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Role of Arene Interactions and Substituents Effect in Conformational (syn/anti) Control of 1,2-Diarylethanes†‡

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Conformational analysis of nine designed flexible 1,2-diarylethanes with different substituents show *syn* conformation due to π–π interactions by ^{1}H NMR in solution, this carries over to the solid state for three compounds while two show *anti* conformation in solid state by X-ray crystallography and remaining compounds do not give diffraction quality crystals.

Keyword
X-ray crystallography, diarylethanes

A knowledge of weak noncovalent forces that control conformation in flexible compounds is of fundamental importance since these are the most important factors controlling the shape and the dynamics of complex polymeric molecules like DNA and proteins. However, these forces are still not well understood and remain a challenge to the chemical community, mainly due to the fact that many of these forces are present simultaneously in drug-receptor complex. Arene interactions constitute one of such forces and in spite of its established importance in chemistry,[1] biology[2] and drug development,[3] its application as a tool in molecular recognition or crystal engineering remains a problem. For example, to answer which molecule having an arene residue at the termini of polymethylene (e.g. ethylene, propylene etc.) linker will show intramolecular folding due to arene (especially offset face-to-face mode) interaction in solution, is not easy even today. Furthermore, when present in solution, determining in which case it is strong enough to survive in solid state is even more difficult.

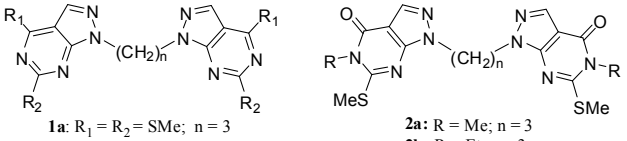
In the literature various models based on different scaffolds to facilitate arene interactions have been proposed for their understanding.[4] These studies can be divided into two main types,

first intermolecular[5] which is important from drug-receptor, protein-DNA, protein-protein interaction etc. and second intramolecular[6] which is important especially from DNA/RNA structures, where in single strand it is intramolecular while in double it is both inter- and intramolecular. Intramolecular arene interaction is also important at the molecular level for developing models for better understanding of arene interactions in general and exploration of newly emerging concept of conformational control in flexible compounds having at least two arene moieties connected by polymethylene linker (e.g. propylene,[6d-6g, 6q,7] and ethylene[6d,6h-6j]) Electronic effects of the substituents are also widely believed to have significant effect on arene interaction,[1,4-6] however, currently there is a lot of debate going on this and new developments are emerging while older concepts are being challenged.[1b]

1,2-Diarylethanes are the simplest unbiased flexible model to understand how two arene moieties (similar/different) interact with each other intramolecularly for controlling observed folded conformation of the molecule both in solution and more importantly in crystal. Interestingly, 1,2-diphenylethane, 1,3-di-phenylpropane and 1,4-diphenylbutane are open in solid state indicating that phenyl moiety is not a good system for studying intramolecular arene interactions in such unbiased flexible models. In the absence of arene interactions, conformation of such 1,2-diphenylethanes due to the steric effect of the bulky arene residues, are normally expected to be *anti* and this is supported by the crystal structures of many 1,2-diphenylethanes having a wide variety of electron donating and withdrawing substituents

in the literature.[8] Even when the *ethylene* linker is between two N atoms conformation remains *anti,* clearly indicating that smaller van der Waals radii of N atom in comparison to C atom alone is not enough reason to show *syn* conformation in crystals.[8f-8h]

On the other hand, a few studies have shown that such structures are capable of existing in *folded* conformation in solution. A study, as early as 1968, by Leonard et al. on nucleic acid bases connected by the *ethylene* and the *propylene* linkers clearly showed, that intramolecular interactions between arene residues were responsible for observed folding in solution.[6d] Later by Itahara on adenine (by ^{1}H NMR)[6h-6j] and by us on pyrazolo[3,4-*d*]pyrimidine (PP) core based *ethylene* linker compounds (by ^{1}H NMR) showed that 1,2-diarylethanes are capable of existing in *syn* conformation in solution.[9] Recently,



