Attractive Intramolecular Edge-to-Face Aromatic Interactions in Flexible Organic Molecules

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ABSTRACT

Recent X-ray crystallographic and NMR evidence indicates that relatively weak intramolecular edge-to-face interactions between aromatic rings can affect or determine the conformation of organic molecules in the solid state and in solution. Experimental estimates indicate that these interactions are energetically attractive by ca. 1.5 kcal mol^{-1} but disfavored in solution by entropic factors due to the restricted internal mobility. Hence, these interactions are more manifest at low temperature in solution or in crystal structures where conformational entropy effects are negligible.

Introduction

Students of organic chemistry have traditionally been taught that bulky hydrophobic alkyl or aryl groups repel each other, and the concepts of "steric repulsion" or "steric hindrance" are well established. As a result, flexible acyclic molecules are normally considered to prefer open conformations where bulky groups are far apart. One long-established exception to this view is the intermolecular attractive charge-transfer interaction between aromatic molecules when one component is electron deficient (e.g., 2,4,6-trinitrobenzene) and the other is electron rich.[1] This stabilizes the face-to-face parallel-stacked geometry **1** (Figure 1) sometimes referred to as a "planar sandwich".

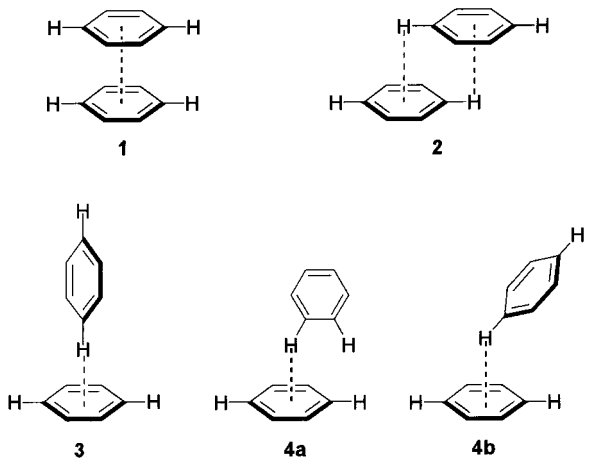

FIGURE 1. Structures of the benzene dimer.

More recently, it has emerged that attractive interactions of a different type exist between aromatic moieties devoid of polar substituents. These "edge-to-face" interactions, though modest in energy terms, can play an important role in such diverse areas as protein folding, base pair stacking in DNA, host−guest binding in supramolecular assemblies, crystal engineering, drug−receptor interactions, and other molecular recognition processes.[2−6]

Edge-to-face packing appears to have been first noted by Cox et al. (1958) in single crystals of benzene.[7] Pioneering work by Burley and Petsko[2,3] established the importance of edge-to-face interactions between aromatic rings in determining the tertiary and quaternary crystalline structure of peptides and proteins. Intermolecular attractive aromatic interactions, which are outside the scope of this Account, have been identified by a number of groups, although the work of Stoddart et al.[6] on the role of attractive aromatic interactions in host−guest binding in macrocyclic compounds could be highlighted.

The possible role of intramolecular edge-to-face aromatic interactions in affecting the conformation of flexible synthetic organic molecules in solution and in the crystalline state has become apparent only during the past decade or so, and in the authors' experience it is still not widely disseminated in the chemistry community. This Account will concentrate on recent developments in this area, but a summary of theoretical work on the benzene dimer[8] is presented initially as it is an important reference system for understanding the nature and geometries of edge-to-face interactions. Older, more general reviews[2−6] or books[9,10] deal with weak molecular interactions in general.

The Benzene Dimer

At least three possible structures for the benzene dimer have been identified from theoretical calculations, viz. offset parallel stacking (sometimes referred to as parallel-

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displaced) (**2**), the T-shaped edge-to-face structure (**3**), and the tilted-T structure (**4a**); see Figure 1.[8] In view of the subsequent discussion of intramolecular aromatic interactions, a second tilted-T structure (**4b**) should also be considered even though it may not be an actual potential energy minimum for the benzene dimer. We propose that structure **4a** be termed an "edge-tilted-T" and **4b** a "face-tilted-T". These differ primarily by 90° rotation about the H-phenyl bond. It is worth observing that there is a smooth progression from the T-shaped structure **3** through the face-tilted-T structure **4b** to the offset-stacked structure **2** as the interplanar angle between the benzene rings decreases from 90° to 0°. All of the intermediate geometries on this coordinate are probably attractive.

Electrostatic and ab initio MO calculations have identified all three types of edge-to-face structure as potential minima, but the calculations sometimes differ as to which structure is the global energy minimum. Some calculations give potential minima structures which are variants of the geometries depicted in Figure 1. For example, variants of structures **1** and **2** result from rotating the upper ring around its six-fold axis with respect to the lower ring, and the edge-tilted-T structure **4a** has been depicted with the upper ring located centrally, or displaced to one side with one of its hydrogen atoms located directly over the center of the lower ring.

