NaHCO<sub>3</sub>, aqueous NaCl and H<sub>2</sub>O, and was then dried and concentrated. The purification involves flash chromatography with a mixture of hexane and dichloromethane (7:3), the yellow solid obtained was crystallized in DME-ethyl acetate (1:1). The product was a yellow solid (yield 50%), mp 192–194 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ 7.08–6.44 (m, 12H); 2.15 (s, 3H); 2.00 (s, 3H); 1.85 (s, 6H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): δ 151.22, 150.95, 149.85, 149.21, 142.38, 137.36, 136.46, 135.07, 134.05, 131.39, 130.93, 130.22, 128.89, 128.78, 128.69, 128.54, 128.49, 128.69, 127.69, 119.15, 116.39, 115.98, 110.32. 21.00, 20.35, 19.79 ppm. Elem. anal.: found C, 88.73; H, 6.01; F, 4.90; C<sub>28</sub>H<sub>23</sub>F requires C, 88.86; H, 6.13; F 5.02.

**1-Mesityl-8-(4-fluoro-2-methylphenyl)biphenylene (3e).** This product was prepared by the coupling procedure described previously from **6** (0.349 g, 1 mmol) and 4-fluoro-2-methylphenylboronic acid (0.231 g, 1.5 mmol). Purification involved flash chromatography with hexane as the eluant. The product was a yellow solid (yield 77%), mp 92–94 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  6.81–6.42 (m, 12H); 2.17 (s, 3H); 1.92 (s, 3H); 1.89 (s, 6H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  168.85, 161.06,

160.85, 152.91, 152.18, 147.16, 140.88, 140.24, 131.84, 131.30, 129.88, 129.38, 129.31, 125.86, 119.65, 115.10, 114.58, 54.76, 22.94, 21.26 ppm. Elem. anal.: found C, 90.23; H, 5.88; N, 3.51;  $C_{29}H_{23}N$  requires C, 90.35; H, 6.01; N 3.63.

**1-Mesityl-8-(4-hydroxy-2-methylphenyl)biphenylene** (3f). This compound was obtained as a yellow solid by demethylation of **3a** with boron tribromide in dichloromethane using standard literature procedures.<sup>25</sup> The pure product was isolated by column chromatography (93%), mp 141–144 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.80–6.77 (2H, m), 6.66–6.51 (7H, m), 6.23–6.20 (2H, m), 4.36 (1H, s), 2.25 (3H, s), 1.90 (9H, br s); <sup>13</sup>C-NMR (125 mHz, CDCl<sub>3</sub>)  $\delta$  155.59, 151.25, 151.19, 150.20, 136.79, 136.76, 153.39, 134.45, 132.22, 131.30, 130.92, 130.55, 130.38, 129.46, 128.32, 128.22, 127.76, 116.39, 115.88, 115.67, 115.56, 111.75, 20.92, 20.36, 19.95; HRMS (EI +) *m/z* calc. for (M +) C<sub>28</sub>H<sub>24</sub>O: 376.1827 found: 376.1813.

1-Bromo-8-(4-methoxy-3-methylphenyl)biphenylene (7a). A stream of Ar was bubbled for 15 min through a solution of 1,8-dibromobiphenylene (0.136 g, 0.44 mmol) and 4-methoxy-3-methylphenyl trimethylstannane (0.151 g, 0.53 mmol) in dry DMF (10 mL). To this mixture, Pd<sub>2</sub>(dibenzylidene acetone)<sub>3</sub> (0.045 g, 0.088 mmol) and triphenylarsine (0.108 g, 0.352 mmol) were added in this order. The mixture was then refluxed for 20 h and then cooled at RT. Water (20 mL) was then added and the mixture was extracted with diethylether ( $2 \times 10$  mL). The combined organic phases were washed with water (10 mL), dried over sodium sulfate and concentrated under vacuum. The resulting residue was purified by flash chromatography (column diameter: 1 cm; column height: 30 cm) with light petroleum as eluant to remove the unreacted 1,8-dibromobiphenylene, then 1-bromobiphenylene and finally triphenylarsine. The eluant was then changed to a 99:1 light petroleum-diethyl ether mixture. With this eluant a mixture of three products was first obtained followed by a final fraction containing the diaryl-substituted biphenylene. The last fraction was discarded and the mixture of three products contained in the previous fraction was purified again by flash chromatography (column diameter: 1 cm; column height: 30 cm) with a 9:1 light petroleum-DCM mixture as eluant to afford the product (0.062 g, 40%) as a colorless solid, mp 96–98 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40–7.32 (m, 2H), 6.91-6.78 (m, 4H), 6.70-6.50 (m, 3H), 3.89 (s, 3H), 2.28 (s, 3H).<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 157.7, 152.9, 150.7, 147.7, 146.2, 133.6, 132.6, 131.8, 130.2, 130.1, 129.5, 129.3, 127.2, 125.9, 115.6, 115.3, 110.6, 109.7, 55.4, 16.2. Elem. anal.: found C, 68.11; H, 4.55; C<sub>20</sub>H<sub>15</sub>BrO requires: C, 68.39; H, 4.30.