1a: $R_1 = R_2 =$ SMe; n = 3
1b: R_1 = O-iso-Pr, $R_2 = SO_2Me$; n = 3
1c: $R_1 = R_2 =$ SMe; n = 2
1d: $R_1 = R_2 =$ SEt; n = 2
1e: R_1 = Cl, R_2 = SMe; n = 3
1f: R_1 = OMe, R_2 = SMe; n = 3
1g: R_1 =O-iso-Pr, R_2 = SMe; n = 3

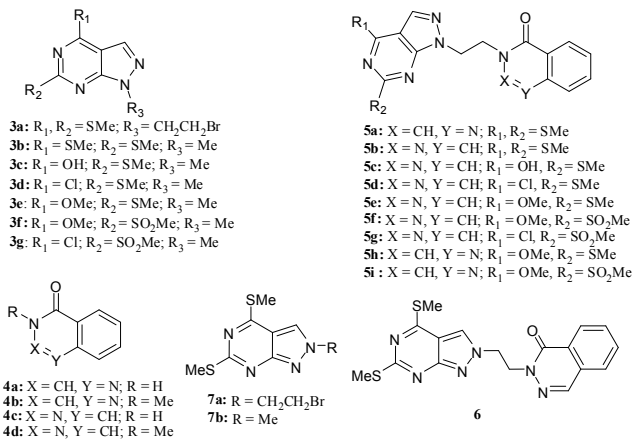
2a: R = Me; n = 3
2b: R = Et; n = 3
2c: R = CH_2Ph; n = 3

Fig. 1. Pyrazolo[3,4-*d*]pyrimidine core based *propylene* and *ethylene linker* compounds.

Dubey *et al.* described that *ethylene* linker compounds with PP cores at their termini show folded conformation in solution both by circular dichroism (CD) and variable temperature ^{1}H NMR studies, however, no solid state evidence for *syn* conformation due to arene interactions was provided.[10] One case, 1,2-bis[5-oxo-3-(*n*-propyl)-4,5-dihydro-3*H*-1,2,4-triazol-4-yl]ethane is known to have a *syn* conformation in the solid state[11] but it is not mentioned whether the extensive hydrogen bonding due to the water present in the molecule or the arene/O…arene interactions is actually responsible for the observed *syn* conformation.

Since 1995, our work on PP core based on flexible *propylene/Leonard* linker compounds has shown that intra- molecular folding is possible due to arene interactions both in solution and more importantly in solid, from crystal engineering angle, as shown by more than a dozen truly flexible symmetrical (**1a**, **1b**, **1e-1g** and **2a-2c**, Fig. 1 and Fig. S1, ESI‡) and two related dissymmetrical compounds (Fig. S1, ESI‡).[7,9] The main difference between **1** and **2** is that pyrimidine of **1** is replaced by pyrimidone system in **2**. Very recently, scope of the PP core for studying arene interaction in flexible symmetrical and dissymmetrical compounds has been considerably increased by replacing truly flexible *propylene/Leonard* linker with less mobile *butylidene* linker (**1o**, Fig. S1, ESI‡).[12] Interestingly, Vogtle refers to singly linked molecules that adopt π-stacked conformations as "protophanes".[13]

These results have prompted us to apply PP core to common 1,2-diarylethanes. Our initial efforts in getting *syn* conformation in solid state due to intramolecular π–π interactions in the *ethylene* linker symmetrical compound based on PP core were not successful.[9c] A careful analysis of the crystal structures (**1**; n = 3, **2a-2c**, Fig. 1 and Fig. S3, ESI‡) revealed that except for **1b** (Fig. 1 and Fig. S3, ESI‡) having bulky groups at both 4- and 6-positions, five membered pyrazolo moieties are at maximum distance from each other (e.g. 4.48 and 4.62 Å between centroids in **1a** and **2a** respectively) while six membered pyrimidine/ pyrimidone residues are partially overlapped (e.g. 3.71 and 3.77 Å between centroids in **1a** and **2a** respectively). Since for the *ethylene* linker homolog **1c** (Fig. 1) of symmetrical *propylene* linker compound **1a** (Fig. 1) both PP moieties have to come close to each other in order to achieve a *syn* conformation and this situation may not be sterically/electronically favourable especially in solid state where competing intermolecular interactions are present to give more favourable *anti* conformation. Therefore, it was decided to replace the pyrazolo residue by the pyrimidone type of moiety, as it was well tolerated in compounds of the series **2** and is also present in nucleic acid bases. Thus, commercially available quinazolinone containing