A pioneering theoretical investigation by Evans and Watts in 1975, using an empirical potential function, indicated the existence of stable edge-to-face geometries for the benzene dimer.[11] Subsequent ab initio MO calculations indicated that the T-structures **3** and **4a** had the lowest energy (−2.2 to −2.4 kcal mol^{-1}).[12−15] The calculated ring center-to-center distance in the T-structure **3** is 5.0−5.2 Å, corresponding to an interacting H-to-ring center perpendicular distance of ca. 2.5−2.7 Å (assuming the ring radius and C−H bond lengths in benzene are 1.40 and 1.08 Å, respectively). Offset parallel arrangements were also calculated to be stable minima. Hunter and Sanders[4] proposed a simple electrostatic model of the charge distribution in aromatic systems which predicts T-shaped (**3**) and offset parallel arrangements (**2**) to be favored but only by ca. 0.5 kcal mol^{-1}. Molecular mechanics calculations (MMP2) also indicate that the T-structure is stabilized by 1.5 kcal mol^{-1} but seriously overestimate the stability of the parallel-stacked structure (**1**).[16]

Recently the structure of the benzene dimer has been intensively investigated by Hobza et al.[17] using high-quality MP2 ab initio calculations. Six potential minima were identified, with the offset parallel-stacked (**2**), T (**3**), and edge-tilted-T (**4a**) having the lowest energy. However, subsequent calculations using a nonempirical model (NEMO) indicate that the T-shaped structure is the sole energy minimum for the benzene dimer.[18] The calculated stabilization energy of the T structure is −2.3 kcal mol^{-1} (MP2)[17] or −1.7 kcal mol^{-1} (NEMO),[18] equivalent to a stabilizing enthalpy of −2.0 kcal mol^{-1} (MP2) or −1.5 kcal mol^{-1} (NEMO) after subtracting zero-point energy (estimated to be 0.3 kcal mol^{-1}).[17] The NEMO calculations indicate that the edge-tilted-T structure **4a** is only 0.1 kcal mol^{-1} less stable than the T structure **3** but is not an actual energy minimum. The offset parallel structure **2** is 0.5 kcal mol^{-1} less stable than **3** and is also a transition structure.[18,19] One might have expected that an edge-to-face interaction would lead to a slight elongation of the interacting C−H bond. However, recent calculations by Hobza et al.[20] suggest that, in fact, a slight shortening of the C−H bond occurs in the benzene dimer, attributed to a compression effect.

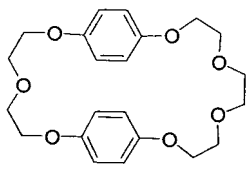
Experimental evidence for the structure of the benzene dimer in solution initially came from electron diffraction, which indicated a perpendicular arrangement of the rings.[21] More recently, ^{1}H NMR investigations of dipolar coupling in liquid benzene indicate that a T-shaped structure is favored by ca. 0.7 kcal mol^{-1} over a parallel-stacked structure.[22] Spectroscopic investigations[23−25] indicate a T-shaped arrangement in the gas phase with a ring center separation of 4.96 Å (corresponding to a H-to-ring center distance of 2.48 Å). The experimental stabilization enthalpy of the benzene dimer is 1.6 ± 0.2 kcal mol^{-1}.[26]

There has been considerable debate about the precise nature of the weak forces involved in edge-to-face aromatic interactions. However, the more recent theoretical investigations indicate that electrostatic quadrupole interactions largely determine the *geometries* of the benzene dimer, but London dispersion interactions contribute to the stabilization *energies* of the resulting structures.[17,19]

Flexible Organic Molecules

Organic chemists have speculated that attractive interactions might sometimes exist between aromatic residues in organic molecules. For example, in 1983 Nishio et al.[27] suggested that attractive intramolecular interactions between aromatic moieties might be a factor in determining the conformational preference of some flexible acyclic alcohols, ketones, and sulfoxides. However, the nature and geometry of the proposed interaction were not explored.

In 1987, Stoddart et al.[28] identified intramolecular aromatic edge-to-face interactions in collapsed empty cavities of crown ethers. In the crystal structure of a bis(paraphenylene)-25-crown-7 (**5**), the hydroquinol rings



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adopt a nearly orthogonal (85°) edge-tilted-T arrangement with a H-to-centroid distance of 2.71 Å (Table 1, Figure 2). The naphthyl rings in the corresponding bis(1,5-dihydroxynaphthyl)-35-crown-9 (**6**) stack similarly (Table 1). Note that in order to ensure distance normalization, all distances quoted in this Account have been recalculated from the data deposited in the Cambridge Structural

Table 1. Geometry of Inter-ring Interactions Determined from X-ray Data[a]

compd	H- - -centroid (Å)	perp dist H- - -ring plane (Å)	offset (Å)	inter-ring angle (°)
5	2.71	2.69	0.27	85
6	2.70	2.66	0.46	87
7	2.70	2.68	0.39	48
8a	2.66	2.63	0.41	43
8c	2.71	2.68	0.40	46
8d	2.58	2.57	0.19	62
8e	2.77	2.73	0.48	53
8f	2.86	2.84	0.33	34
9	2.49	2.48	0.27	82
10	2.45	2.45	0.07	80
11	2.97	2.84	0.85	57
14	3.36	2.67	2.04	62
16	2.97	2.78	1.03	69
17	2.90	2.80	0.73	90
18	2.94	2.84	0.76	86
20	2.38	2.35	0.38	61
21e (i)	2.69	2.53	0.91	83
21e (ii)	2.77	2.69	0.66	76
21g (i)	2.95	2.65	1.30	82
21g (ii)	3.01	2.81	1.09	89
23a (i)	2.95	2.82	0.84	51
23a (ii)	3.05	2.94	0.82	51
24a (i)	2.77	2.65	0.80	51
24a (ii)	3.05	2.95	0.77	51
29	2.64	2.59	0.54	53

[a] Calculated from the Cambridge Structural Database[29] using C−H distance 1.083 Å.

