Exploring symmetry related bias in conformational data from the Cambridge Structural Database: A rare phenomenon?

Aim

To explore some well known cases where symmetry effects bias the distribution of conformational geometric information and to find the conditions that lead to this bias

Introduction

One frequently presented argument against using small molecule crystal structure data in conformer generation is that the close packing observed within crystal structures can significantly bias the observed conformations away from gas phase norms. In particular, mention is often made of several well known examples of what could be termed 'symmetry driven' conformational bias.

The most frequently quoted case concerns biphenyl having four *ortho* hydrogens.[1] Biphenyl itself has a minimum-energy conformation with an inter-ring torsional angle of around 40° from gas-phase electron diffraction and *ab initio* calculations[2], with H…H repulsions preventing ring coplanarity. However a ConQuest search for biphenyl, retrieving the ring-ring torsion in each case, yields the histogram shown in Figure 1a. The peaks in the distribution at ±30°-40° away from 0° and 180° correspond well with the gas phase results. However the distribution also exhibits sharp peaks at 0° and 180° arising from planar biphenyl moieties.

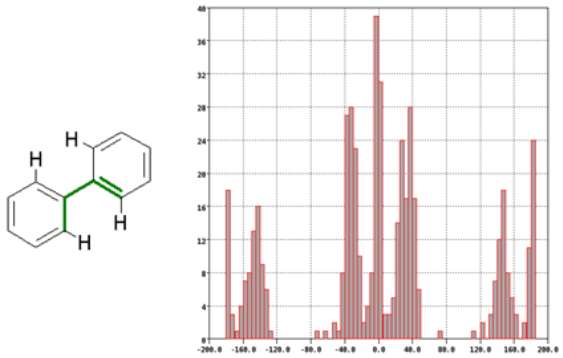

Figure 1a

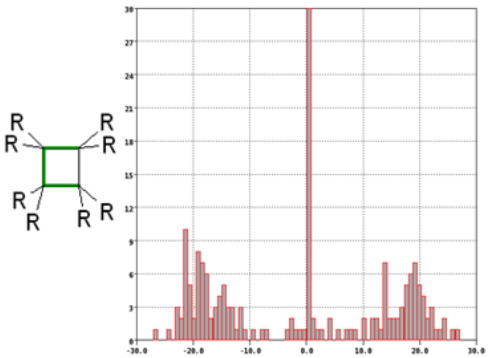

Figure 1b

Figure 1a - Distribution of torsion angles in biphenyl analogues

Figure 1b - Distribution of ring torsion angle in cyclobutane analogues (torsion marked in green)

Another case of apparent conformational bias is observed for cyclobutanes, which are expected to favour a puckered conformation to avoid eclipsed interactions between ring substituents.[3] However

a CSD search for 'free' cyclobutanes, i.e. rings that are not fused or bridged, shows a sharp anomalous peak at 0° in the distribution of dihedral angle of pucker about the ring diagonals (Figure 1b). The sharp peak again represents planar structures, cf. biphenyl above.

We can get insight into the relationship between chemical structure and the tendency for forced planarity to occur by carrying out focused substructure searches in ConQuest.

Method

Biphenyl Search: Figure 2 illustrates a suitable ConQuest substructure search query, which uses some of the geometric object definitions available in ConQuest, such as centroids and planes, and the ability to define geometric features using these objects. TOR1 is the biphenyl inter-ring torsion and abs(DIST1) specifies the vertical (i.e shortest) distance between the centroid of one of the rings and the plane of a second phenyl ring in a stacked molecule. We can specify that this ring is parallel to the first by constraining on the angle between the stacked ring planes, ANG1, to be in the range 0°-5°. It is important to specify that these rings must be in different molecules and this is done by specifying a 'contact' constraint, but with a long maximum contact distance of 10Å between the ring centroids, DIST2, not shown here to avoid an over-cluttered diagram.

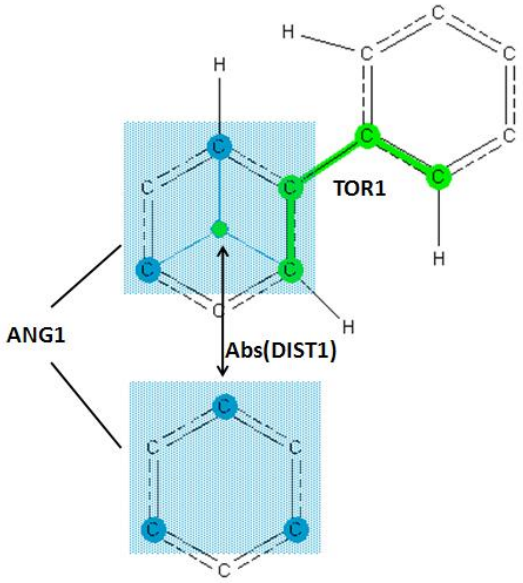

Figure 2 - ConQuest Search for biphenyl substructures that also monitors stacking distance between parallel phenyl rings. DIST2 (not shown) between the centroids of the two rings for which Abs(Dist1) is measured, ensures they are in different structures.

