Substituent Effects on the Stability of Arene−Arene Complexes: An AM1 Study of the Conformational Equilibria of *cis*-1,3-Diphenylcyclohexanes

Vance E. Williams, Robert P. Lemieux,* and Gregory R. J. Thatcher*

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

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Molecular orbital calculations at the AM1 level have been performed on *cis*-1,3-diarylcyclohexane systems (**1**, **2**) in order to provide a theoretical model and suggest novel experimental models for the investigation of arene−arene π-stacking. Energy minima were located for diaxial conformers (a) in which aryl rings are coplanar and π-stacked and (b) in which aryl rings adopt an edge-to-face or intermediate conformation. The average face-to-face distance varies from 4.1 to 4.4 Å, outside the van der Waals contact distance of 3.4 Å, and the minimum inter-ring distance varies from 3.1 to 3.5 Å. The diaxial−diequatorial conformational equilibria ($\Delta E_{\text{ax-eq}}$) were calculated for a large series of *para*-substituted and *meta*-substituted 1,3-diarylcyclohexanes and plotted against $\Sigma\sigma_p$, $\Delta\sigma_p$, and $E_{\text{HOMO}} - E_{\text{LUMO}}$. The best correlation was observed using electrostatic potentials calculated at the electron density surface on the π-face of individual arenes. Similar correlations were observed for conformational equilibria associated with the improved 1,3-dimethyl-1,3-diarylcyclohexane series (**3**). More limited correlations were drawn for the diaxial−diequatorial conformational equilibria involving (i) edge-to-face diaxial *cis*-1,3-diarylcyclohexanes and (ii) π-stacked diaxial *cis*-1,3-diarylcyclohexanes in which one aryl ring is perfluorinated (**5**, **6**). In all cases, the results (a) showed good agreement with literature data on related experimental systems and (b) demonstrated the dominance of arene−arene electrostatic contributions to conformational energy over the negligible orbital mixing and charge-transfer interactions.

Introduction

Interactions between aromatic rings, either via π-stacking or face-to-edge complexes, are at the origin of many phenomena in organic and biological chemistry. These interactions are proposed to play an important role in the stabilization of DNA[1] and in determining the tertiary structure of many proteins.[2] Aromatic π-stacking can also play a key role in asymmetric induction[3,4] and in the chiral recognition mechanisms upon which some HPLC chiral stationary phases are based.[5] Inclusion complexes such as cyclophanes and molecular clefts provide examples of molecular recognition in which arene−arene interactions are important.[6−8] Furthermore, the stability and macroscopic properties of many liquid crystal phases have been shown to originate from such interactions.[9,10] While π-stacking is often invoked to explain the above phenomena, there remains some confusion as to the origins of these interactions. It is often argued that the combination of electron-rich and electron-poor arenes favors π-stacking through charge-transfer (CT) complexation, although there is a growing body of experimental[11−14] and theoretical[15−20] evidence suggesting that dispersion forces and electrostatic interactions are at the basis of aromatic π-stacking.

Recently, Cozzi and Siegel investigated the kinetics of *syn*−*anti* epimerization of substituted 1,8-di-*o*-tolylnaphthalenes, with each tolyl ring bearing a *para*-substituent, and found that the barrier to epimerization increases with ring substituents of increasing electron-withdrawing character.[12] A linear correlation was found between the barrier to epimerization and the sum of σ_p Hammett constants for the two ring substituents; this relationship was used to support the argument that electrostatic effects far outweigh CT effects in the interactions of π-stacked arenes. The opposite trend in substituent effects was observed for 1,8-diphenylnaphthalenes in which one of the phenyl rings is perfluorinated.[21] These results were ascribed to the reversed charge distribution in the quadrupole of the perfluorinated ring, which causes electrostatic interactions between the perfluorinated and unfluorinated phenyl rings in a π-stacked arrangement to be attractive instead of repulsive. The

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* Authors to whom correspondence should be addressed. E-mail: lemieux@chem.queensu.ca; thatcher@chem.queensu.ca.

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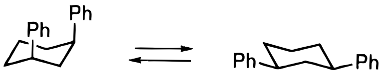
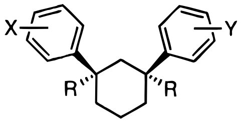
Scheme 1



validity of these systems as models of π-stacked arene complexes may be questioned since the phenyl and tolyl rings are sterically constrained well within their van der Waals contact distance of 3.4 Å.[22]



1: R = H; X,Y = *p*-(H, Me, NO_2, NH_2, CN, OH, OMe, F, Cl)
2: R = H; X,Y = *m*-(H, Me, NO_2, NH_2, CN, OH, OMe, F, Cl)
3: R = Me; X,Y = *m*-(H, NO_2, NH_2, CN)

In order to provide a further experimental model for π-stacked arenes that might circumvent this shortcoming, we have undertaken a computational study of the substituted *cis*-1,3-diphenylcyclohexanes **1**−**3**. These systems can adopt conformations in which the two aromatic rings are either diaxial or diequatorial (Scheme 1). Although the diequatorial conformer is favored on steric grounds, any relatively stabilizing interaction between the phenyl rings should shift the equilibrium toward the diaxial conformer. In principle, it should be possible to experimentally detect and quantify any substituent effect on π-stacking of the aromatic rings in **1**−**3** from the corresponding shift in position of the conformational equilibrium. In the present paper, results of semiempirical AM1 calculations performed on these systems are discussed. While arene−arene interactions have been previously investigated at both the semiempirical and the ab initio levels, to the best of our knowledge, there has been no computational study of substituent effects on the stability of such intramolecular complexes.