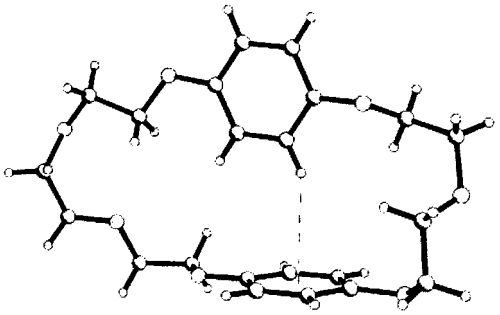
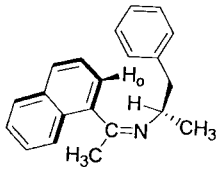


FIGURE 2. Solid-state structure of crown ether **5**.[28]

Database, using the neutron diffraction-based default C−H distance of 1.083 Å.[29]

Jennings et al. appear to have been the first to identify and attempt to quantify an attractive intramolecular edge-to-face interaction in a simple synthetic acyclic organic molecule in both solution and the solid state.[30] The investigation was prompted by the chance observation of an unexpected upfield shift of a naphthyl proton in the ^{1}H NMR spectrum of solutions of imine **7**. An X-ray crystal



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structure of imine **7** (Figure 3) revealed a crowded conformation with the naphthyl and benzyl rings in a face-tilted-T orientation. The angle between the naphthyl and

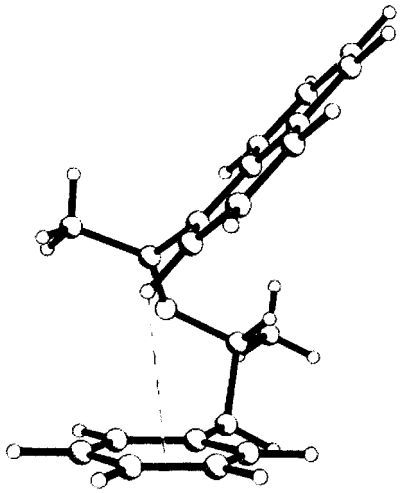

FIGURE 3. Solid-state structure of imine **7**.[30]

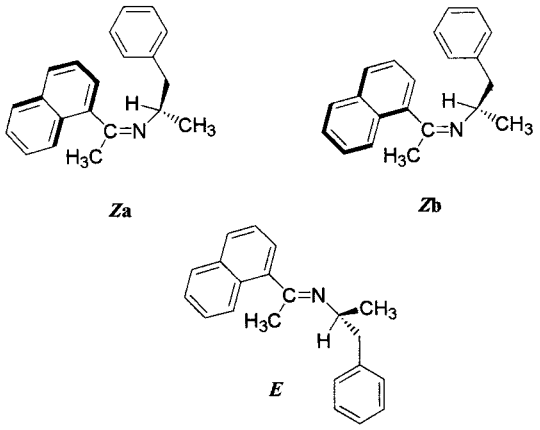

FIGURE 4. Stereoisomers of **7**.

benzyl ring planes was 48°. The edge hydrogen atom on the 1-naphthyl ring (labeled H_o) was projected into the face of the benzylic ring at a close-contact perpendicular distance of 2.68 Å and offset by only 0.39 Å from the benzyl ring center (Table 1).

^{1}H NMR spectra of imine **7** revealed the presence of three stereoisomers in solution due to *E*/*Z* isomerism about the imino bond and, in the *Z*-isomer, slow rotation (atropisomerism) about the naphthyl−imino bond (Figure 4). Dissolution of crystals of **7** in the NMR probe at −50 °C afforded a clean spectrum of the isomer **Za**, exhibiting the anomalous upfield aromatic signal, thus establishing that the crystal structure corresponded to the ***Z*a** form. The unusual signal at δ 5.9 was assigned to the naphthyl β-proton H_o by selective ^{13}C{H^1} decoupling experiments on the imino carbon resonance, and its upfield shift was attributed to the ring current shielding arising from the close edge-to-face association of the naphthyl and benzyl rings.

Since our initial findings we have investigated other flexible acyclic molecules **8** possessing imine, nitrone, and alkene spacer linkages between terminal aryl rings.[31−33] Data for some representative compounds are given in Tables 1 and 2. ^{1}H NMR analyses and X-ray crystal structures indicated the presence of similar crowded geometries in solution and the solid due to the edge-to-face association

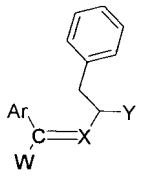

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Table 2. Upfield Aromatic Chemical Shifts in the Major Atropisomer (A) of Selected Imines, Nitrones, and Alkenes[30−33]

compd	Ar	W	X	Y	%A[a]	δH_o[b]
7	1-$C_{10}H_7$	Me	N	Me	62	5.90
8a	1-$C_{10}H_7$	CMe_2OH	N	Ph	70	5.87
8b	2-BrC_6H_4	Me	N	Ph	60	5.65
8c	1-$C_{10}H_7$	Et	N−O	Me	72	5.60
8d	2-$MeOC_6H_4$	Me	N−O	Ph	65	5.73
8e	2-$CF_3C_6H_4$	Me	N−O	H	100[d]	6.18
8f[c]	1-$C_{10}H_7$	Me	N−O	CO_2Me	64	5.38
8g	1-$C_{10}H_7$	Me	CH	Me	55	6.42

[a] In $CDCl_3$ at 20 °C. [b] In CD_2Cl_2 solution at 20 °C. [c] Compound **8f** has a para-nitro substitutent on the benzyl ring. [d] No atropisomers possible.