**1-Bromo-8-(3-methylphenyl)biphenylene (7b).** This product was prepared as described above from 1,8-dibromobiphenylene (0.155 g, 0.5 mmol) and 3-methylphenyl trimethylstannane (0.153 g, 0.6 mmol). Purification involved a first flash chromatography (column diameter: 1 cm; column height: 30 cm) with light petroleum as eluant to afford a mixture of 1-bromobiphenylene, 1,8-dibromobiphenylene and the product. This mixture was then chromatographed again with the same eluant (column diameter: 1 cm; column height: 30 cm) to afford the pure product which was isolated as a colorless solid in 31% yield, mp 100–103 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ 

7.34–7.30 (m, 3H), 7.21–7.16 (m, 1H), 6.91–6.89 (m, 2H), 6.84–6.79 (m, 1H), 6.70–6.59 (m, 3H), 2,43 (s, 3H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  152.9, 150.9, 149.7, 146.2, 137.4, 133.8, 132.6, 130.2, 130.1, 129.6, 129.3, 128.6, 127.9, 125.7, 116.1, 115.4, 110.7, 21.5. Elem. anal.: found C, 70.97; H, 4.36; C<sub>19</sub>H<sub>13</sub>Br requires: C, 71.04; H, 4.08.

1-Bromo-8-(3-methyl-4-chlorophenyl)biphenylene (7c). This product was prepared as described above from 1,8-dibromobiphenylene (0.155 g, 0.5 mmol) and 4-chloro-3-methylphenyl trimethylstannane (0.173 g, 0.6 mmol). Purification involved a first flash chromatography (column diameter: 1 cm; column height: 30 cm) with light petroleum as eluant to afford a mixture of 1-bromobiphenylene, 1,8-dibromobiphenylene and the product. This mixture was then chromatographed again with the same eluant (column diameter: 1 cm; column height: 30 cm) to afford the pure product which was isolated as a colorless solid in 26% yield, mp 99-101 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.40 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.94–6.79 (m, 3H), 6.67–6.62 (m, 3H), 2,45 (s, 3H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 152.8, 150.6, 149.7, 146.3, 136.0, 135.4, 134.1, 132.7, 132.5, 131.9, 129.8, 129.7, 129.5, 128.7, 127.3, 116.3, 115.5, 110.5, 20.0. Elem. anal.: found C, 63.99; H, 3.56; C<sub>19</sub>H<sub>12</sub>BrCl requires: C, 64.16; H, 3.40.