Calculations

All calculations were performed using the Spartan 3.0.4 molecular modeling program[23] running on an IBM RISC 6000 workstation. Geometry optimizations were performed at the AM1 semiempirical level;[24] the size of the molecules considered precluded the use of ab initio methods. Structures were optimized in the diaxial and diequatorial conformations without any constraints; all energies corresponding to local energy minima were obtained by full geometry optimization with thorough searching of the conformational space. The torsional energy profile for the phenyl rings of **1** and **3** (X, Y = H) in the diaxial conformation were obtained by constraining the torsional angle defined by C-6, C-1, C-1′, and C-2′ and performing a full geometry optimization on the remainder of the molecule. These partial geometry optimizations were performed in increments of 10°. Calculation of electrostatic potential surfaces and HOMO/LUMO energy gaps were performed at the AM1 level for *meta*-substituted toluenes (**4**) using geometry-optimized structures. Electrostatic potential surfaces were mapped onto the electron density surface (0.002 e/Å isosurface) at medium resolution.

Results and Discussion

Structure and Geometry. Geometry optimizations were performed for all of the 45 possible X/Y functional group combinations of compound **1**, and structures corresponding to energy minima for both the diaxial and diequatorial conformations were rigorously determined. The minimum energy structure of the diaxial conformer of **1** (X, Y = H) is shown in Figure 1 as a representative example. In all of the diaxial conformers considered in this series, structures corresponding to global energy minima were located with the two aromatic rings approximately coplanar, and with an average inter-ring distance (center to center) of 4.4 Å and a minimum inter-ring distance of 3.5 Å (Figure 1). In all compounds (**1**), the diequatorial conformer is favored by at least 7 kcal/mol over the diaxial conformer. The exact value $\Delta E_{\text{ax-eq}}$ was seen to vary from 7 kcal/mol to over 8 kcal/mol, depending on the nature of the substituents X and Y. As a control experiment, $\Delta E_{\text{ax-eq}}$ was calculated at the AM1 level for a series of *meta*- and *para*-substituted phenylcyclohexanes. The calculated value of 3.2 kcal/mol for phenylcyclohexane is in excellent agreement with the experimentally determined ΔG_0 value of 3.0 kcal/mol.[25] A systematic decrease in $\Delta E_{\text{ax-eq}}$ with increasing electron-withdrawing character of the substituent was calculated. However, the magnitude of this effect is small (<0.15 kcal/mol) and unable to account for the corresponding trend observed for *cis*-1,3-diphenylcyclohexanes.

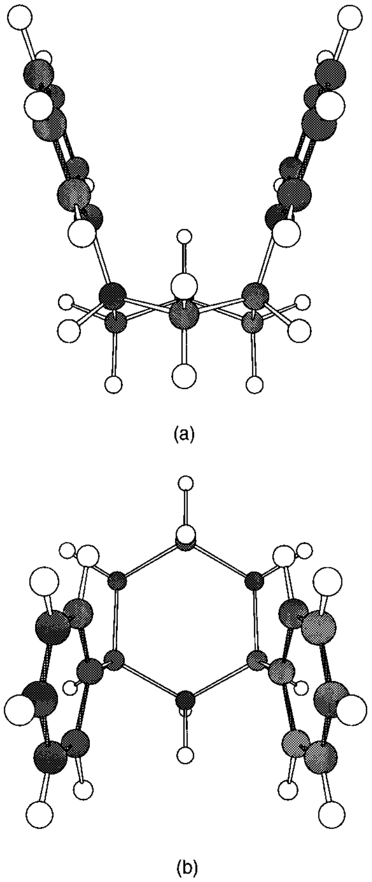


Figure 1. Geometry-optimized structure of the diaxial conformer of *cis*-1,3-diphenylcyclohexane (**1**, X, Y = H) in a π-stacked orientation: (a) side view, (b) top view.