3a: R_1, R_2 = SMe; $R_3 = CH_2CH_2Br$
3b: R_1 = SMe; R_2 = SMe; R_3 = Me
3c: R_1 = OH; R_2 = SMe; R_3 = Me
3d: R_1 = Cl; R_2 = SMe; R_3 = Me
3e: R_1 = OMe; R_2 = SMe; R_3 = Me
3f: R_1 = OMe; $R_2 = SO_2Me$; R_3 = Me
3g: R_1 = Cl; $R_2 = SO_2Me$; R_3 = Me

5a: X = CH, Y = N; R_1, R_2 = SMe
5b: X = N, Y = CH; R_1, R_2 = SMe
5c: X = N, Y = CH; R_1 = OH, R_2 = SMe
5d: X = N, Y = CH; R_1 = Cl, R_2 = SMe
5e: X = N, Y = CH; R_1 = OMe, R_2 = SMe
5f: X = N, Y = CH; R_1 = OMe, $R_2 = SO_2Me$
5g: X = N, Y = CH; R_1 = Cl, $R_2 = SO_2Me$
5h: X = CH, Y = N; R_1 = OMe, R_2 = SMe
5i : X = CH, Y = N; R_1 = OMe, $R_2 = SO_2Me$

4a: X = CH, Y = N; R = H
4b: X = CH, Y = N; R = Me
4c: X = N, Y = CH; R = H
4d: X = N, Y = CH; R = Me

7a: R = CH_2CH_2Br
7b: R = Me

6

Fig. 2. *Ethylene* linker compounds (**5**) derived from PP core (**3**) and quinazolinone/phthalazinone (**4**) and reference compounds.

pyrimidone residue was selected for the study. The reaction product from the reaction of 1-(2-bromoethyl)-4,6- dimethylsulfany-l*H*-pyrazolo[3,4-*d*]pyrimidine, (**3a**)[9a] with quinazolinone (**4a**) gives **5a** (Fig. 2) which by ^{1}H NMR ($CDCl_3$) analysis shows intramolecular folding when compared to the reference compounds (**3b** and **4b**, Fig. 2 and Table S4, ESI‡). However, all attempts to get single crystal of **5a** for X-ray crystallography failed forcing us not to pursue this study for the time being. Next, phthalazinone (**4c)** which is isomeric with quinazolinone and also commercially available was selected to replace one PP core of **1a** (Fig. 1 and ESI‡).Thus, reaction of phthalazinone (**4c**) with **3a** in DMF in presence of anhydrous potassium carbonate gave the desired *ethylene* product **5b** in good yield (ESI‡). To our satisfaction the new *ethylene* linker compound **5b** also shows significant up-field shift in ^{1}H NMR ($CDCl_3$) as compared to the reference compounds, **3b** and **4d** (Fig. 2 and Table S4, ESI‡) thus, indicating folded conformation. More importantly, **5b** gives good crystal and the solid state structure of **5b** shows a *syn* conformation (Fig. 3). The torsion angle formed by NCCN atoms involving the *ethylene* linker and two N atoms connecting it is 60.58º, confirming *syn* conformation. The distance between two N atoms linking two arene moieties is 2.95 Å which is less than sum of van der Waals radii of two N atoms (3.10 Å i.e. 2x1.55 Å for N) and less than 3.09 seen in **1b** with extra C in its linker. The distance between centroids of five member pyrazole ring of PP core and six member pyrimidone ring of phthalazinone system is 4.28 Å which is similar to distance of 4.28 Å between centroids of six member pyrimidine and six member heterocyclic ring of phthalazinone system (Fig. 3). core and six member pyrimidone ring of phthalazinone system is 4.28 Å which is similar to distance of 4.28 Å between centroids of six member pyrimidine and six member heterocyclic ring of phthalazinone system (Fig. 4). It is important to mention that 4.23 Å is the maximum distance seen in folded compounds (**1a**, **1b**, **1e-1g** and **2a-2c**, Fig. 1and Table S2, ESI‡) that shows such distance in the range of 3.69-4.23 Å. The distance between centroids of nine membered PP core and six membered pyrimidone ring of phthalazinone system is 4.15 Å. Some close distances between two six membered pyrimidine and pyrimidone ring of phthalazinone are C7A…N11= 3.42, N7…N10 = 3.42 and N7…C17 = 3.50 Å

