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Theoretical Study of the Conformations and Strain Energies of [*n*,*n*]Metaparacyclophanes: Indication of Stable Edge-to-Face and Displaced Face-to-Face Conformers for *n* = 4

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We have studied [*n*,*n*]metaparacyclophanes—model compounds exhibiting edge-to-face and displaced stacked aromatic−aromatic interactions—using semiempirical calculations for $n = 2-5$ and ab initio calculations for $n = 2-4$. For $n = 2$ and 3, the strain energies govern the conformational preference, while for $n = 4$ and 5 the aromatic−aromatic and strain energies are equally important. The 3,12-dithio[4,4]metaparacyclophanes exhibit edge-to-face aromatic−aromatic intereactions, while the [4,4]metaparacyclophanes and 2,11-dithio[4,4]metaparacyclophanes exhibit displaced stacked aromatic−aromatic interactions.

Introduction

Intermolecular interactions pervade virtually all areas of science. The question of how these weak interactions determine the physical and chemical properties of various systems is an area of intense experimental and theoretical activity. Thus, it is of particular interest to examine the quantitative contributions of different types of interactions when they coexist in a system. In this context, various types of intermolecular interactions involving aromatic systems, viz., aromatic−aromatic,[1,2] cation−π,[3−6] π−H,[7,8] π−p_z[9] have been investigated in the recent past. Of these, the aromatic−aromatic interaction, which is albeit weak (~2 kcal/mol), has received a lot of attention because of its stellar role in biomolecular recognition. These interactions are also known to play a significant role in stabilization of protein tertiary structures and enzyme−substrate complexes.[10]

The aromatic−aromatic nonbonded interactions can be categorized into face-to-face or edge-to-face interactions. Of these, the latter are energetically favored by a small extent[11−13] and, hence, found more frequently in biological systems.[1a] Various theoretical[11,12] and experimental[13,14] studies have been carried out on the benzene dimer to investigate the aromatic−aromatic interactions. Recently, the displaced face-to-face interaction was found to be as stable as the edge-to-face interaction, while the face-to-face interaction is known to be less stable.[12] Therefore, the aromatic−aromatic nonbonded interaction should now be categorized into two competing edge-to-face and displaced face-to-face (or displaced stacked) interactions.

For the better study of aromatic−aromatic interactions in organic and biomolecular systems, it is a prerequisite to design model compounds of the aromatic−aromatic

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interactions and elucidate the interactions governing the conformational stability. There have been few model compounds for the edge-to-face interactions and the displaced-stacked interactions. For the study of the intramolecular ring interactions, Kim and co-workers[15]studied [*n*,*n*]-cyclophane systems and synthesized 3,12-dithio[4,4]-metaparacyclophanes, which were suggested to be viable model compounds for the edge-to-face interactions. Gellman and co-workers[16] reported thiocyclophanes that would promote possibly edge-to-face aromatic−aromatic interactions. The crystal structures of the above thiocyclophanes are in favor of the edge-to-face aromatic−aromatic interactions. However, a few of them do not have the edge-to-face conformation but favor the face-to-face conformation. For example, chemical shifts in proton NMR show an indication to favor the edge-to-face conformation even in the case when the crystals give the face-to-face conformation. In certain cases, the packing effect in crystallization can be more important than weak aromatic−aromatic interactions.

Therefore, to have model systems for these aromatic−aromatic interactions, it is of importance to find the quantitative comparison of the molecular strain energy with the energy gain of the edge-to-face or displaced stacked aromatic−aromatic interactions. Although the strain energy can be estimated using empirical potential functions,[17] the evaluation of strain energy by semiempirical or ab initio calculations is tenuous. The empirical results are not reliable enough to compare the small strain energy with the small aromatic−aromatic interaction energy. Here, we investigate [*n*,*n*]metaparacyclophanes and their derivatives as possible model compounds of the edge-to-face and displaced stacked interactions. Thus, to investigate the competition of strain energy and the aromatic−aromatic interactions in these compounds in a more accurate way, we have devised a scheme to calculate the strain energy using semiempirical calculations.