Although coplanar (or displaced coplanar) arene rings are found in many arene complexes, in a number of cases, the lowest energy form of arene complexes is not a π-stacked but rather an edge-to-face, or "T-shaped",

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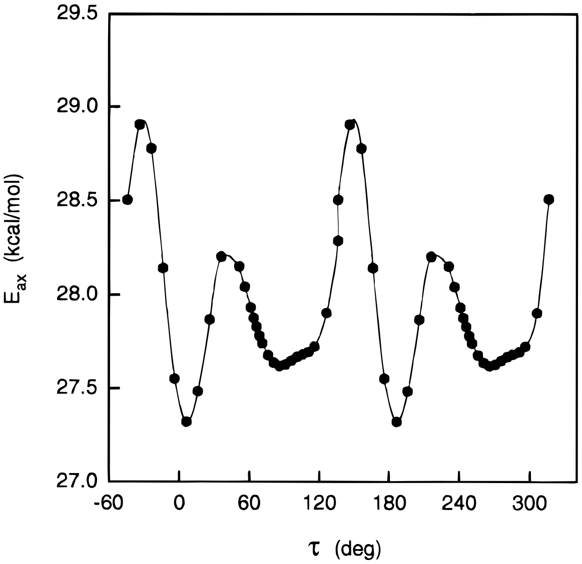

Figure 2. Energy profile for compound **1** (X, Y = H) as a function of the torsional angle τ defined by C-6, C-1, C-1′, and C-2′.

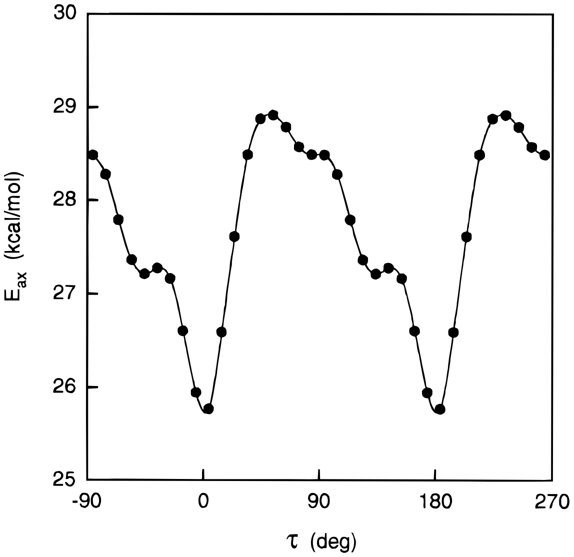

Figure 3. Energy profile for compound **3** (X, Y = H) as a function of the torsional angle τ defined by C-6, C-1, C-1′, and C-2′.

complex.[18,26−32] In order to assess the energetic preference of the two phenyl rings in **1**−**3** to adopt either a π-stacked or edge-to-face orientation, energy profiles were calculated for **1** and **3** (X, Y = H) as a function of the torsional angle τ, which is defined by C-6, C-1, C-1′, and C-2′. The profile calculated for **1** shows two pairs of symmetry-related minima, one corresponding to the π-stacked orientation at $\tau = 0°$ and 180° and the other to an edge-to-face orientation at $\tau = 90°$ and 270° (Figure 2). In this case, the π-stacked orientation is favored by only 0.3 kcal/mol over the edge-to-face orientation, which suggests that both orientations will be accessible in the diaxial conformation. The small preference for the stacked conformer in **1**, which is opposite to that found for the benzene dimer in the gas phase,[18] is probably caused by constraints placed on the phenyl rings by the cyclohexane backbone. The energy profile calculated for **3** shows global minima at $\tau = 0°$ and 180° for the π-stacked orientation and local minima corresponding to orientations intermediate between π-stacked and edge-to-face (Figure 3), which is consistent with the closer proximity of the two phenyl rings in **3** and steric destabilization of any edge-to-face conformer. The preference for the π-stacked orientation for **3**, on the order of 1.5 kcal/mol, is much more pronounced than for **1**.

In the elegant 1,8-diarylnaphthalene system developed by Cozzi and Siegel,[12,21] information on ground state π-stacked conformers is obtained from measurements of rotational barriers ($\Delta G^{\ddagger}_{\text{rotation}}$) and requires certain assumptions about differential substituent effects on ground and transition states. The 1,3-diarylcyclohexane system is designed to allow direct observation of π-stacking by measurement of the diaxial−diequatorial conformational equilibrium. The structural constraints of the cyclohexane system, in which the minimum π-stacked face-to-face distance is greater than the van der Waals distance, appear to offer advantages over the 1,8-diarylnaphthalene system. However, the greater steric flexibility of the cyclohexane system allows access to edge-to-face and intermediate conformations. Clearly, if coplanar π-stacking is the focus of study, this represents a disadvantage of the simple cyclohexane system.