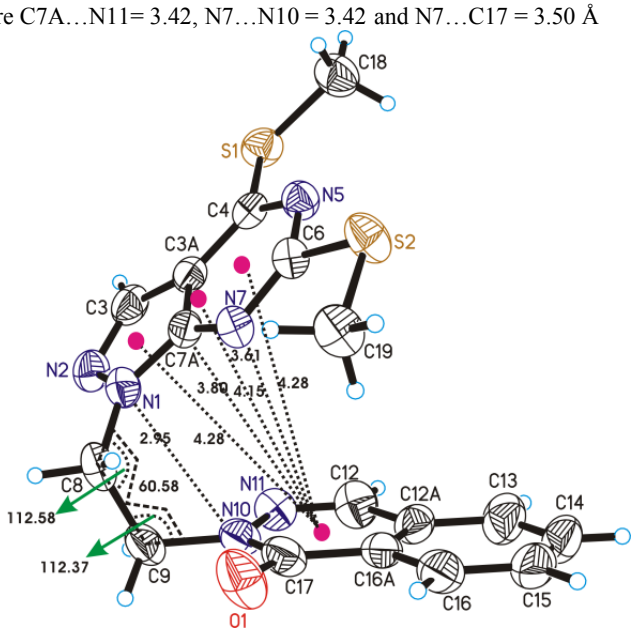


Fig. 3. ORTEP diagram of **5b** (at 30% probability level) showing *syn* conformation with intramolecular π–π interactions.

confirming intramolecular stacking. Finally, there is no intra-molecular S…arene (4.96 and 5.07 Å)[3a] or significant CH–π interactions[14] confirming that *syn* conformation is due to intramolecular π–π interactions. The variable temperature (-50 to 50 °C) ^{1}H NMR study on **5b** shows increase in the magnitude of up-field shift (difference of two SMe protons) with decrease in the temperature indicating that molecule exists in folded and unfolded state at room temperature in $CDCl_3$. Surprisingly, the N^2- isomer (**6**, ESI‡) of **5b** prepared similarly from 2-(2-bromoethyl)-4,6-dimethylsulfany-l*H*-pyrazolo[3,4-*d*]- pyrimidine (**7a**)[9a] and phthalazinone does not show much up-field shift in its ^{1}H NMR (Table S4, ESI‡) indicating the absence of intramolecular folding due to different positions of linker. It is important to mention here that such drastic change in the conformation due to different positions of linker in two isomeric compounds was also observed in the *propylene* linker compound **1a** and its N^2- isomer.[15] The variable temperature (-50 to 50 °C) ^{1}H NMR study on N^2- isomer, **6** does not show a comparable change in the chemical shift (difference of two SMe protons) in its ^{1}H NMR further confirming presence of only open form (Table S3, ESI‡). To test the robustness of *syn* conformation in **5b** formed due to intramolecular arene interaction, substituents effects, were studied. The compound **5c** prepared from **5b** (ESI‡) also shows up-field shift for methylsulfanyl group in ^{1}H NMR indicating folded conformation, however, crystals of **5c** suitable for crystallography could not be prepared, presumably due to presence of ionisable H (from lactam) capable of forming stronger H-bonding. Replacement of the 4-SMe group in **5b** by common electron withdrawing Cl group via **5c** gives **5d** (ESI‡) which also shows significant up-field shifts in its ^{1}H NMR in comparison to **4d** and **3d** (Fig. 2, **3a** and **3b,** Table S4, ESI‡). indicating folded conformation in solution. The solid state

structure of **5d**, however, shows an *anti* conformation (torsion angle = 172.38º, Fig. 4) with distance between two N atoms linking two arene moieties of 3.72 Å. Furthermore, a comparable distance of 3.70 Å was also shown by our earlier symmetrical

