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AROMATIC-AROMATIC RING INTERACTIONS TESTED IN CYCLOPHANES

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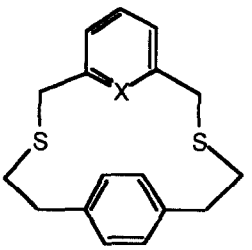
Abstract : The through-space aromatic-aromatic ring interactions which are reported to play an important role in the protein folding and enzyme substrate complexing were examined using *torsional strain-free* cyclophanes, i.e., 3,12-dithia[4,4]metaparacyclophanes as model compounds.

It is well known that weak bondings such as hydrophobic interactions play an important role in biological systems,[1] but their exact nature at the molecular level has not yet been fully established and remains the subject of intensive research. Recently, Burley and Petsko reported the existence of energetically favorable non-bonded interactions between aromatic side chains in crystalline proteins, and proposed that these intermolecular aromatic-aromatic ring interactions may contribute significantly to the stabilization of protein tertiary structures.[2] Singh and Thornton,[3] and Gould et al.[4] made similar observations. Such interactions were also reported to be present in X-ray crystal structures of non-protein compounds.[5-8] Several theoretical treatments on the subject have appeared.[9] We thought that *torsional strain-free* cyclophanes with a certain aromatic-aromatic ring distance would serve as good model for testing and studying such through-space interactions between aromatic rings. That has, indeed, proven to be the case, and we herein wish to report the X-ray crystal structure analyses of these model cyclophanes. To our knowledge, these are the first examples in which the effect of the non-bonded aromatic-

aromatic ring interactions is examined using simple model compounds.



1 : X=CH
2 : X=C-CH_3
3 : X=N⬭

3,12-Dithia[4,4]metaparacyclophanes (**1-3**) were chosen for the present study because they are expectedly free from torsional strain.[10] The X-ray crystal structure[11] of **1**[12] reveals that the two aromatic rings are oriented in a tilted geometry[13,14] with a dihedral angle of 56.8° (Fig. 1). The C10-H is shown to be located not directly above the center of the bottom ring but rather over the C19-C20 bond with the distance of 3.14 Å, which is in agreement with the prediction made by Gould et al.[4] The centroid to centroid distance is found to be 4.96 Å. This result is congruous with the observations made with crystalline proteins.[2,3,4] The NMR spectrum of **1** showed the C10-H resonance signal at 6.39 ppm. The upfield shift of the C10-H signal compared with the signals of other aromatic protons of **1** (6.88(s, 4H), 6.92(d, 2H), 7.07(t, 1H)) indicates that the C10-H is shielded by the anisotropic ring current of the bottom ring as expected from the observed crystalline geometry.