Hammett Correlations. Hammett σ_p values provide an empirical measure of the electron-withdrawing/-donating character of *para*-substituents X and Y, with $\sigma_{pX} + \sigma_{pY}$ ($\Sigma\sigma_p$) approximating the total π-electron density of two interacting rings.[33] For compound **1**, a negative slope for a plot of ΔE_{ax-eq} versus $\Sigma\sigma_p$ would suggest a dominant destabilizing electrostatic interaction between the two arene rings. However, orbital mixing or charge transfer interactions may also show good correlations for *para*-substituted rings, for example, anomeric hyperconjugation.[34] Since electron-withdrawing substituents (positive σ_p) may lower E_{LUMO} while electron-donating substituents (negative σ_p) may increase E_{HOMO}, a negative slope and good correlation for a plot of ΔE_{ax-eq} versus $|\Delta\sigma_p|$ might be argued to indicate dominance of orbital mixing or CT interactions. The plot of ΔE_{ax-eq} versus the sum of Hammett σ_p values ($\Sigma\sigma_p$) for series **1** shows a trend similar to that observed experimentally by Cozzi and Siegel[12] for the 1,8-di-*o*-tolylnaphthalene system (Figure 4). The stabilization of the diaxial conformer increases as the substituents X and Y become more electron withdrawing, which indicates that the relative stability of the diaxial conformer in **1** is controlled primarily by electrostatic destabilization between the two aromatic rings. By contrast, a plot of ΔE_{ax-eq} versus $\Delta\sigma_p$ shows

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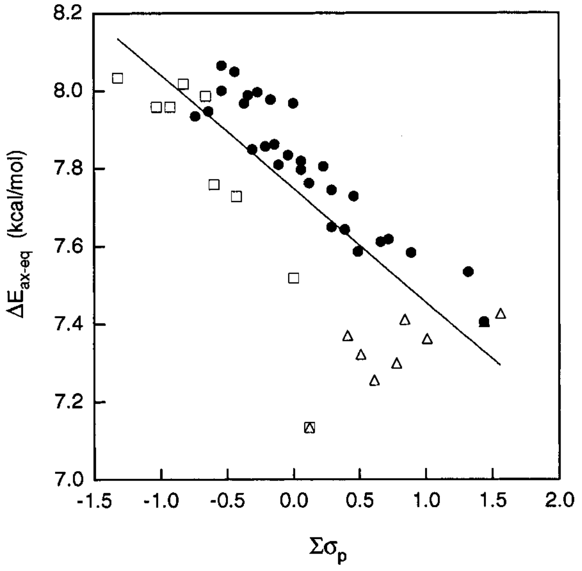

Figure 4. Plot of $\Delta E_{\mathrm{ax-eq}}$ versus $\Sigma\sigma_{\mathrm{p}}$ for compound **1**, with the diaxial conformer in a π-stacked orientation: X = NO_2 (triangles), X = NH_2 (squares), all others (filled circles). The line represents the least-squares fit.

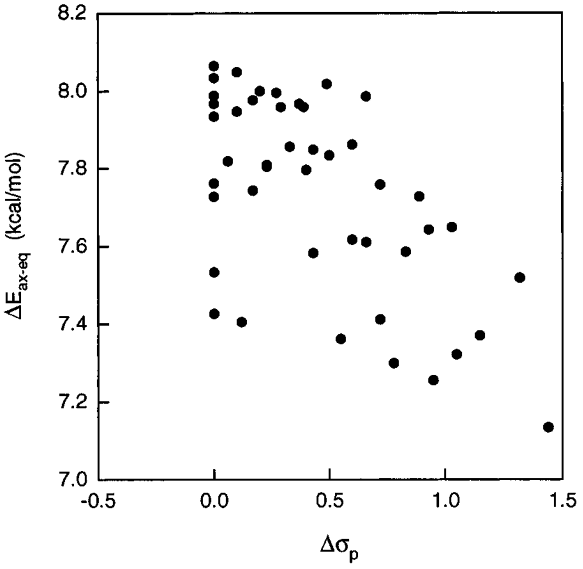

Figure 5. Plot of $\Delta E_{\mathrm{ax-eq}}$ versus $\Delta\sigma_{\mathrm{p}}$ for compound **1**, with the diaxial conformer in a π-stacked orientation.

no evident trend (Figure 5), which suggests that orbital mixing and CT complexation are not dominant factors in this case. These observations are qualitatively compatible with the dominance of electrostatic interactions with a negligible contribution from charge transfer.

A closer inspection of the results in Figure 4 reveals that, although there is a reasonable linear correlation between $\Delta E_{\mathrm{ax-eq}}$ and $\Sigma\sigma_{\mathrm{p}}$, the correlation varies with individual families (X = constant, Y = varied). In particular, at one extreme of the σ_{p} scale, the X = NH_2 family gives a more negative slope and is displaced from the straight line; at the other extreme, the X = NO_2 family appears to give a *positive* slope, i.e., as the electron-withdrawing ability of Y increases, destabilization of the π-stacked diaxial conformation increases. Furthermore, the calculations suggest that the compound with the most stable diaxial conformer, displaced enormously from the straight line correlation, is that with X = NO_2 and Y = NH_2, a result that would be consistent with stabilization via CT complexation.