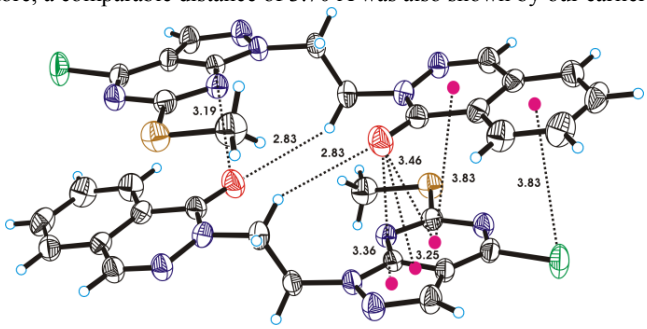


Fig. 4. Crystal structure of **5d** showing open conformation with intermolecular C-H....O, O…arene, Cl-arene and π–π interactions

ethylene compound **1d** (Fig. 1) with *anti* conformation.[9c] A careful analysis of the crystal structure of **5d** shows strong O...arene dimerization (3.25 Å) with closest distance between O...C of 3.19 Å which is less than van der Waals radii of O and C atoms and intermolecular O···Ar interactions are of current interest.[16] Additional C-H…O (2.83, 3.61 Å and 138.1º),[17] Cl…arene (3.83 Å)[18] and π–π interactions (3.83 Å) are also present in this dimer. It is interesting to mention here that symmetrical **1e** with Cl group at similar 4-position is also devoid of intramolecular π–π interactions.[7f]

Next, electron withdrawing Cl group is replaced by the common electron donating methoxy group. New compound **5e** obtained by the reaction of **5b** with sodium methoxide (ESI‡) again shows up-field shift in its ^{1}H NMR like compounds **5b-5d**, (Table S4, ESI‡) indicating intramolecular folding, however, crystals of **5e** suitable for crystallography could not be prepared.

Next, 6-SMe group of **5e**, which defied our attempts to give diffraction quality crystal, is replaced by the strong electron withdrawing SO_2Me group by oxidation to give new compound **5f**. Once again **5f** shows up-field shift in its ^{1}H NMR like compounds **5b-5e**, (Table S4, ESI‡) indicating folded conformation. The solid state structure of **5f** shows a *syn*

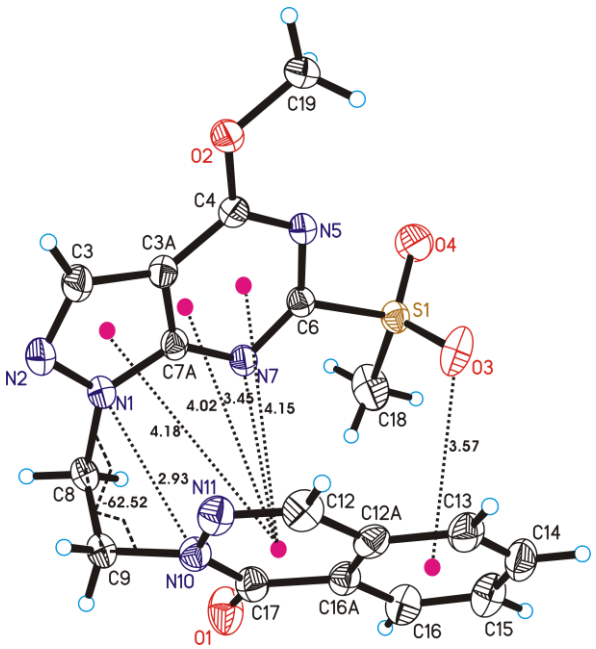


Fig. 5. ORTEP diagram of **5f** (at 30% probability level) showing *syn* conformation with intramolecular π–π interactions and O…arene interactions.

conformation (torsion angle = 62.52º, Fig. 5). The distance between two N atoms linking two arene moieties is 2.93 Å which is very comparable to 2.95 seen in **5b**. It is important to mention here that symmetrical **1j** (Fig. S1, ESI‡) with OMe group at similar 4-position and SO_2Me group at 6-position is also folded due to intramolecular π–π interactions.[7d]

Encouraged by this result on **5f** it was decided to convert **5d** in to sulfone (**5g**) and see its effect on conformation. New sulfone **5g** shows up-field shift in its ^{1}H NMR like compounds **5b-5e**, (Table S4, ESI‡) indicating folded conformation. The solid state