Two searches were carried out, one with TOR1 restricted to ±2˚ and one with TOR1 restricted to 20-30˚. Strict filters were placed on structures to be retrieved by the search: 3D coordinates determined, R factor <5%, not disordered, no errors, not catena bonds, no ions, no powder structures and only organic structures. The first search generated 94 hits, the second 76 hits.

Cyclobutane Search: Figure 3 shows the cyclobutane search used. The ring is fully substituted with atoms of unspecified element type, and the bonds to each atom are specified as acyclic to avoid retrieval of fused and bridged systems.

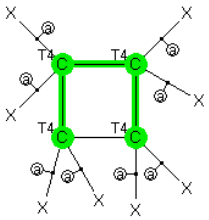

Figure 3 - ConQuest search for non-fused cyclobutane rings

Two searches were carried out, one with TOR1 restricted to ±1˚ and one with TOR1 restricted to 20-25˚. The same strict filters were placed on the search as described above fro biphenyl. The first search retrieved 33 hits, the second search retrieved 35 hits.

Results

Biphenyl: We can analyse the geometric data retrieved in the ConQuest search using Vista, the data analysis module of the CSDS. Calculated density (d_c) information is stored for every CSD entry, hence it is also possible to import d_c into Vista to examine possible density variations for the two searches.

Figure 4 shows the histogram of abs(DIST1) (a) for the planar biphenyls, and (b) for the twisted biphenyls. For both data sets parallel phenyl-phenyl stacking appears to be common. However, the planar biphenyls (a) show clear preferred stacking distances of ~3.2, ~6.4 and ~9.4, which are close multiples of 3.2Å and are characteristic of phenyl-phenyl close packing: in graphite the stacking distance is 3.35Å. In contrast, the packing distance distribution for twisted biphenyls is considerably more diffuse.

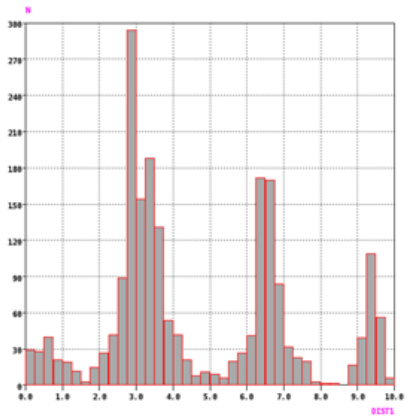

Figure 4a

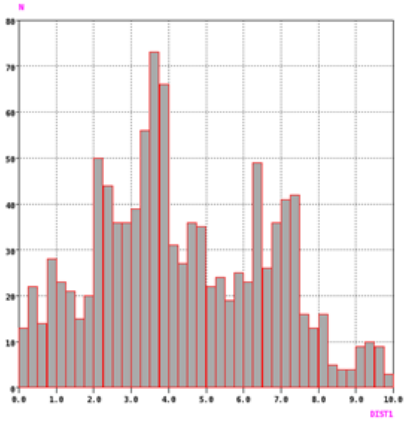

Figure 4b

Figure 4a - Parallel stacking distances between phenyl rings for biphenyl torsion ±2˚

Figure 4b - Parallel stacking distances between phenyl rings for biphenyl torsion 20-30˚

We can also plot the densities for both sets of hits (Figure 5a,b). The modal density is ~1.3 g cm^{-3} for the planar biphenyls and ~1.26 g cm^{-3} for the twisted biphenyls. The mean densities can also be obtained directly from the Vista output. These are respectively 1.36 ± 0.004 g cm^{-3} and 1.325 ± 0.004 g cm^{-3}. These data clearly imply that planar biphenyls pack better than twisted biphenyls.