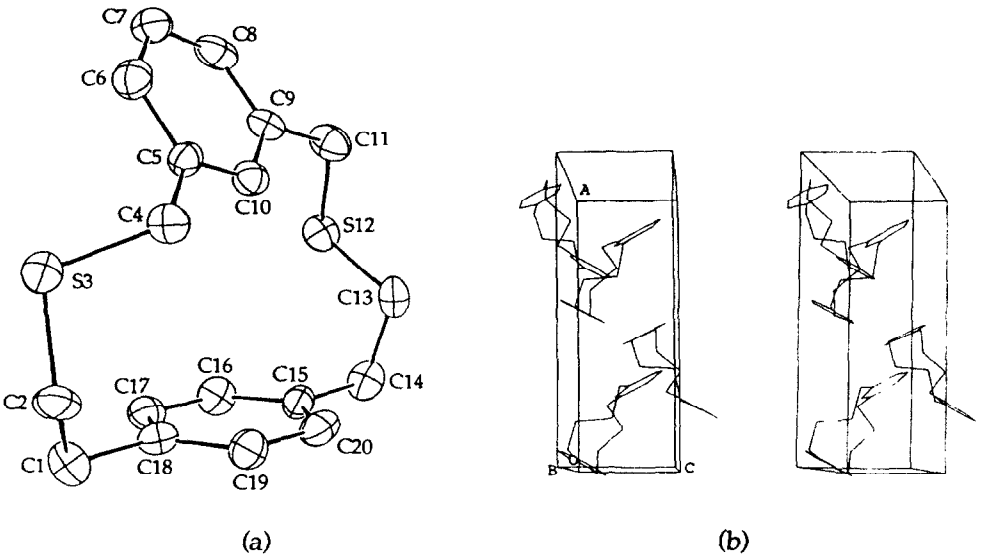


Figure 1. An ORTEP drawing of **1** (a) and its crystal packing diagram of the unit cell (b).

In comparison, the aromatic rings of **2**[15] are situated in an offset face-to-face stacking geometry with the interplanar separation distance of 4.08 Å and the displacement distance of 1.05 Å (Fig. 2).[11] The NMR signal of both protons at the positions of C16 and C17 are shifted upfield, appearing at 6.48 ppm as a singlet. Apparently, the two protons are shielded by the ring current of the upper ring.

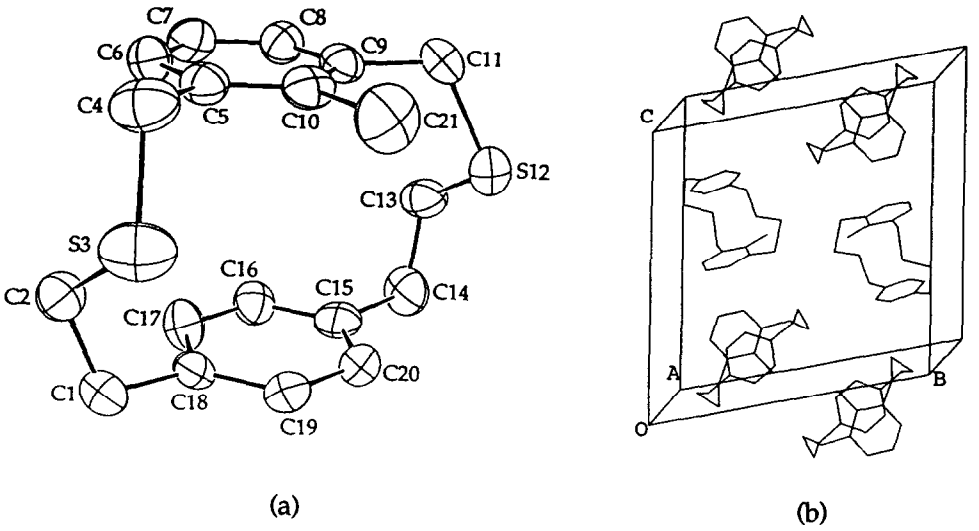


Figure 2. An ORTEP drawing of one of the two crystallographically independent molecules of **2** found in the unit cell (a) and the packing diagram of the unit cell (b). The dihedral angle and the interplanar distance of the two phenyl rings are 1° and 4.08 Å, respectively. The structure of the other molecule reveals the dihedral angle of 11.7° and interplanar distance of 3.64 Å.

It is noticeable that in the case of **3**,[16] the pyridine ring takes a parallel conformation to the benzene ring with the lateral displacement of 1.46 Å (Fig. 3).[11] The distance between the two ring centers is found to be 3.71 Å. It is somewhat surprising to see that all four aromatic protons of the bottom ring show resonance signals at 6.93 ppm, but this may be envisioned on the basis of the fast lateral movements of both rings as a result of the electrostatic repulsive interaction which operates between them.