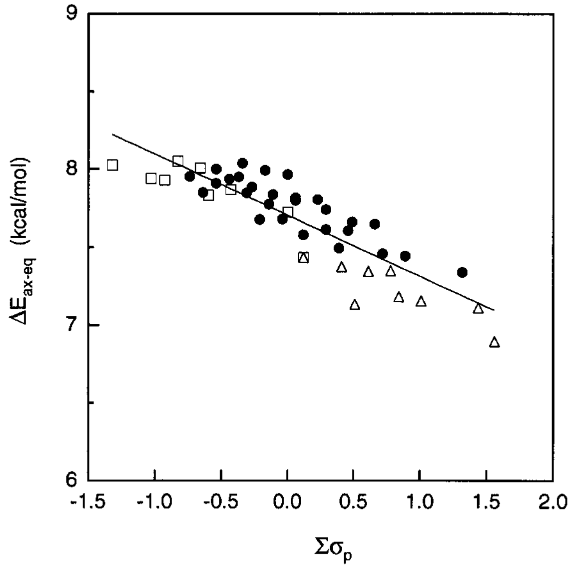

Figure 6. Plot of $\Delta E_{\mathrm{ax-eq}}$ versus $\Sigma\sigma_{\mathrm{p}}$ for compound **2**, with the diaxial conformer in a π-stacked orientation: X = NO_2 (triangles), X = NH_2 (squares), all others (filled circles). The line represents the least-squares fit.

In order to determine whether CT effects were at the origin of the observed trends, the effect of direct noncovalent interactions between the substituents X and Y themselves needed to be considered. Such interactions, and their effect on the stabilization of the diaxial conformer, were investigated by performing AM1 calculations on the *meta*-substituted 1,3-diphenylcyclohexane **2** with the substituents X and Y oriented *anti* to one another in the diaxial conformation, thus eschewing any noncovalent interaction between X and Y that may influence series **1**. The resulting plot of $\Delta E_{\mathrm{ax-eq}}$ versus $\Sigma\sigma_{\mathrm{p}}$ shows a linear correlation that is independent of the nature of X (Figure 6). These results confirm that dipole–dipole interactions between X and Y rather than CT complexation are at the origin of the deviations observed for **1** when X = NO_2 or X = NH_2 and further support the argument favoring the dominance of electrostatic interactions (*vide supra*).

Electrostatic Potentials and HOMO–LUMO Gaps. Correlations with empirical Hammett parameters are particularly useful for rationalization of experimental energy data, but computationally derived wavefunctions may provide more exact correlations. To further investigate the importance of electrostatic and CT contributions to arene π-stacking, correlations were sought between the relative stabilities of the diaxial conformers in **2** with terms that explicitly represent electrostatic and CT interactions. Applying frontier molecular orbital theory, the interaction between two aromatic rings can be approximated by eq 1, where Q is the total charge on

$$\Delta E = -\sum \frac{Q_{xm}Q_{yn}}{\epsilon R_{mn}} + \frac{2(c_x c_y \beta)^2}{E_{\mathrm{homo}(x)} - E_{\mathrm{lumo}(y)}} \qquad (1)$$

atoms m and n on rings x and y, ϵ is the local dielectric constant, R_{mn} is the distance between atoms m and n, $c_x c_y$ are orbital coefficients, and β is the resonance

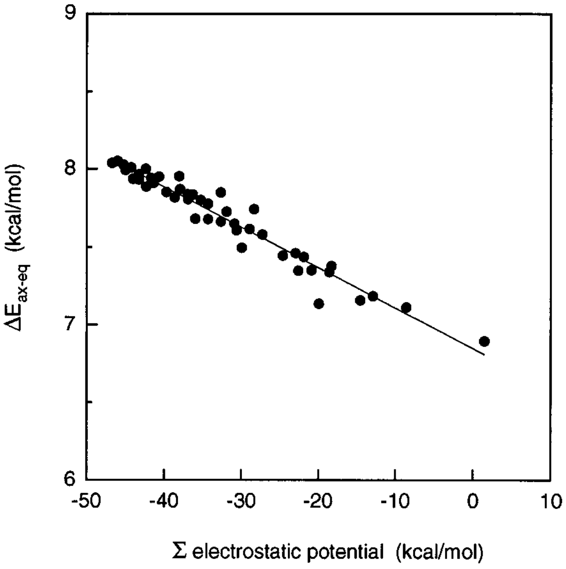

Figure 7. Plot of $\Delta E_{\mathrm{ax-eq}}$ versus the sum of arene electrostatic potentials for compound **2**, with the diaxial conformer in a π-stacked orientation. The line represents the least-squares fit.

integral.[35] The first term represents the electrostatic (Coulombic) contribution, while the second term represents the contribution from overlap of frontier molecular orbitals. Since the distance between aromatic rings in **1** and **2** is largely invariant to substituent effects, the first term can be estimated by measuring electrostatic potentials at the faces of the phenyl rings. If the electrostatic term plays an important role in the stabilization of the diaxial conformer, there should be a strong correlation between the sum of the average electrostatic potentials of each phenyl ring and $\Delta E_{\mathrm{ax-eq}}$.