Most of the cyclophanes studied so far are the cases of $n = 2$, for which the side chains are not long enough to release strain in the molecules. Both [2,2]parapara- and [2,2]metaparacyclophanes have stacked phenyl ring conformations with highly distorted rings due to the strain.[18] Thus, to have the model compounds with the edge-to-face and displaced face-to-face interactions, it needs to release strain in cyclophane systems. Thus, we investigated many cyclophane systems that are expected to have different strains: [*n*,*n*]metaparacyclophanes ($n = 2-4$), 2,11-dithio[4,4]metaparacyclophanes, and 3,12-dithio[4,4]-metaparacyclophanes.

Calculation Methods

The initial geometry optimizations for various conformers of [*n*,*n*]metaparacyclophanes were carried out with semiempirical PM3 calculations[20] using a MOPAC suite of programs.[21] Using ab initio calculations, we obtained more accurate energies of stable conformers using a suite of Gaussian 94 programs.[22] Hartree−Fock (HF) calculations were carried out, and the electron correlation effects were included with the second-order Moller−Plesset perturbation theory (MP2) using frozen core orbitals. We also carried out density functional theory (DFT) calculations using nonlocal density function of Becke's 3 parameter employing the Lee−Yang−Parr functional (B3LYP),[23] which is known to be one of the most reliable gradient-correction methods. For all ab initio calculations (HF, MP2, and the DFT calculations), the 6-31G* basis set was used. All the geometries were optimized at each calculational level except for the MP2 case, in which the HF (or DFT) optimized geometries were used. Since these MP2 results are similar to the DFT (B3LYP/6-31G*) results, our further discussion will be based mostly on the DFT results (which has the corresponding optimized geometries) as well as MP2 results.

To study the conformational changes of [*n*,*n*]metaparacyclophanes, the intrinsic reaction paths have been searched from the transition states. For $n = 2$ and 3, the intrinsic paths from the transition states to the minima were confirmed. The potential surface of the very flexible conformer of $n = 4$ was investigated from the scan of torsional side angles. After investigating the potential surfaces, for $n = 2$ and 3, we selected the T-shaped conformer of C_2 symmetry and the stacked conformer of C_s symmetry, which show the edge-to-face and displaced stacked interactions, respectively. We also investigated 3,12-dithio[4,4]metaparacyclophanes and 2,11-dithio[4,4]metaparacyclophanes in a similar way.

Results

The PM3, HF, MP2, and DFT results of [*n*,*n*]metaparacyclophanes ($n = 2-4$) are listed in Table 1, and they show important structural parameters of the C_2 and C_s structures and energies of the C_2 conformers relative to the C_s conformers. The structural parameters are defined in Figure 1, and the optimized structures are shown in Figure 2.

The angle θ indicates whether the interphenyl interactions are the edge-to-face or the displaced face-to-face. For all the C_2 conformers, the interphenyl angles are 90°. The *p*-phenyl ring distortion angle (ϕ) of C_2 conformers decreases drastically from ~35° ($n = 2$) to ~7° ($n = 4$), indicating that the strain energies of side chains have been drastically reduced for $n = 4$. The distance between two benzene centroids ($d_{\mathrm{R-R}}$) increases up to ~5.5 Å for $n = 4$, which is reported to be near the optimal distance for the edge-to-face interactions by both theory (5.5 Å)[12] and experiment (5.5 Å).[24] For $n = 5$, the distance also seems to be ~5.5 Å and the angle ϕ of a low-lying energy conformer becomes −3°. It is thus expected that the conformers of $n = 4$ are most favorable for cyclophanes to give edge-to-face interactions.

According to the PM3 results, the stacked C_s conformers are more stable than the T-shaped C_2 or C_s conformers for all cases of $n = 2-4$. For $n = 2$ and 3, the C_s conformers have the minimum energy structures and the C_2 conformers are the transition-state structure, while for $n = 4$, both C_s and C_2 conformers are the minimum energy structures.[25]

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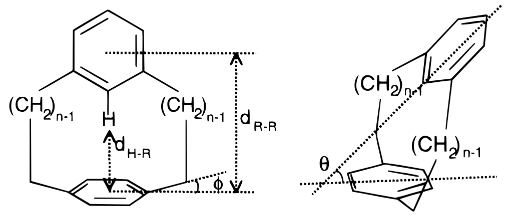
Table 1. Energies and Structures of [*n*,*n*]Metaparacyclophanes and Dithio[4,4]metaparacyclophanes[a]