The X-ray crystal structure analyses and the NMR spectral data of the three cyclophanes strongly suggest that there exist through-space interactions between the two aromatic rings of these compounds.[17] The tilted conformation of the phenyl rings in **1** is apparently the result of the electrostatic attractive interaction between the δ(+)-H at the 10 position and the π-electron cloud of the other ring.[2b,9a] This type of conformation corresponds to the tilted geometry of aromatic rings which is most commonly observed in crystalline proteins.[2,3,4] On the other hand, in the case of **3** where there is present no δ(+)-H

but instead a pair of electrons, a repulsive interaction is in operation, leading to the slipped face-to-face geometry. The geometry has been predicted by the recently proposed model of Hunter and Sanders.[9d] In the case of **2**, the tilted geometry becomes impossible because of the C10-CH_3 group, and thus the slipped face-to-face geometry results. This type of conformation is also commonly observed in crystalline proteins.

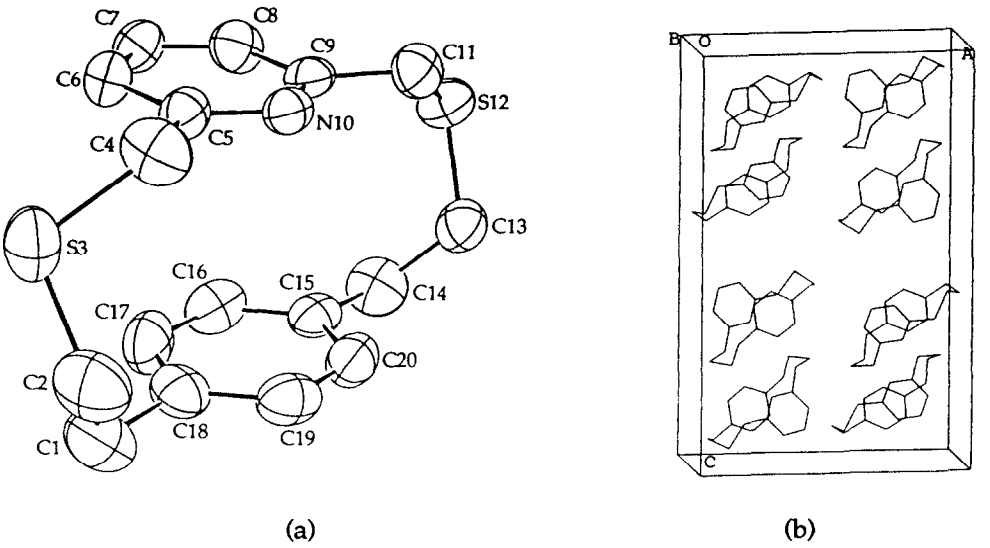


Figure 3. An ORTEP drawing of one of the two crystallographically independent molecules of **3** found in the unit cell (a) and the packing diagram of the unit cell (b). The dihedral angle and the interplanar distance of the two phenyl rings are 4.3° and 3.58 Å, respectively. The structure of the other molecule differs slightly from the shown by having the dihedral angle of 3.4° and the interplanar distance of 3.41 Å.

In conclusion, we have shown the existence of non-bonded interactions between aromatic rings using *torsional strain-free* cyclophanes as model compounds. These results together with those of others[2,3,4] support the proposal of Burley and Petsko,[2] and others[3,4] that the through-space inter-aromatic ring interactions may constitute a new class of weak bondings which play an important role in the biological compounds such as enzymes. Further study on the non-bonded aromatic-aromatic ring interactions using cyclophanes and the applications of this type of the weak bondings to molecular recognition is in progress.