The calculated AM1 wavefunctions were used to determine electrostatic potential maps for *meta*-substituted toluenes (**4**) as models for the two interacting phenyl rings in **2** (diaxial conformation). The electrostatic potential on the electron density surface at the center of the phenyl ring was taken as a measure of the electrostatic potential of the π-system. Values of $\Delta E_{\mathrm{ax-eq}}$ calculated for **2** were then plotted against the sum of electrostatic potentials for the corresponding pairs of *meta*-substituted toluenes (Figure 7). Although this approach makes a gross simplification of charge distribution by attempting to describe the electrostatic character of each phenyl ring by a single point charge, a striking linear correlation between electrostatic potentials and $\Delta E_{\mathrm{ax-eq}}$ is evident ($r^2 = 0.95$). It is clearly important that this point charge is at the electron density surface and explicitly includes a consideration of the dominant influence of the π-electron clouds.[15]

The second term in eq 1 can be estimated by assuming that orbital overlap between the two rings is approximately constant over the series, thus making the numerator a constant. Values of $\Delta E_{\mathrm{ax-eq}}$ for **2** were plotted against $(E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}})^{-1}$ calculated for the corresponding pairs of *meta*-substituted toluenes (Figure 8). In this case, no correlation exists between the degree of stabilization of the diaxial conformer and the corresponding HOMO/LUMO gap. These results again demonstrate the dominance of electrostatic contributions to the energetics of π-stacking and the negligible role of CT and orbital mixing interactions. Indeed, the relative unimportance of CT interactions was presaged 30 years ago by Dewar and Thompson,[36] while Mulliken stated that "the stability of these weak [π–π] complexes must be attributable in appreciable part to the action of classical Coulomb and/or polarization forces".[37]

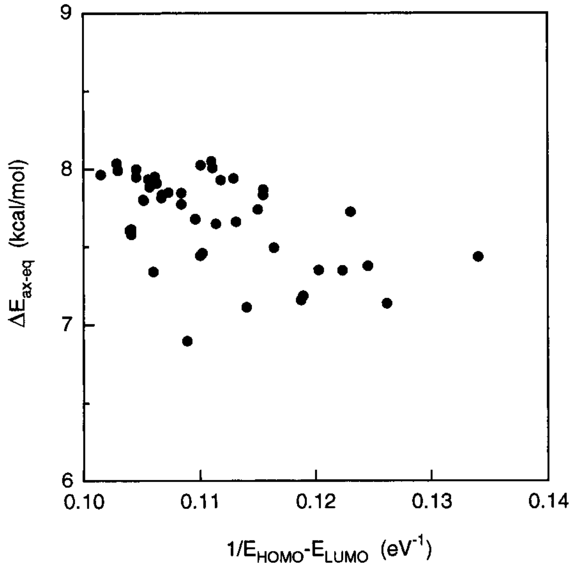

Figure 8. Plot of $\Delta E_{\mathrm{ax-eq}}$ versus $(E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}})^{-1}$ for compound **2**, with the diaxial conformer in a π-stacked orientation.

Assessment of Models. Series **1** is unsuitable as an experimental model for π-stacked arenes because of the influence of interactions between *para*-substituents. Circumventing this problem in series **2** still leaves two problems. Firstly, our calculations suggest that substituent effects would lead to relatively small changes in $\Delta E_{\mathrm{ax-eq}}$, on the order of ≤ 1 kcal/mol, although this number is comparable with values experimentally observed by Cozzi and Siegel in the 1,8-diarylnaphthalenes. More importantly, the conformational equilibrium in series **2** favors the diequatorial conformer by at least 7 kcal/mol ($K_{\mathrm{eq}} \approx 10^5$) and would not be measurable by dynamic NMR. Another problematic feature of series **1** and **2** is the large inter-ring distance of 4.4 Å, larger than the interplanar distance of 3.4 Å often observed in arene–arene dimers. As a result, relative contributions from electrostatic interactions might be exaggerated in these systems compared to the corresponding intermolecular π-stacked aggregates.[22] In order to improve the accuracy of our model, and to further shift the conformational equilibrium toward the diaxial conformer, methyl substituents were introduced at the 1- and 3-positions of the cyclohexane ring in **2** to give compound **3**. Calculations at the AM1 level give a $\Delta E_{\mathrm{ax-eq}}$ value lowered to 1.4 kcal/mol for **3** (X, Y = H), thus suggesting that K_{eq} for the conformational equilibrium might be measurable experimentally. Furthermore, the results show that the coplanar aromatic rings in **3** are forced closer to one another than in **1**, with an average inter-ring distance of 4.1 Å and a minimum inter-ring distance of 3.3 Å.