	[*n*,*n*]metaparacyclophanes							dithio[4,4]metaparacyclophanes					
	$n = 2$		$n = 3$		$n = 4$			3,12-dithio[4,4]-			2,11-dithio[4,4]-		
symmetry	C_2 e−f	C_s d−s	C_2 e−f	C_s d−s	C_2 e−f	$C_s{}^T$ e−f	$C_s{}^S$ d−s	C_2 e−f	$C_s{}^T$ e−f	$C_s{}^S$ f−f	C_2 e−f	$C_s{}^T$ e−f	$C_s{}^S$ d−s
d_{R-R}	4.1	3.4	4.5	3.9	5.5	5.3	4.1	5.0	5.7	4.4	5.4	5.7	4.0
d_{H-R}	1.7	2.8	2.1	2.8	3.0	3.3	4.2	2.4	3.4	4.8	2.82	3.6	3.8
θ	90.0	18.6	90.0	33.2	90.0	55.7	1.8	90.0	45.6	20.0	90.0	43.1	0.0
ϕ	34.8	28.9	16.6	9.6	7.2	7.3	0.8	2.9	1.4	5.3	1.1	1.9	0.3
$\Delta\phi$	7.1	0^*	3.6	0^*	6.3	6.5	0^*	1.5	0^*	3.9	0.8	1.6	0^*
Δd_{R-R}	−1.4	−2.1	−1.0	−1.6	0.0	−0.2	−1.4	−0.5	0.2	−1.1	−0.1	0.2	−1.5
ΔE_{PM3}	21.6	0^*	3.5	0^*	1.7	1.1	0^*	0.7	0^*	0.1	0.4	0.2	0^*
ΔE_{HF}	22.5	0^*	7.0	0^*	6.9	4.7	0^*	0.6	0^*	4.3	2.4	3.7	0^*
ΔE_{MP2}	22.6	0^*	6.8	0^*	7.1	5.3	0^*	0^* (4.4)	0.4 (0^*)	4.2	0.2	0.5	0^*
ΔE_{DFT}	19.4	0^*	6.0	0^*	6.4	3.9	0^*	3.9	0^*	4.6	0.6	2.0	0^*
ΔE_{EXP}	20.8[17,25]	0^*	8.3[19]	0^*									
$E_{strain}{}^{PM3}$	44.0	22.4	8.9	5.4	3.4	2.5	1.4	4.7	-0.3^*	1.4	3.9	3.5	3.0
$\Delta E_{strain}{}^{PM3}$	21.6	0^*	3.5	0^*	2.0	1.1	0^*	4.4	0^*	1.1	0.9	0.5	0^*
$\Delta E_{strain}{}^{MM3}$	23.0	0^*	10.9	0^*	7.0	5.3	0^*	7.0	5.2	0^*	5.8	3.8	0^*

[a] e−f, d−f, and f−f donote edge-to-face, displaced-stacked, and face-to-face conformations, respectively. d_{R-R} is the distance between two benzene centroids. d_{H-R} is the distance between hydrogen at the 8 position and the *p*-benzene centroid. θ is the angle between two benzene rings; ϕ is the angle representing the distortion of the *p*-benzene ring. The structural parameters are optimized values at the DFT (B3LYP)/6-31G* level. ΔE_{HF}, ΔE_{MP2}, and ΔE_{DFT} are the HF, MP2, and DFT predicted values based on the 6-31G* basis set. ΔE_{PM3}, ΔE_{HF}, and ΔE_{DFT} were obtained at the optimized geometries at each calculational level, while ΔE_{MP2} was obtained at the HF-(or DFT-)-optimized geometries. Notation ΔX ($X = \phi$ and E) is used to denote the relative value with respect to each most stable conformer (*). Δd_{R-R} is the relative value with respect to the optimal edge-to-face distance between two benzene centroids (5.5 Å). Energies are in kcal/mol; distances in angstroms; angles in degrees. The strain energy differences calculated by the scheme of the MM3 method ($\Delta E_{strain}{}^{MM3}$) are larger than those of PM3 ($\Delta E_{strain}{}^{PM3}$). Superscript T denotes the T-shaped and superscript S the stacked conformation.



(a) **(b)**

Figure 1. Structural parameters of [*n*,*n*]metaparacyclophanes: (a) front view and (b) side view.