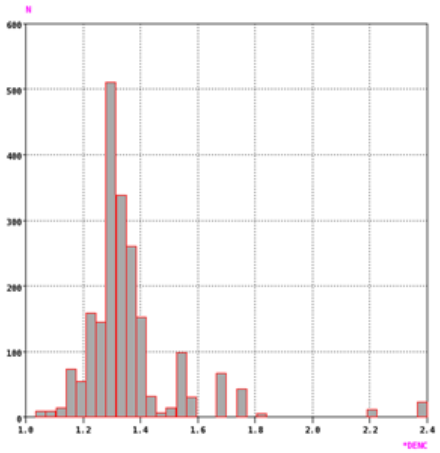

Figure 5a

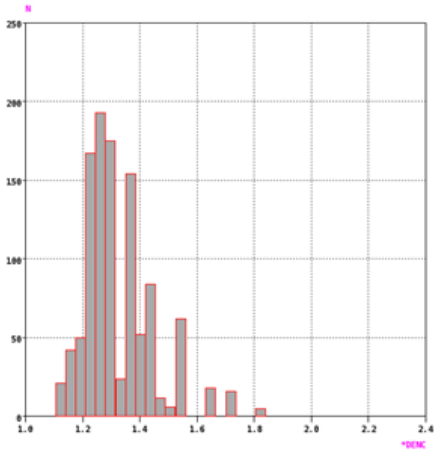

Figure 5b

It is possible to visualise the symmetry elements for each crystal structure using the Mercury module of the CSDS. Observations of centres of inversion within the crystal structures of the planar biphenyls are of major interest and Figure 6 shows one example. In this example the inversion centre is found at the centre of the inter-ring bond, and two conditions are necessary for this to occur. First, the 2D chemical structure must have a (topological) centre of inversion at this point, and secondly this topological centre must coincide with a crystallographic inversion centre in the 3D structure. This second condition requires co-planarity of the two phenyl rings. Omitting seven structural duplicates from the list of 94 leaves 87 independent structures. In 63 cases the biphenyl has 2D topological symmetry and 61 of these are coincident with a crystallographic inversion centre as in Figure 6. The remaining two topologically-symmetric biphenyls choose not to use that symmetry in 3D, maybe because they exist in co-crystals. 24 planar biphenyls do not have a topological centre of symmetry and 15 of these crystalise in space groups that lack 3D inversion centres.

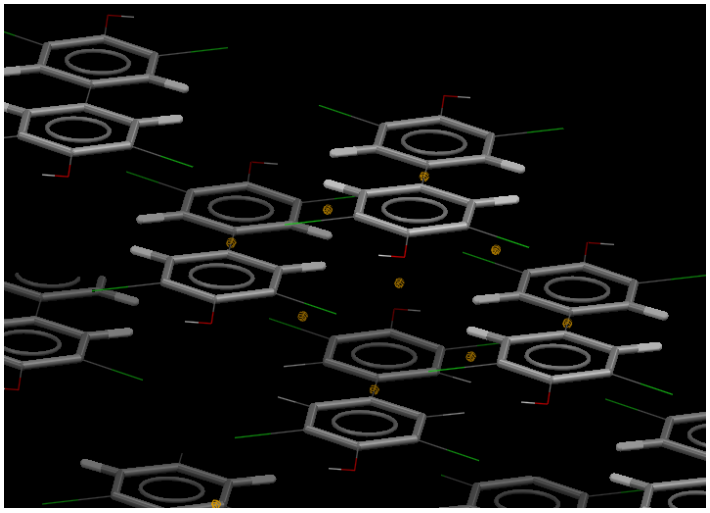

Figure 6 - GAKVAP showing centres of crystal inversion symmetry

Only 13 of the 76 non-planar biphenyls are topologically centrosymmetric about the biphenyl bond. 7 of these are co-crystal structures and some of the remaining 6 appear to be poorly refined. It is clear that topologically centrosymmetric biphenyls are much more likely to be planar within single component crystal structures than not.

Cyclobutanes: We can compare the densities of planar and non-planar cyclobutane structures as we did for the biphenyl structures. We find that the planar cyclobutanes have average density of 1.39 ± 0.028 g cm^{-3}, the puckered cyclobutanes have an average density of 1.30 ± 0.028 g cm^{-3}, so once again the planar structures are denser, i.e. the packing is improved.

If we analyse the centres of inversion within the crystal structures containing planar cyclobutanes (within a puckering angle of 1°) we find that, of the 29 unique molecular structures (4 are redeterminations), 25 have crystallographic centres of inversion at the centre of the cyclobutane ring (Figure 7 gives an example). This again requires that the 2D structure of the molecule in question must also be topologically centrosymmetric through that point. In only 3 cases does a topologically centrosymmetric cyuclobutane compound not have a crystallographic inversion centre at the middle of the cyclobutane ring, and there is only one example of a topologically non-centrosymmetric compound in this subset.