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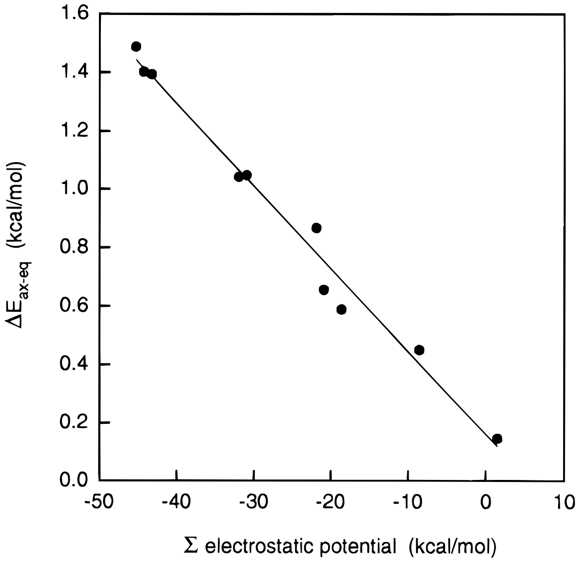


Figure 9. Plot of $\Delta E_{\text{ax-eq}}$ versus $\Sigma\sigma_p$ for compound **3**, with the diaxial conformer in a π-stacked orientation. The line represents the least-squares fit.

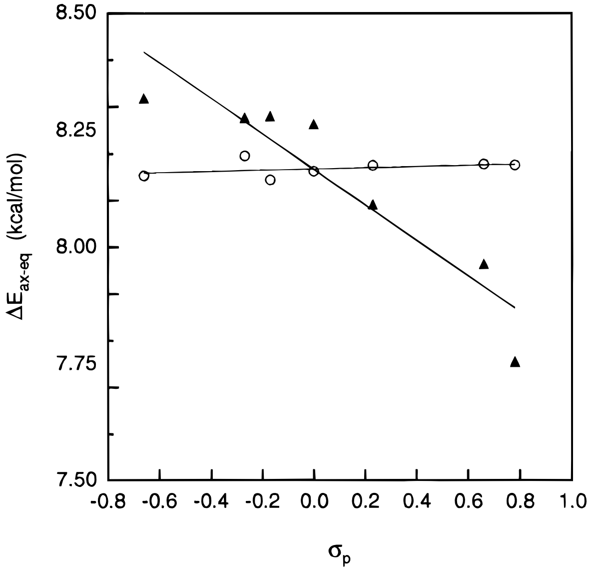


Figure 10. Plot of $\Delta E_{\text{ax-eq}}$ versus $\Sigma\sigma_p$ for compound **1**, with the diaxial conformer in an edge-to-face orientation: variations in H-bond donor ring substituent X (triangles), variations in H-bond acceptor ring substituent Y (circles). The two lines represent least-squares fits.

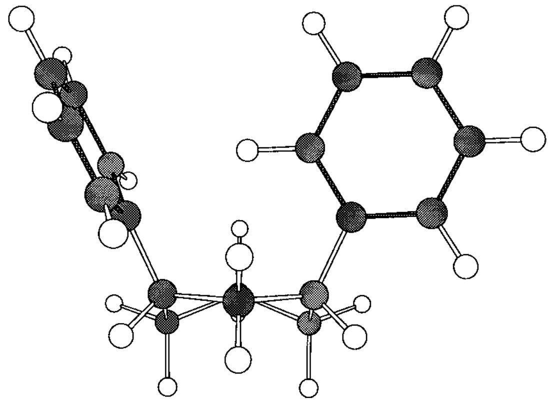


Figure 11. Geometry-optimized structure of the diaxial conformer of *cis*-1,3-diphenylcyclohexane (**1**, X, Y = H) in an edge-to-face orientation.

A plot of $\Delta E_{\text{ax-eq}}$ versus the sum of electrostatic potentials for the corresponding pairs of *meta*-substituted toluenes for the series **3** gives a linear correlation comparable to that obtained for **2** (Figure 9). The repeated good correlation suggests that the decrease in inter-ring distance does not influence the predominance of electrostatic interactions in controlling the relative conformational stability. More importantly, these results reveal a greater sensitivity of the conformational equilibrium toward substituent effects, with a range of $\Delta E_{\text{ax-eq}}$ values on the order of 1.4 kcal/mol. The stabilization energies calculated for **3** as a function of X and Y are of the same order of magnitude as those experimentally measured for other π-stacked arenes.[6,11,12] An additional advantage of the constrained proximity of the aryl rings in series **3** is the diminished accessibility of noncoplanar, edge-to-face conformers, thus providing an improved model for π-stacking interactions.

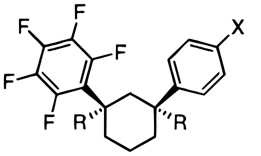
No attempt was made to incorporate electron correlation and exchange effects within the present series of calculations. Experimentally observed deviations from the excellent theoretical correlation with electrostatic contributions (Figure 9) could provide support for the influence of dispersion forces on arene π-stacking. The 1,3-diarylcyclohexane series **3** represents an improved system for examination of arene π-stacking interactions. Further adjustments and hence improvements of 1,3-diaryl six-membered ring systems are of course possible, including inclusion of endocyclic heteroatoms.