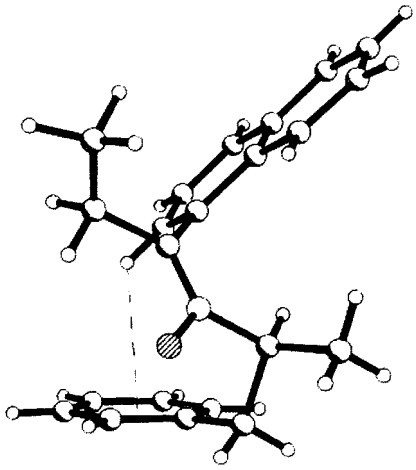
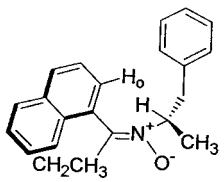
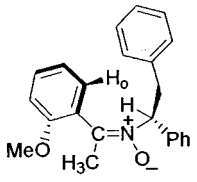


FIGURE 5. Solid-state structure of nitrone **8c**.[31]

of the aryl rings. Thus, the X-ray crystal structures of the major atropisomer of nitrones **8c**−**f** showed that the naphthyl β-hydrogen or the analogous hydrogen at position 6 on the 2-substituted phenyl ring (H_o) was directed over the face of the benzyl ring at a perpendicular distance of 2.57−2.73 Å and offset from the ring center by 0.19−0.48 Å (Table 1, Figures 5 and 6).[31,32]



8c



8d

Due to allylic A(1,3) steric strain, the N-alkyl moiety in these compounds adopts a conformation with the allylic hydrogen atom lying essentially in the imino plane in a cisoid arrangement. The benzylic ring in the major atropisomer ***Z*a** is directed out of the imino plane and on the same face as the ortho hydrogen H_o (Figures 5 and 6) which is shifted upfield (Table 2). In the minor atopisomer ***Z*b**, H_o lies on the opposite face of the imino plane to the benzylic ring and cannot engage in an edge-to-face interaction. However, in the minor atropisomer of the naphthyl compounds (Table 2), the naphthyl B-ring lies on the same face of the imino system as the benzylic ring, and the peri hydrogen is also shifted upfield of the normal aromatic region (but not as far upfield as H_o in the major atropisomer). X-ray crystallographic studies on the minor atropisomer of nitrone **8f** indicate a tilted-T arrangement between the naphthyl peri hydrogen and the phenyl ring with a H-to-ring plane distance of 2.84 Å (Table 1).[33]

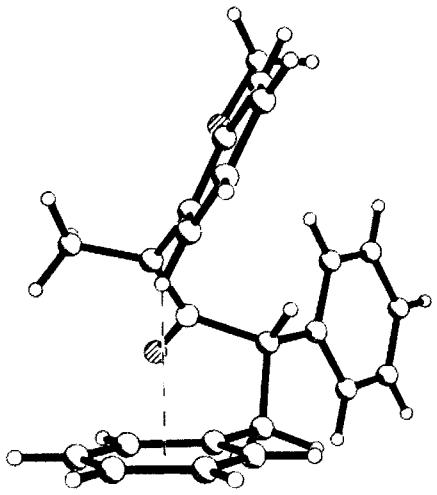
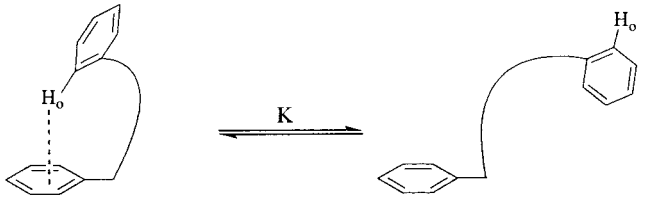


FIGURE 6. Solid-state structure of nitrone **8d.**[32]

In all of the cases investigated, the signal position of H_o was found to be significantly temperature dependent, moving farther upfield as the temperature was lowered. This allowed us to attempt to extract the thermodynamic parameters associated with this phenomenon. The temperature dependence of the H_o signal was rationalized in terms of a fast equilibrium (Scheme 1) between at least two conformational states of the more crowded atropisomer (***Z*a** in the imines and alkenes, ***E*a** in the nitrones).[30,31] One conformer (**I**) approximates to the crowded geometry existing in the solid state, and the other represents a more open unidentified conformer (**II**) (or a time average over of a number of open conformers) which has the aryl rings remote from each other (Scheme 1). The position of equilibrium is temperature dependent, and conformations **I** and **II** interconvert rapidly on the NMR time scale at all accessible temperatures. Thus, the observed chemical shift value (δ_{obs}) for H_o represents a weighted average of the chemical shift values of H_o over all contributing conformers at a particular temperature. Interactive manipulation of the above equations using various input values of $\Delta S°$, $\Delta H°$, δ_I, and δ_{II} enables the chemical shift value of H_o (δ_{calc}) to be estimated as a function of temperature, generating δ_{calc} vs temperature curves. The values of $\Delta S°$ and $\Delta H°$ were then varied to optimize agreement between calculated (δ_{calc}) and experimental (δ_{obs}) plots of the H_o chemical shift vs temperature.

The results for several systems give values of 1.2−1.5 kcal mol^{-1} for the enthalpic stabilization of the crowded

Scheme 1



Conformation **I**

H_o shift: δ_I

Fractional population P_I

Conformation **II**

H_o shift: δ_{II}

Fractional population: $1 - P_I$

$$\text{Observed } H_o \text{ shift } (\delta_{obs}) = P_I\delta_I + (1 - P_I)\delta_{II} \quad (1)$$

$$K = (1 - P_I)/P_I = \exp[(T\Delta S^o - \Delta H^o)/RT] \quad (2)$$

Table 3. Conformational Enthalpy and Entropy Values Derived from ^{1}H NMR Studies[30−33]

compd[a]	solvent	temperature range (°C)	$\Delta H°$ (kcal mol^{-1})	$\Delta S°$ (cal mol^{-1} K^{-1})	$\Delta G°$ [b] (kcal mol^{-1})
7	isooctane	−100 to +95	1.3	2.8	0.49
8b	CD_2Cl_2	−80 to +30	1.2	2.5	0.47
	$C_2D_2Cl_4$	−35 to +110	1.5	2.7	0.71
8e	CD_2Cl_2	−90 to +20	1.4	3.4	0.40
	$C_2D_2Cl_4$	−25 to +130	1.2	3.4	0.20
8f	CD_2Cl_2	−98 to +20	1.2	2.2	0.59
	$C_2D_2Cl_4$	−35 to +130	1.4	2.5	0.72
8g	CD_2Cl_2	−94 to +29	1.2	3.7	0.11