Comparing the DFT-optimized energies of the T-shaped and the stacked conformations, the energy difference is ~20 kcal/mol for $n = 2$ and ~6 kcal/mol for $n = 3$. For $n = 4$, the tilted C_s conformer ($C_s{}^T$) is ~4 kcal/mol less stable than the stacked C_s conformer ($C_s{}^S$). Intrinsic reaction paths starting from the transition-state conformers (C_2) of $n = 2$ and 3 show that the C_2 conformers are the transition states.[19] This is in good agreement with previous experiments.[2]

For $n = 4$, the strain is very small, so the conformational change is highly flexible. Thus, we examined the possibility of any other stable conformers of $n = 4$ by constructing the two-dimensional energy contour map, where we found that the conformational changes from C_2 to $C_s{}^S$ conformers depend on their paths. The PM3 energy contour map with respect to the scanning parameters (α and β) is shown in Figure 3. The counterclockwise scanning of the dihedral angle α gives a tilted conformer ($C_s{}^T$), but the clockwise scanning results in another conformer ($C_s{}^S$), which is displaced-stacked structure. The energies of C_2 and $C_s{}^T$ conformers are similar, but the energy of the $C_s{}^S$ conformer is lower by ~2 kcal/mol. The energy barrier for the conformational change from C_2 to $C_s{}^S$ is ~5 kcal/mol as shown in Figure 3.

The predicted activation barrier for the conformational change from C_2 to C_s (i.e., benzene ring flipping) for [2,2]-metaparacyclophane is ~20 kcal/mol, which is in good agreement with the NMR experimental value of 20.8 kcal/mol.[19,26] The activation barrier is ~7 kcal/mol for $n = 3$ and the predicted value from NMR experiment is 8.3 kcal/mol.[19]

The aromatic−aromatic interactions are very weak with little variation, while the strain energies show very large variation as the chain length varies. To find model compounds showing the edge-to-face interaction, we investigate the strain energy with respect to the side chain length. Although, for the cyclophane systems, the definition of strain energy and the method of calculation are not clear yet, we have devised a useful approximate method to calculate the ring strain energies from semiempirical and ab initio calculations[27,28] for the cyclophane system, as illustrated in Figure 4. However, in this case, the strain energy may include the aromatic−aromatic interaction energies. Since the strain energy is dominant in most cases, it will be simply denoted as strain energy in this paper. The dissociation of the C−C bond in [*n*,*n*]-metaparacyclophane is accompanied by the C−C bonding energy loss and the strain energy release. Therefore, to

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(28) The unstrained counterpart may include a small strain energy including the steric repulsion between two benzene rings. However, it can be considered nearly unstrained. The strain energy discussed here is actually the energy difference between the strained systems and the reference systems (i.e., nearly unstrained system). In order for the scheme to be useful, the following assumptions have been made. First, the linear counterparts do not have high strain energy compared to the cyclic counterparts. Since we are interested in the additional strain energy accompanying cyclization, we disregard the small strain energy for linear counterparts. Second, the minor modification of the system (the addition of two C−H bonds) should not change the heat of formation. This assumption is satisfied in the present system, because the reaction site is five bonds apart from the dissociation site. For the unstrained counterparts, we simply break the C−C bond of the side chains and let them release the strain energy during optimization.