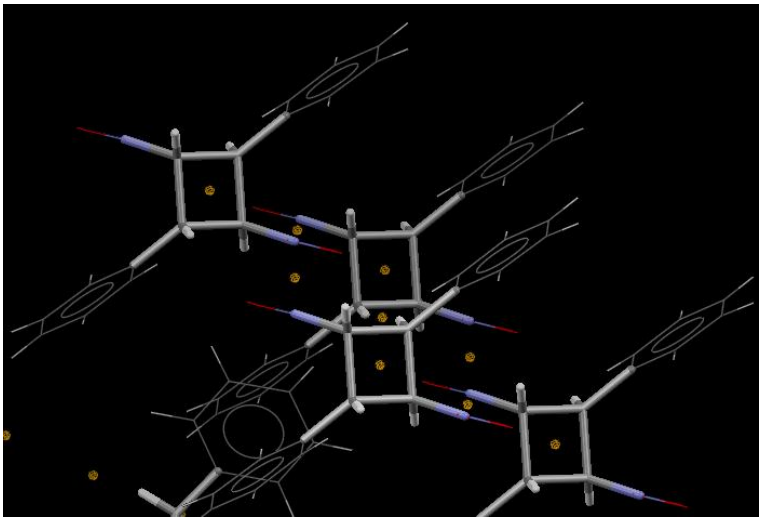

Figure 7 - VOPFUR showing centres of crystal inversion symmetry

If we look at the subset of puckered cyclobutanes (34 unique examples) 32 of these molecules are not topologically centrosymmetric in their 2D structures. The two that are centrosymmetric have very large substituents, which appear to force the ring to pucker (Figure 8). Thus, cyclobutanes with a topological centre of symmetry at the ring centre have a strong preference to use this symmetry in their crystal structures and therefore have a planar geometry.

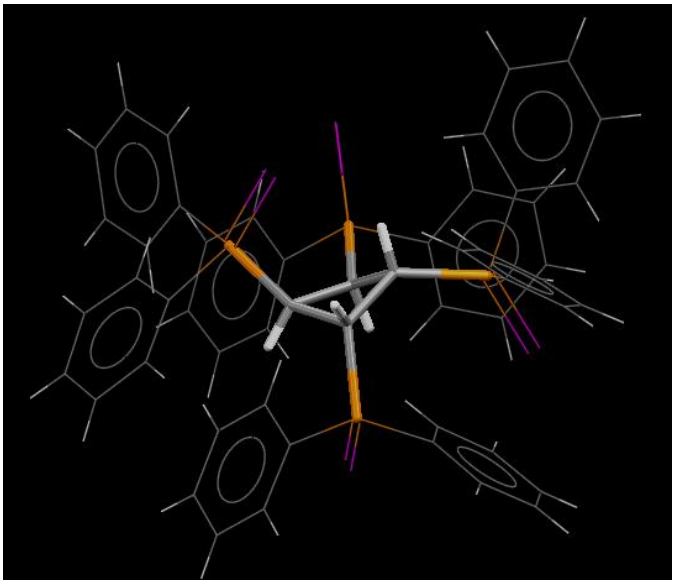

Figure 8 - 3D structure of BAZWAB indicating a puckered cyclobutane ring.

Conclusions

We have studied two different cases where 'symmetry biasing' of torsional distributions occurs. For both biphenyls and cyclobutanes we find that the structures retrieved are dominated by chemical molecules having 2D (topological) inversion symmetry at the centre of the geometric feature of interest. These molecules have a strong preference for forming crystal structures in which this topological symmetry coincides with a crystallographic (3D) inversion centre. Such crystal structures tend to have higher density and, at least in the biphenyl case, are found to have more regular packing, than similar structures with no inversion centres.

Positioning on 3D centres of symmetry is obviously denied to topologically non-centrosymmetric molecules, while topologically centrosymmetric molecules do not necessarily have to use this symmetry in their crystal structures. Therefore the majority of planar structures of biphenyl and cyclobutane are associated with 2D (topological) centrosymmetric chemistry and it follows that the over-representation of planar geometry in these two cases is largely a consequence of an over-representation within the CSD, of molecules that have a 2D (topological) centre of symmetry.

It follows from this that symmetry biased distributions in the CSD are unlikely to be very common as their presence depends on a large population of molecules which are centrosymmetric about the feature of interest. Nevertheless the possibility of such biases occurring should be borne in mind. A characteristic feature of such a bias will be one or more sharp peaks at angles which evenly segment the full rotational space available to the feature. Thus in Figure 1a we get such peaks at 0° and 180°, and in Figure 1b at 0°. These peaks are overlaid against broader distributions that are very comparable with the distributions calculated from the gas phase and which can be used to predict the true conformational behaviour of the substructure in question.

References

1. C. P. Brock, R.P. Minton, *J. Am. Chem. Soc.,* **111**, 1989, 4586.
2. J. Murakami, M. Ito and K. Kaya, *J. Chem. Phys*., **74**, 1981, 6505.
3. T. Egawa, T. Fukuyama, S. Yamamoto, F. Takabayashi, H. Kambara, T. Ueda and K. Kuchitsu*, J. Chem. Phys.*, **86,** 1987, 6018.

Products

CSD – the world's only comprehensive, fully curated database of crystal structures, containing over 500,000 entries

Conquest – a flexible CSD search engine for building informative datasets

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