[a] See Table 2 for structures. [b] Calculated at 20 °C.

edge-to-face conformer **I** (Table 3). These estimates of the stabilization enthalpy of conformation **I** agree remarkably well with the best experimental value of 1.6 ± 0.2 kcal mol^{-1} for the stabilization enthalpy of the benzene dimer[26] and with theoretical calculations of the interaction enthalpy of a T-shaped structure (−1.5 to −2.0 kcal mol^{-1}, see benzene dimer section).[17,18] However, other factors such as vicinal interactions may also contribute to the enthalpy difference between conformers **I** and **II**.

These results (Table 3) indicate that entropy factors significantly disfavor the edge-to-face geometry **I**. Indeed at room temperature the $T\Delta S°$ term greatly reduces the free energy difference $\Delta G°$ between the conformations. Variable-temperature studies of other compounds in this series provide similar overall results. These observations are not unexpected since a crowded edge-to-face geometry **I** with restricted torsional mobility would have unfavorable entropy with respect to an open geometry **II**. The important consequence of these results is that the free energy difference $\Delta G°$ probably does not provide a good measure of the *energetic* preference for edge-to-face interactions in solution, and where possible enthalpy and entropy contributions should be evaluated.

In 1993, Grossel et al.[34] reported intramolecular aromatic edge-to-face interactions in *cis*-1,4-dihydro-4-tritylbiphenyls **9** and **10**. X-ray crystallographic investigations showed that the cyclohexadiene ring is almost planar (Figure 7). The isolated aryl ring is orientated parallel to the C_1-C_4 axis of the dihydroaromatic ring, and its ortho hydrogen H_o is projected into the face of one of the trityl phenyl rings at a perpendicular distance of 2.48 Å in **9**

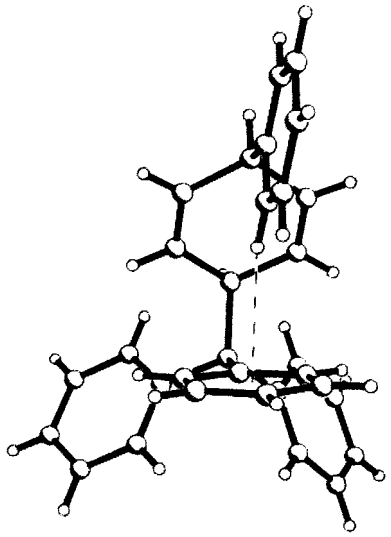
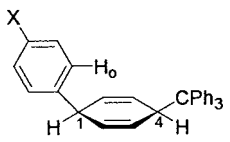


FIGURE 7. Solid-state structure of **9**.[34]

and 2.45 Å in **10** (Table 1). The upfield shift of H_o along with homoallylic $J_{1,4}$ coupling constants typical of hydrogens orientated in a pseudoequatorial position indicates the existence of a sterically crowded geometry in solution. Variable-temperature ^{1}H NMR studies showed a further upfield shift of 0.6 ppm for H_o at −70 °C in CD_2Cl_2.



9 X = H

10 X = Br

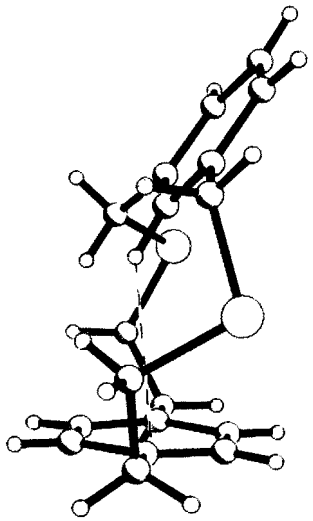
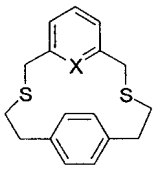


FIGURE 8. Solid-state structure of **11**.[35]

Earlier in the same year, Kim et al.[35] reported that the X-ray crystal structure of the 3,12-dithia[4,4]metaparacyclophane **11** showed the two aryl rings orientated in a face-tilted-T manner with an inter-ring angle of 57° and a perpendicular H−ring plane distance of 2.84 Å (Figure 8, Table 1). However, the interacting hydrogen atom is significantly offset from the ring centroid by 0.85 Å; hence,

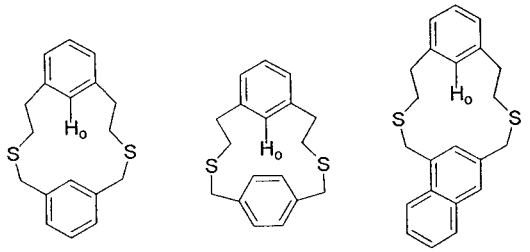
the edge-to-face interaction is probably not optimal. In solution, ^{1}H NMR analysis revealed an unusually high field aromatic signal at δ 6.39 assigned to the interacting proton. The X-ray crystal structures of the two other



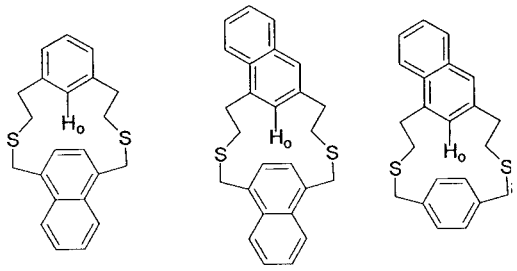
11 X = CH
12 X = C-CH$_3$
13 X = N

cyclophane members of the series (**12** and **13)** showed that the aromatic rings are orientated in an offset face-to-face stacked fashion. A similar T-type interaction is not possible here as the "edge" hydrogen atom is replaced by a methyl group in **12** and by a nitrogen lone pair in **13**.