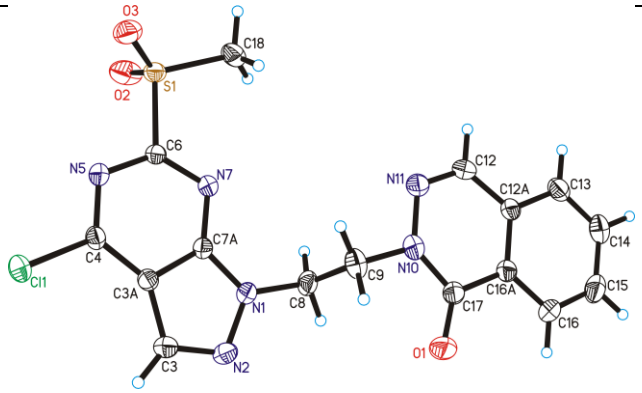


Fig. 6. ORTEP diagram of **5g** (at 30% probability level) showing *syn* conformation with intramolecular π–π interactions and O…arene interactions.

structure of **5g**, however, shows *anti* conformation (torsion angle = 173.81º, N1…N10 = 3.71 Å, Fig. 6). This result is quite interesting in showing that the strong electron withdrawing SO_2Me group alone is not responsible for *syn* conformation seen earlier in **5f**. Presumably, involvement of Cl group at 4-position in many intermolecular noncovalent interaction in both compounds (**5d** and **5f)** is possible reason for the existence of open conformation.

Finally, third sulfone **5i** was prepared from **5h** following similar method as described for **5f** and **5g**. The sulfone **5i** shows up-field shift in its ^{1}H NMR like compounds **5b-5e**, (Table S4, ESI‡) indicating folded conformation in solution. The solid state structure of **5i** shows *syn* conformation (torsion angle = 59.97º, Fig. 7). This result is very comparable to that of **5f** (and **5b**) except the fact that **5i** has minimum value of torsion angle out of three folded structures (**5b**, **5f** and **5i**). Furthermore, other intermolecular distances in **5i**, in general, are also smaller in comparison to other two folded compounds (**5b** and **5f**). A careful analysis of compound **5i** revealed the presence of much weaker CH…π interaction. The closest H contacts with six member phenyl ring of quinazolinone are 2.85 and 2.94 Å. Earlier, we have reported an unusual folded conformation of a dissymmetrical propylene linker compound (**8a**, Fig. S1, ESI‡) with PP core and phthalimido moiety solely due to CH…π interaction (Table 1).[71] Similar comparison of two other compounds (**5b** and **5f**) showed much less acceptable distances for the presence of CH…π interaction (Table 1). It is important to mention that while all four different compounds (Table 1) with one PP moiety show unusual intramolecular folding they have different reasons for folding. The first three compounds belong to ethylene series while last one is propylene linker compound. In **5b** intramolecular folding is almost solely due to arene interaction while in **8a** it is solely due to CH…π interaction. Though compound **5i** shows two very good distances (2.85 and 2.94 Å) for CH…π interaction of which the first is sub-van de**r** Waal, the distance of 4.201 Å between C(19) and involved centroid is

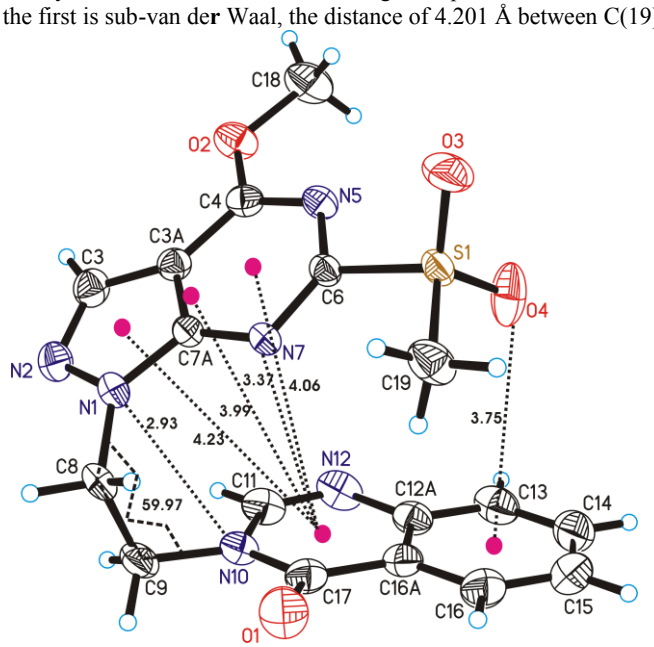


Fig.7. ORTEP diagram of **5i** (at 30% probability level) showing *syn* conformation with intramolecular π–π interactions and O…arene interactions.