Edge-to-Face Interactions. Edge-to-face orientations were shown to be energetically accessible for diaxial conformers of **1** and less so for **3** (*vide supra*). It has been argued that edge-to-face complexes are stabilized by electrostatic interactions between the electron-poor σ-skeleton and electron-rich π-clouds of arenes.[17] A simpler analysis involves hydrogen bonding to the electron-rich π-face. Substituent effects on the stability of edge-to-face complexes were investigated by performing two sets of AM1 calculations on compound **1**. In one set, $\Delta E_{\text{ax-eq}}$ values were calculated for **1** as a function of the substituent on the H-bond donor ring (X = H, NO_2, CN, Cl, OMe, Me) while the substituent on the H-bond acceptor ring was kept constant (Y = H). In the second set, the substituent on the H-bond donor ring was maintained constant (X = H) while the substituent on the H-bond acceptor ring was varied (Y=H, NO_2, CN, Cl, OMe, Me). A plot of $\Delta E_{\text{ax-eq}}$ versus Hammett σ_p values shows a linear correlation for the first set of calculations (Figure 10; variations in X), which is comparable in amplitude to that obtained for the π-stacked orientation in **1** (Figure 4). These results are in good agreement with the experimental work of Wilcox.[27] By contrast, virtually no substituent effect is observed for the second correlation (Figure 10; variation in Y). Increasing the electron-donating character of substituent Y on the acceptor ring should stabilize an edge-to-face complex through its influence on the electrostatic potential of the π-face of the acceptor ring. However, in the edge-to-face conformers of **1**, the *ortho*-hydrogen of the donor ring is constrained closer to the *ipso* carbon of the acceptor than to the π-face (Figure 11). Significantly, these results suggest that the relative stability of the diaxial conformer in series **1** and **2** should increase with substituents of increasing electron-withdrawing character, whether the phenyl rings are in a π-stacked or edge-to-face orientation.

Table 1. Relative Energies for the Diaxial Conformer of 5 and 6

	$\Delta E_{\text{ax}-\text{eq}}$ (kcal/mol)	
X	**5** (R = H)	**6** (R = Me)
H	10.23	0.98
Me	10.20	0.94
NH_2	10.20	0.90
NO_2	10.26	1.25

Perfluoroarene−Arene Interactions. In order to draw further correlations with the experimental work of Cozzi and Siegel,[12,21] the conformational equilibria of systems **5** and **6**, containing a single perfluorinated ring, were investigated. Calculations at the AM1 level on diequatorial and coplanar diaxial conformers show the conformational equilibria of **5** to be largely independent of the nature of substituent X (see Table 1). Ascribing this lack of substituent effect to the large inter-ring distance in **5**, calculations were performed on the corresponding 1,3-dimethylcyclohexane series **6**, thus forcing the phenyl rings closer together (cf. series **3**). Indeed, the $\Delta E_{\text{ax}-\text{eq}}$ values calculated as a function of substituent X for series **6** show a trend consistent with that observed experimentally by Cozzi and Siegel for the corresponding 1,8-diarylnaphthalene system: the π-stacked diaxial conformer is progressively stabilized as the electron-donating ability of the substituent X is increased.[21] These results provide further support for the hypothesis that arene−arene π-stacking is controlled primarily by electrostatic interactions, whether they are destabilizing, as in compounds **1**−**3**, or stabilizing as a result of reversed charge distribution in the quadrupole of one phenyl ring, as in compound **6**.



5: R = H; X = H, NO_2, NH_2, Me
6: R = Me; X = H, NO_2, NH_2, Me

Conclusion

Semiempirical AM1 calculations on the conformational equilibria of compounds **1**−**3** as a function of empirical Hammett parameters, calculated electrostatic potentials, and frontier MO energy gaps are consistent with experimental results, suggesting that arene−arene π-stacking is controlled primarily by electrostatic rather than CT interactions.[11−14] In particular, an excellent correlation is obtained between the position of conformational equilibria (for **2** and **3**) and the electrostatic potential calculated at a point on the electron density surface of the π-face of individual component arenes (**4**). The calculations are also consistent with the reverse trend in substituent effects recently observed for π-stacked systems in which one of the arenes is perfluorinated. Further calculations on edge-to-face diaxial conformers illustrate that a similar dependence on electrostatic contributions to that calculated for coplanar π-stacked rings is possible. The *meta*-substituted 1,3-dimethyl-1,3-diarylcyclohexane system **3** is shown to be a promising potential model system for experimental examination of π-stacking. However, in all systems, the magnitude of the calculated electrostatic effects is small (≤1.0−1.4 kcal/mol).

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