Gellman et al.[36] investigated other [4,4]thiocyclophanes (**14**−**19**). The crystal structures of the meta,meta cyclophanes **14** and **16** are reported to show a face-tilted-T arrangement with inter-ring angles of 62° and 69°, respectively, whereas the meta,para compounds **17** and **18**



14 **15** **16**



17 **18** **19**

have an offset T geometry with the rings essentially orthogonal. However, we calculate from the deposited crystal data that the "interacting" hydrogen in **14** and **16** is well offset from the ring centroid, by 2.04 and 1.03 Å, respectively (Table 1, Figure 9). Cyclophane **15** adopts a parallel-displaced arrangement (**2**) with an interplanar angle of only 4°.[36] The existence of similar geometries in solution was supported by ^{1}H NMR studies of **14**−**19**, which showed the H_o signal shifted 0.43−1.47 ppm upfield of its position in model compounds devoid of edge-to-face interactions. As was observed in our work,[30,31] the H_o signal moves farther upfield on lowering of the temperature to −78 °C.[36] This suggests a temperature-dependent conformational equilibrium and an increased population of the energetically favored but entropically disfavored

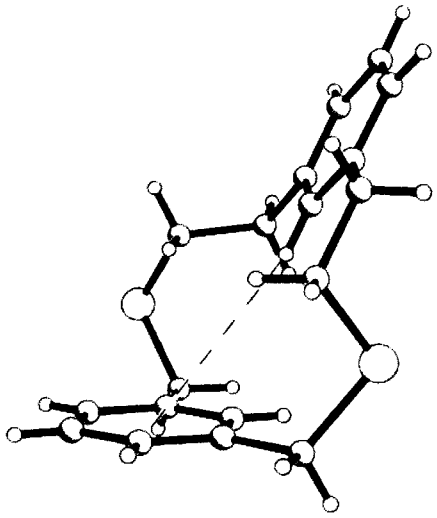


FIGURE 9. Solid-state structure of **14**.[36]

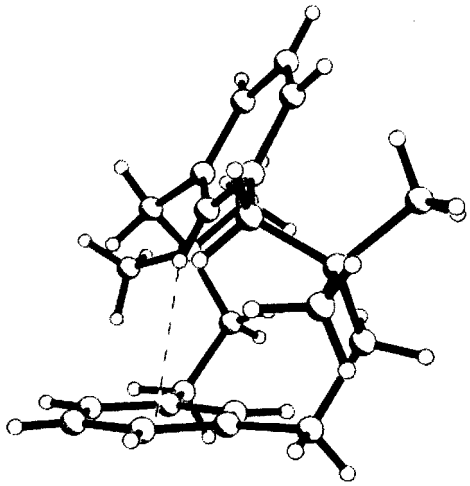
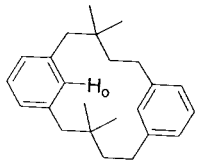


FIGURE 10. Solid-state structure of **20**.[37]

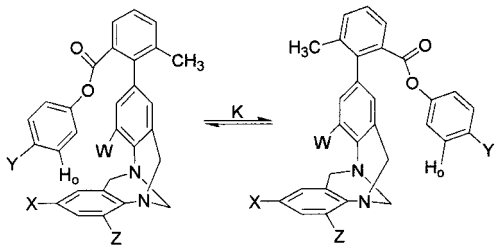
edge-to-face conformer at lower temperatures. Gellman et al.[36] also pointed out that the crystal structure of the [4,4]cyclophane **20** previously reported by Fukazawa et al.[37] (Figure 10) is indicative of an intramolecular face-tilted-T interaction. Our analysis of the published X-ray data[37] for **20** indicates a very short edge-to-face interaction with H_o only 2.35 Å above the face of the second aromatic ring and offset from its centroid by only 0.38 Å (Table 1).



20

More recently, Hong et al.[38] have reported semiempirical and ab initio MO calculations on the conformations of [*n*,*n*]metaparacyclophanes. Classical strain energies govern the conformational preference for $n = 2$ and 3, but attractive aromatic−aromatic interactions are equally important for $n = 4$. An offset parallel geometry is calculated to have the lowest energy for [4,4]metapara-

cyclophanes and their 2,11-dithio derivatives, whereas the tilted-T or T geometries appear to be favored for the 3,-12-dithio[4,4]metaparacyclophanes investigated experimentally by Kim et al.[35]



21(a-f) Y = (a) H, (b) CH_3, (c) OCH_3, (d) CN, (e) NO_2, (f) I, W = Z = H, X = CH_3
21(g) Y = NO_2, W = X = Z = CH_3
22(a-g) X = (a) NO_2, (b) CN, (c) Br, (d) I, (e) CH_3, (f) OH, (g) NH_2, W = Y = Z = H

FIGURE 11. Conformations of dibenzodiazocine esters **21** and **22**.[39,40]