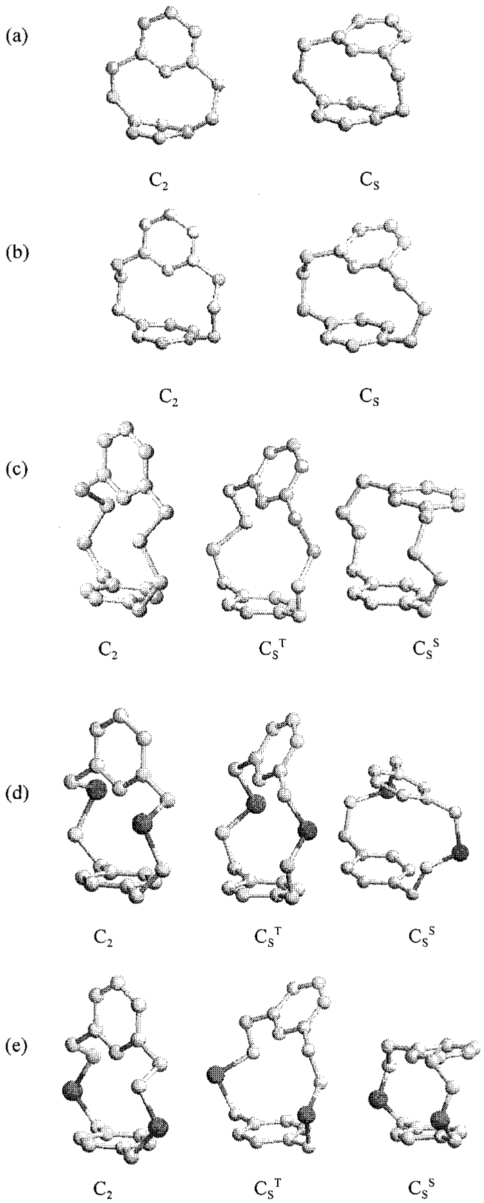
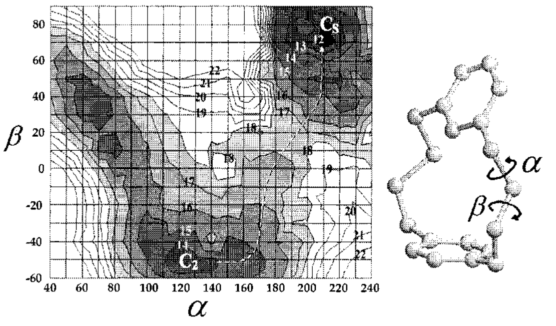


Figure 2. Structures of (a) [2,2]-, (b) [3,3]-, (c) [4,4]-, (d) 3,12-dithio[4,4]-, and (e) 2,11-dithio[4,4]metaparacyclophanes. All the hydrogens are not shown. Superscripts T/S in C_S^T/C_S^S denote T-shaped/stacked conformers.



(a) (b)

Figure 3. (a) PM3 energy contour map of [4,4]metaparacyclophane for the given angles of α and *β* (in degrees). The arrow represents the transition pathway for the conformational change from C_2 to C_s^S. (b) Schematic views of the parameters (α and *β*) scanned anticlockwise and clockwise along the C−C bonds, respectively. Angle 0°/180° indicates the cis/trans form.

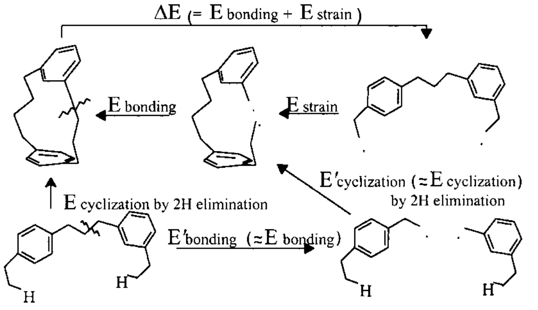


Figure 4. Estimation of the strain energies of [4,4]metaparacyclophane.

obtain only the strain energy, we must remove the C−C bonding energy from the dissociation of the cyclophane. For this reason, first, we break the second C−C bond of the side chain, and let it release the strain energy during the MM3 structure optimization.[29] Then, we optimize the result by PM3 calculation, to obtain the energy of unstrained radical one. Second, we attach two hydrogens on each terminal carbon and then break it into two radical fragments in order to find the unconstrained C−C bond dissociation energy. In this case, the two fragments are made by breaking another C−C bond of the counter side chain that has no strain. Then, the second C−C bond dissociation energy of the unconstrained one is almost equal to the bond energy loss in the first C−C bond dissociation of the cyclophanes (without the strain energy). As a result, the energy difference in two dissociation schemes is simply regarded as strain energy. The strain energies based on the above scheme are listed in the lower part of Table 1.

The strain energy is very large for $n = 2$, while it is very small for $n = 4$. It should be noted that, for $n = 2$ and 3, the conformational stability favoring the C_s conformers is mainly due to the strain energies because the aromatic−aromatic interaction energies are much smaller. These strain energies are responsible for the activation barriers between two same C_s conformers. For $n = 4$, the difference in strain energy between C_s^T and C_s^S is only ∼1 kcal/mol, so that the strains compete with the aromatic−aromatic interaction energies (∼2 kcal/mol).[10] Thus, the relative conformational stability for $n = 4$ is governed by the aromatic−aromatic interactions along with the strain energies. The typical displaced-stacked C_s^S conformer is found to be more stable than the edge-to-face C_s^T conformer. Thus, C_s^S conformer can be considered as a model compound for displaced-stacked interaction.