beyond 4.0 Å, generally considered upper limit. This may be explained by the fact that main conformation controlling factor in **5i** is intramolecular π…π interaction and not CH…π interaction. In view of this explanation contribution of CH…π interaction seems much less for **5f** and **5b** (Table 1). Finally, another compound (**8b**, Fig. S1, ESI‡) in which 4-SMe group of **8a** was replaced by pyrrolidino moiety intramolecular folding due to CH…π interaction disappeared resulting in normal extended/open Out of three sulfones two with 4-OMe group are folded and one with 4-Cl in place of OMe is open. Two folded isomeric sulfones

differ in having either phthalazinone or quinazolinone residue. Striking, similarity of three solid state *syn* conformations of **5b**, **5f** and **5i** having different substituents and different arenes (phthalazinone or quinazolinone) is noteworthy and shows that folded motif mainly due to intramolecular π–π interactions is robust from crystal engineering point of view.

In conclusion, all the nine compounds (**5a-5i**) are folded due to intramolecular π–π interaction in solution as shown by their ^{1}H NMR data. This PP core based dissymmetric ethylene model shows very good tolerance for various substituents (SMe, OMe, OH, Cl and SO_2Me) in solution. A similar trend was followed by our *propylene/Leonard* compounds in solution. For the three compounds (**5b**, **5f** and **5i**) with limited variation in substituents (SMe, OMe and SO_2Me) these interactions are strong enough so that *syn* conformation carries over to solid state, while for two chloro compounds (**5d** and **5g**) it changes to *anti* conformation in solid due to strong intermolecular interactions. Apparently, two arene systems not only have to come close enough (< 3 Å, as in **5b**, **5f** and **5i**) at the point of contact (which is much less than 3.4 Å for two benzenoid system thus causing severe steric hindrance), intramolecular π–π interactions have also to compete with other strong intermolecular interactions to show *syn* conformation in 1,2-diarylethanes. A careful consideration of these factors may help in designing of new 1,2-diarylethanes capable of existing in *syn* conformation in solid state. In our view, this study is the first in literature where a systematic study

Table 1: Important CH…π interaction data obtained from X-ray crystallographic studies on **5b**,**5f**, **5i** and **8a**.

Comp. No.	Distance between C(19) & C16A / Å	Distance between C(19)H & C16A (C(18)H & C16A in **5f**) / Å	Distance between C(19) and C16 (C(18)H & C16 in **5f**) / Å	Distance between C(19)H & C16 (C(18)H & C16 in **5f** / Å	Distance between centroids of phenyl ring of phthalazinone/quinazolinone/ phthalimide & C(19) (C(18) in **5f**) / Å
5b	4.106	3.168	3.992	3.049	4.563
5f	4.240	3.379	4.073	3.248	4.387
5i	3.720	2.852	3.64	2.945	4.201
8a	3.579	2.985	3.611	3.274	3.602

for the ability of arene interactions to control the conformation both in solution and solid state together with the dramatic substituents effect on solid state conformation has been demonstrated. Interestingly, 4-SMe, 4-OMe and 6-SO_2Me groups were also tolerated in symmetrical *propylene/Leonard* compounds for showing folded conformation in solid. This work together with our earlier work on *propylene/Leonard* and *butylidene* linkers for 1,3-diarylpropanes, opens a new window for conformation control in flexible 1,2-diaryethanes. In addition, worthiness of PP core as a novel system for studying arene interactions, both in solution and solid, is demonstrated once again. Above all conformational control due to different common substituents of organic/medicinal chemistry, in solid state is demonstrated which is very important from molecular recognition and crystal engineering angles. These models may provide an important experimental basis for further development of computational/theoretical models for better understanding of arene interactions in flexible compounds both at molecular and supramolecular level.

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