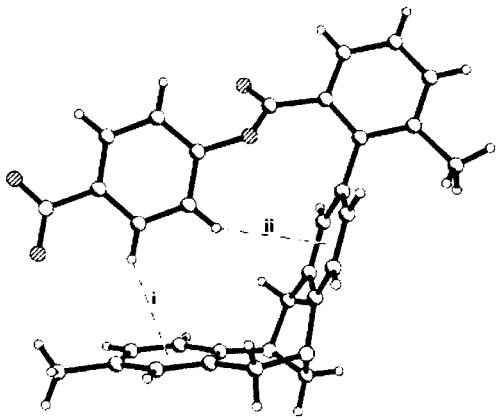
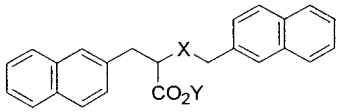


FIGURE 12. Solid-state structure of **21e**.[39]

In 1994, Wilcox and co-workers[39] proposed that intramolecular aryl−aryl interactions determine the preferred conformation of phenylesters **21** and **22** which possess a dibenzodiazocine backbone. Their novel system was described as a "molecular torsion balance" since the two limiting conformations (Figure 11) are separated by a considerable barrier (>18 kcal mol^{-1}) to rotation about the central biaryl bond, making them individually observable by NMR. Evidence for an edge-to-face interaction was provided by the observed upfield shift of the meta phenoxy proton H_o in the favored crowded conformer, and by X-ray diffraction investigations of **21e** (Figure 12, **i**) and **21g**. Both crystal structures adopt the folded geometry with the phenoxy ring in an edge-tilted-T arrangement relative to the proximate dibenzodiazocine ring. The H_o-to-ring plane distances are reasonably short (Table 1), but H_o is significantly offset from the centroid. As noted by Wilcox et al., a second edge-to-face interaction exists in **21e** (Figure 12, **ii**) and **21g** involving the ortho phenoxy proton**,** but this interaction can be present in both rotamers. Integration of the ^{1}H NMR signals provided equilibrium constants and the equilibrium free energies ($\Delta G°$) for the conformational interchange. In all cases, there is a small but significant free energy preference of 0.24−0.65 kcal mol^{-1} for the folded conformation, consistent with an attractive interaction in the latter. The corresponding methyl esters used as a control showed no significant conformational preference.

However, in a subsequent investigation, Wilcox et al.[40] found that the corresponding esters where the phenyl group was replaced by isopropyl surprisingly showed a significant preference ($\Delta G° = -0.34$ to -0.64 kcal mol^{-1}) for the folded conformation. No aryl−aryl interaction is possible in these isopropyl esters. Wilcox et al. suggested that attractive alkyl−aryl (CH-π) interactions may be present in the isopropyl esters where the methyl groups can make close contact with the face of the dibenzodiazocine ring in the folded conformation.[40] Recently, Nakamura and Houk[41] have reported molecular mechanics calculations on the Wilcox torsion balance system. Their results indicate a significant energetic (enthalpic) preference of 1−3 kcal mol^{-1} in favor of the folded conformation for cyclohexyl and *tert*-butyl as well as aryl dibenzodiazocine esters both in the gas phase and in chloroform solution using solvation model calculations. The authors claim that the importance of edge-to-face interactions in this system is brought into question by these results and postulate that the observed preference for the folded conformation could be due to dispersion forces rather than a specific electrostatic edge-to-face aromatic interaction. However, one must be cautious in comparing calculated energetic data with experimental free energy differences ($\Delta G°$) since entropy effects can contribute significantly to the latter.

Gellman et al.[42,43] have investigated the possible role of aryl−aryl interactions in determining the conformation of compounds **23** and **24** which contain a flexible four-atom spacer unit composed of single bonds. Crystal



23 a X = CH_2, Y = H
b X = CH_2, Y = Na

24 a X = S, Y = H
b X = S, Y = Na

structures of the carboxylic acids **23a** and **24a** show that the naphthyl rings adopt a face-tilted-T arrangement involving two neighboring peri hydrogens with an interplanar angle of 51° in both compounds (Figure 13, Table 1). The ^{1}H NMR spectra of these compounds exhibit small upfield shifts of some aromatic signals (−0.1 to −0.3 ppm), especially those associated with peri hydrogens. The small size of these upfield shifts in comparison with those observed in other systems (see above), together with some lack in proton specificity, indicates that the folded conformation observed in the crystal is not dominant in solution. Entropic factors in a system involving relatively free rotation about four single bonds in the linking unit could militate against the dominance of a single associated conformer in solution.

More recently, Gellman et al.[44,45] have synthesized other amide-based model compounds **25**, **26**, and **27**. As a result

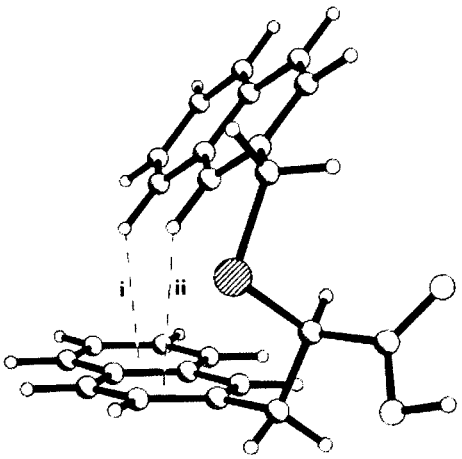
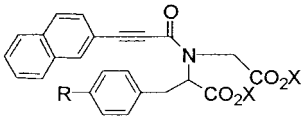
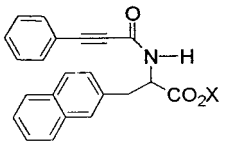


FIGURE 13. Solid-state structure of carboxylic acid **24a**.[43]

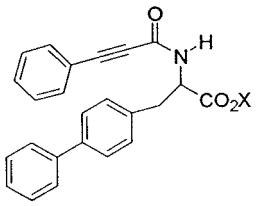
of slow rotation about the amide bond, *E* and *Z* isomers were observable by NMR. Both salts (X = Na) and esters