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References and Notes

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10. PM3 calculation for the torsional strain energies of [m,n]metaparacyclophanes indicated that the cyclophanes of m=n=4 and 5 are practically strain free(personal communication from Kim, K. S.). Furthermore, it is expected that the replacement of a methylene group in both bridging alkyl chains with sulfur would further improve the conformational freedom of the cyclophanes [Mitchell, R. H. in *Cyclophanes, Vol. 1* (Eds.: Keehn, P. M.; Rosenfeld, S. M.), Academic Press, New York, **1983**, p. 275.].
11. (a) Crystal data for **1**: $C_{18}H_{20}S_2$, M_r=300.49, orthorhombic, $Pna2_1$, a=15.843(2), b=17.070(2), c=5.7024(4) Å, V=1542.2(2) Å^3, Z=4, D_{calcd}=1.293 gcm^{-3}, μ (Mo Kα)=3.2 cm^{-1} R=0.051 and R_w=0.051 for 1092 absorption corrected reflections with $I > 3\sigma(I)$); (b) Crystal data for **2**: $C_{19}H_{22}S_2$, M_r=314.52, triclinic, P1, a=7.817(2), b=15.035(3), c=15.622(4) Å, α=78.69(2)°, β=75.77(2)°, γ=75.02(3)°, V=1702.7(8) Å^3, Z=4, D_{calcd}=1.227 gcm^{-3}, μ (Mo Kα)=2.9 cm^{-1}, R=0.052 and R_w=0.054 for 2054 absorption corrected reflections with $I > 3\sigma(I)$).Two crystallographically independent molecules exist in the asymmetric unit, overall structures of which are similar; (c) Crystal data for **3**: $C_{17}H_{19}NS_2$, M_r=301.48, monoclinic, $P2_1/c$, a =16.037(8), b=7.6574(9), c=25.21(1) Å, β=90.18(3)°, V=3096(2) Å^3, Z=8, D_{calcd}=1.290

gcm^{-3}, μ (Mo Kα)=3.2 cm^{-1}. R=0.050 and R_w=0.050 for 2413 absorption corrected reflections with $I > 3\sigma(I)$. Two structurally similar crystallographically independent molecules exist in the asymmetric unit. In all three cases, data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation ($\lambda(K\alpha_1)$=0.70926 Å) and structures were solved by direct methods and refined anisotropically for non-H atoms. Hydrogen atoms were located from difference electron density maps and their positional and thermal (1.2 times that of attached atom) parameters were fixed in the final refinement cycles.

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13. The presence of intermolecular edge-to-face ring interactions was also observed: The C7-H of the top ring (C5-C10) interacts with the bottom ring (C15-C20) of a neighbor molecule with the ring distance of 3.57 Å and the dihedral angle of 57.3°. At the same time, the top ring interacts with the C17-H of the bottom ring of another neighbor molecule with the corresponding distance and angle of 3.60 Å and 57.3°, respectively.
14. There are numerous cyclophanes in the literature whose X-ray crystal structures show the two aromatic rings to have a tilted or parallel geometry, but these geometries are most likely the results of molecular torsional strain rather than the intramolecular non-bonded ring interaction, considering they have short alkyl chain bridges. The aromatic-aromatic ring distance in these cyclophanes are known to be about 3 Å, which are considerably shorter than those (~5.5 Å) observed in crystalline proteins and benzene dimers [Keehn, P. M. in *Cyclophanes, Vol. 1* (Eds.: Keehn, P. M.; Rosenfeld, S. M.), Academic Press, New York, **1983**, p. 72.].
15. Compound **2** was synthesized in 42% yield by the condensation of 2,6-dibromomethyltoluene with 1,4-bis(2-mercaptoethyl)benzene under high dilution conditions; m.p.=113-114°C; ^{1}H NMR(300MHz, $CDCl_3$, 25°C) δ 1.98(s, 3H), 2.27-2.37(m, 4H), 2.82-2.89(m, 4H), 3.50(d, 2H), 6.48(s, 2H), 6.76(d, 2H), 6.88(s, 2H), 6.90(t, 1H); Satisfactory C, H, S analyses.
16. Compound **3** was prepared in a similar route to that used for **2**; m.p.=167-169°C; ^{1}H NMR(300MHz, $CDCl_3$, 25°C) δ 2.60-2.76(m, 8H), 3.81(s, 4H), 6.93(s, 4H), 7.25(d, 4H), 7.61(t, 1H); Satisfactory C, H, N analyses.
17. Although the possibility that the observed geometries of the model compounds are the results of crystal packing rather than the intramolecular ring interactions cannot be completely ruled out, it is highly unlikely considering that the NMR spectral data are in good agreement with the X-ray crystal structures as described above.