1-Pentafluorophenyl-8-(4-methoxy-3-methylphenyl)biphenylene (4a). A mixture of 7a (0.051 g, 0.146 mmol), pentafluoroiodobenzene (0.133 mL, 1.03 mmol) and copper-bronze (0.093 g, 1.46 mmol) was heated at 200 °C for 44 h under stirring in a stoppered thick-walled vial. The cooled mixture was extracted with hot chloroform  $(2 \times 5 \text{ mL})$  and filtered to remove the insoluble materials. The filtrate was concentrated under vacuum and the resulting residue was purified by flash chromatography (column diameter: 1 cm; column height: 25 cm) with a light petroleum-DCM 9:1 mixture as eluant. The second eluted fraction ( $R_{\rm f} = 0.4$ ) contained the product which was isolated as a pale-yellow solid in 15% yield (10.3 mg), mp 180–182 °C. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ 6.90–6.86 (m, 2H), 6.83–6.79 (m, 3H), 6.75 (d, J = 7.0 Hz, 1H), 6.72–6.69 (m, 2H), 6.53 (d, J = 8.2 Hz, 1H), 3.84 (s, 3H), 2.07 (s, 3H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 157.8, 152.5, 151.5, 148.0, 146.0 and 142.6 (C-F ortho), 142.6 and 139.2 (C-F meta), 139.2 and 135.9 (C-F para), 133.5, 130.4, 129.6, 129.3, 128.3, 126.1, 125.3, 117.3, 116.0, 115.9, 113.3, 108.7, 55.2, 15.9. <sup>19</sup>F-NMR (476 MHz, CDCl<sub>2</sub>F):  $\delta$  –143.35, -158.15, -164.78. Elem. anal.: found C, 71.01; H, 3.59; C<sub>26</sub>H<sub>15</sub>F<sub>5</sub>O requires: C, 71.24; H, 3.45.

**1-Pentafluorophenyl-8-(3-methylphenyl)biphenylene** (4b). This compound was prepared by the Ullmann procedure described above starting from of **7b** (0.055 g, 0.171 mmol) and pentafluoroiodobenzene (0.156 mL, 1.21 mmol). The flash-chromatographic purification was carried out using pentane as the eluant (column diameter: 1 cm; column height: 25 cm). The product had  $R_f$  0.45. It was isolated in 42% yield as a white solid, mp 195–97 °C. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.05 (d, J = 9.0 Hz, 1 H), 6.97 (t, J = 9.0 Hz, 1 H), 6.92–6.85 (m, 3H), 6.83–6.80 (m, 2H), 6.78–6.71 (m, 3H), 2.21 (s, 3H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  151.9, 151.5, 150.9, 147.4, 144.6 and 142.6 (C–F *ortho*), 141.6 and 139.6 (C–F *meta*),

138.4, 138.2 and 136.2 (C–F *para*), 137.6, 133.7, 129.6, 129.4, 129.3, 128.5, 127.8, 127.7, 127.4, 124.0, 117.4, 116.3, 116.1, 21.5. <sup>19</sup>F-NMR (476 MHz, CDCl<sub>2</sub>F):  $\delta$  –143.45, –158.01, –164.54. Elem. anal.: found C, 73.30; H, 3.42; C<sub>25</sub>H<sub>13</sub>F<sub>5</sub> requires: C, 73.53; H, 3.21.

1-Pentafluorophenyl-8-(4-chloro-3-methylphenyl)biphenylene (4c). This compound was prepared by the Ullmann procedure described above starting from 7c (0.050 g, 0.141 mmol) and pentafluoroiodobenzene (0.128 mL, 1.0 mmol). The flashchromatographic purification was carried out using pentane as the eluant (column diameter: 1 cm; column height: 25 cm). The product had  $R_f$  0.45. It was isolated in 19% yield as a white solid, mp 184.5–185.5 °C. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.06 (d, J = 8.2 Hz, 1 H), 6.93–6.87 (m, 3 H), 6.82–6.71 (m, 5H), 2.22 (s, 3H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 151.5, 151.4, 150.9, 147.6, 144.6 and 142.6 (C-F ortho), 141.6 and 139.6 (C-F meta), 138.3 and 136.3 (C-F para), 137.0, 135.5, 133.7, 132.4, 129.6, 129.5, 129.2, 128.7, 128.1, 125.6, 117.5, 116.6, 116.1, 21.5. <sup>19</sup>F-NMR (476 MHz, CDCl<sub>2</sub>F):  $\delta$  –143.04, -156.57, -164.09. Elem. anal.: found C, 67.67; H, 2.85; C<sub>25</sub>H<sub>12</sub>ClF<sub>5</sub> requires , 67.81; H, 2.73.

#### Acknowledgements

This work was supported by the Swiss and US National Science Foundations (KKB and JSS) as well as the CNR in Italy (FC). Universidad Autónoma de Nuevo-León (Monterrey, México) is acknowledged for generous donations of diffractometer time (GA). Don Truhlar (University of Minnesota) is acknowledged for generously providing access to the M06-2X functional and computer time on the Minnesota Supercomputer. Dr Anthony Linden is acknowledged for help on crystallographic details.

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