The same approach has been applied to thiocyclophanes, since a sulfur atom may behave like a methylene group (−CH_2) in cyclophanes in the aspect of strain. The optimized structures of 3,12-dithio[4,4]metaparacyclophane and 2,11-dithio[4,4]metaparacyclophane are in a good agreement with their crystal structures.[15,16] In the case of 3,12-dithio[4,4]metaparacyclophanes, the most stable structure is slightly distorted from the T-shaped C_s form, which has negligible strain energy. The strain energy of T-shaped 3,12-dithio[4,4]metaparacyclophane is −0.3 kcal/mol. This negative value indicates that the geometry is stabilized by the aromatic−aromatic interaction. Thus, the edge-to-face interaction can play a dominant role in

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(29) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H.; Molecular Mechanics. The MM3 Force Field for hydrocarbons I, II, and III. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

this configuration. The lowest energy of 2,11-dithio[4,4]-metaparacyclophane is found in the displaced-stacked conformation. Thus, in this case, though the strain energy is small but still slightly larger than the aromatic−aromatic interaction energy, the relative strain energies between different conformers are the smallest (∼1 kcal/mol). Therefore, the aromatic−aromatic interaction plays a significant role in determining the configuration, so that the displaced-stacked conformer (C_s^S) is the most stable conformer, competing with the edge-to-face conformer (C_2).

Our results support that [4,4]metaparacyclophane (C_s^S), 3,12-dithio[4,4]metaparacyclophane (C_s^T), and 2,-11-dithio[4,4]metaparanaphthalenophane (C_s^S) are indeed model compounds of the aromatic−aromatic interactions with the interphenyl angles of 2°, 46°, and 0° (and also 90°), respectively. When an N atom in 3,12-dithio-[4,4]metaparacyclophane is substituted for the −CH group involved in aromatic−aromatic interactions, the conformation changed to a stacked form in our calculations because there is no more effective edge-to-face interaction stabilizing the T-shaped form, as confirmed by its crystal structure.[15] Thus, the 3,12-dithio[4,4]-metaparacyclophane that was synthesized by Kim and co-workers[15] can be considered as a model compound for the edge-to-face interaction. The [4,4]metaparacyclophane is predicted to be a model compound of the displaced-stacked interation with an interphenyl angle of ∼2° (C_s^S). The 2,11-dithio[4,4]metaparacyclophane that was synthesized by Gellman and co-workers[16] is a model compound of the displaced-stacked interaction (C_s^S, $\theta = 0°$), while the structure also favors the edge-to-face interaction (C_2, $\theta = 90°$). Thus, in this compound, the orientation of the interphenyl angle (0° or 90°) is determined by the molecular environment effect, so that it would be a useful model compound for the investigation of aromatic−aromatic interactions.

Concluding Remarks

PM3, HF, MP2, and DFT calculations were performed to investigate the conformational stability of [*n*,*n*]metaparacyclophanes. We devised a scheme to calculate the strain energies of the cyclophane systems. For $n = 2$ and 3, the strain energies govern the conformational stability and, hence, lead to face-to-face structures. For $n = 4$, the aromatic−aromatic interaction energy is of comparable magnitude to the strain energy, and hence, both of them determine the stability of the structures. The cyclophane system for $n = 4$ has three stable conformers with C_2, T-shaped C_s, and displaced-stacked C_s^S symmetries. The calculations of the energies and the geometries of dithio-[*n*,*n*]metaparacyclophanes show that the 3,12-dithio[4,4]-metaparacyclophanes designed by Kim and co-workers[15] are the first edge-to-face interaction model compounds possessing small strains. The substitution of the carbon at the edge position with a nitrogen results in the stacked crystal structure without the edge-to-face interaction, which strongly supports the assertion that the egde-to-face interaction is an important factor in sustaining the T-shaped structure. It should be noted that model compounds for edge-to-face interactions have also recently been designed by the groups of Wilcox,[1c] Hunter,[1d] and Gellman.[16] The 2,11-dithio[4,4]metaparacyclophane designed by Gellman and co-workers[16] is found to be the first model compound of the displaced stacked interactions, while it also favors the edge-to-face interactions. Additionally, the [4,4]metaparacyclophanes are expected to be good model compounds of the displaced stacked interactions.

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