25 a R = H
b R = CH_3
c R = CH_2CH_3
d R = $CH(CH_3)_2$
e R = C_6H_5
f R = C_6H_{11}
g C_6H_4R = 2-naphthyl



26 a X = Na
b X = CH_3



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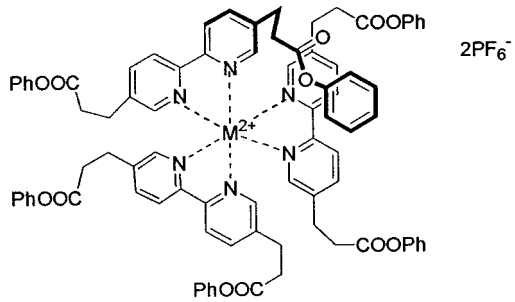
(X = Me) showed a preference for the more crowded *E* isomer in solution ($\Delta G°_{EZ} = -0.1$ to -0.7 kcal mol^{-1}). X-ray crystallographic analysis of the *E* form of two representative esters (**25e** and **25g**) showed that they both adopt folded conformations with close edge-to-face associations. Monte Carlo calculations on these compounds also indicated that the most highly populated conformer had the naphthyl and aryl moieties "clustered". An increase in thermodynamic preference for the *E* isomer of the sodium salts **25a**−**g** (X = Na) in deuterium oxide with increasing bulk of the para substituents (R) was attributed to a hydrophobic effect in aqueous solution enhancing clustering. Hunter et al.[46] have reported NMR evidence for an interaction between the edge of the pyridine ring and the face of the ester phenyl ring in bipyridyl complexes **28**.



28 (a) M = Fe
28 (b) M = Ru

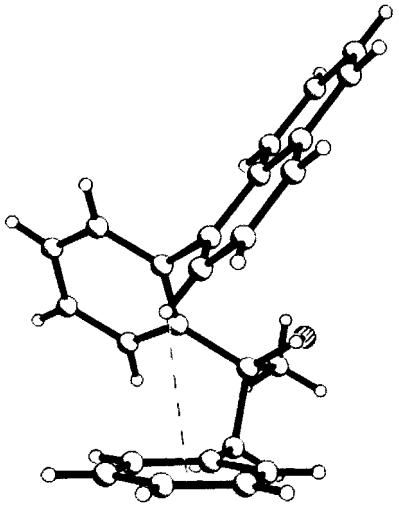
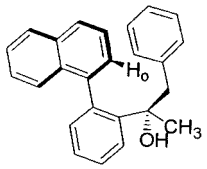


FIGURE 14. Solid-state structure of **29**.[32]

We have recently obtained evidence for intramolecular edge-to-face interactions between the 1-naphthyl and pendant phenyl groups in biaryl alcohol **29**.[32] This com-



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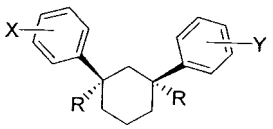
pound exists in solution as a mixture of two atropisomers due to restricted rotation about the biphenyl bond combined with the stereogenic benzylic center. The ^{1}H NMR spectrum of the more abundant isomer in deuteriochloroform solution exhibited an unusually high field aromatic doublet signal at δ 6.19 attributed to the naphthyl proton H_o. The X-ray crystal structure (Figure 14) shows a face-tilted-T orientation of the naphthyl and phenyl rings with H_o lying 2.59 Å vertically above the face of the benzyl ring (Table 1).

Lemieux et al.[47] have reported a semiempirical AM1 molecular orbital investigation of intramolecular aryl−aryl interaction using *cis*-1,3-diphenylcyclohexanes (**30**) as a model system. Calculations on the diaxial conformer indicated two favored geometries, one with the phenyl rings stacked face-to-face in an off-parallel-stacked arrangement and the other ca. 0.3 kcal mol^{-1} higher in energy with the rings in a distorted edge-tilted-T arrangement. However, as noted by these authors, the geometry of the edge-tilted-T structure is probably not optimized

as the interacting hydrogen lies vertically above the ipso carbon rather than above the ring center, due to geometric



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constraints imposed by the short three-carbon spacer moiety. Nevertheless, these calculations indicate that the energy of the edge-tilted-T conformation is lowered when electron-withdrawing substituents are present in the phenyl ring interacting in edge fashion. This would be consistent with a simple electrostatic model involving a somewhat electropositive ortho hydrogen interacting favorably with the face of the adjacent π-cloud. However, a more sophisticated model should consider the quadrupolar electrostatic interactions between the rings and the possible role of dispersion effects. Similarly, the absence of correlation between the calculated relative energy of the face-to-face stacked axial conformer and the HOMO−LUMO energy gap is also consistent with a dominant electrostatic interaction. These theoretical results are consistent with earlier NMR work on face-to-face aromatic interactions in 1,8-di-*o*-tolylnaphthalenes which indicate the importance of electrostatic quadrupole moments.[48,49]

Conclusion and Outlook

There are now sufficient examples to establish that weak attractive intramolecular interactions between aromatic rings can play a significant role in determining the preferred conformation of flexible organic molecules. As awareness of these interactions increases, it is likely that more examples will come to light. Evidence will come from X-ray crystal structures or in solution by unexpected upfield shifts of selected aromatic protons in ^{1}H NMR spectra. The latter effects are more likely to be detected at low temperatures as entropy factors militate against associative interactions in solution at ambient temperature or above. Examples of the intermolecular counterpart of this effect will also continue to be encountered in molecular packing in crystals and in host−guest interactions and other molecular recognition situations.

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