Acta Crystallographica Section B
Structural Science
ISSN 0108-7681

Conformation and geometry of cyclopropane rings having π-acceptor substituents: a theoretical and database study

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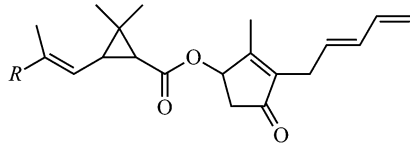
Received 22 September 2010
Accepted 26 November 2010

The $3e'$ orbitals of cyclopropane have the correct symmetry to interact with low-lying unoccupied orbitals of π-acceptor substituents and maximum overlap occurs when the two orbital systems are parallel, *i.e.* when the π-acceptor bisects the ring in projection down the substituent bond. Since the cyclopropyl group is a common component of active pharmaceutical and agrochemical ingredients, it is important that these strong conjugative interactions are well modelled by computational techniques, and clearly represented in experimental crystal structures. Here we show that torsion angle distributions derived from crystal structure data in the Cambridge Structural Database are in excellent correspondence with torsional energy profiles computed using density functional theory (DFT) for a range of substituents: —COO*R*, —CONR_2, —NO_2, vinyl and phenyl. We also show that crystal structure information is invaluable in modelling conformations of compounds that contain multiply substituted rings, where steric interactions require some substituents to adopt energetically disfavoured conformations. Further, conjugative interactions with π-acceptors lead to significant asymmetry in the cyclopropane ring bond lengths and again the experimental and computational results are in excellent agreement. Such asymmetry effects are additive, and this explains bond-length variations in cyclopropane rings bearing two or more π-acceptor substituents.

1. Introduction

Cyclopropane, the smallest and most highly strained saturated carbocycle, has a number of anomalous chemical and structural properties (Charton, 1970; de Meijere, 1979), and a complete issue of *Chemical Reviews* (Vol. 103, Issue 4) is devoted to various aspects of cyclopropane structure and chemistry (see de Meijere, 2003). The reactivity of cyclopropane closely resembles that of a C=C double bond, and the ring forms electronic interactions with electron-acceptor and electron-donor substituents which lead to asymmetry in the ring C—C bond lengths (Allen, 1980). In the case of π-acceptor substituents (*e.g.* —COOH, NO_2, vinyl *etc.*) the electronic interactions and bond-length asymmetry effects are conformation-dependent.



(I) $R = CH_3$
(II) $R = CO_2CH_3$

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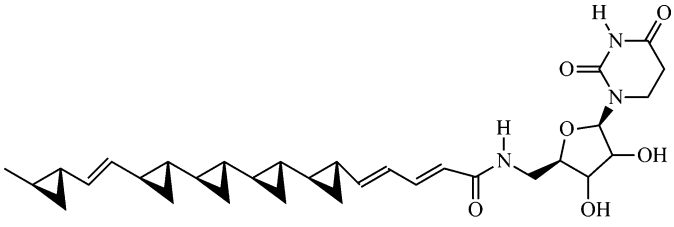
Our interest in the cyclopropyl group arises from its common occurrence in active agrochemical ingredients (AAIs) and active pharmaceutical ingredients (APIs). The best known cyclopropyl-containing AAIs are the pyrethroid insecticides, derived from pyrethrins [(I) and (II)] which are natural insecticides produced by pyrethrum plants (*chry-chrysanthemum cinerariaefolium*). Synthetic analogues now include allethrin, biphenthrin, cyphenothrin, permethrin and decamethrin, all of which attack the nervous systems of insects. Cyclopropyl rings also occur in a wide range of APIs, including antibiotics (ciprofloxacin, sparfloxacin), anti-convulsants (prazepam), antidepressants (midalcipran), anti-retrovirals (abacavir) and the chemically esoteric antifungal antibiotic FR-900848 which contains five cyclopropyl units and is better known as jawsamycin [(III), see Barrett & Kasdorf, 1996]. Recently, Bender *et al.* (2008) have shown that, by comparison with other esters, cyclopropanecarboxylates of APIs have improved stability as prodrugs: physiologically inactive precursors which are converted into active drugs by enzymatic action *in vivo*, thus improving the bioavailability of the parent API. This improved stability is ascribed to conjugative interactions involving the ring and the substituent carbonyl group.



(III)

Given the prevalence of cyclopropyl compounds in AAIs and APIs, it is important to be able to model their conformational preferences and geometries accurately during their discovery, development and formulation stages. Modelling is used, for example, to understand interactions at receptor sites and likely poses in protein–ligand docking experiments, to assess likely intermolecular interactions in any crystalline formulation, or to derive conformations for use in crystal structure prediction directed towards polymorph screening. Since crystal structures of putative AAIs or APIs may not be immediately available, reliance must usually be placed on *ab initio* calculations of conformation and geometry, and cyclopropane derivatives have, in the past, posed some challenges for these procedures. This was certainly the case some 30 years ago when the first detailed study of conformation and bond-length asymmetry in cyclopropyl rings was carried out (Allen, 1980) using the crystal structure data then available in the Cambridge Structural Database (CSD: Allen, 2002). However, readily available *ab initio* software, now including both quantum chemical and DFT methods, has developed rapidly. This is exemplified by recent theoretical studies of cyclopropanecarboxylic acid and related compounds (Badawi *et al.*, 1998, 2008), carried out to explain their vibrational spectra, and similar computational studies associated with gas-phase electron diffraction (*e.g.* Traetteberg *et al.*, 1988; Shen & Traettberg, 2003) or spectroscopic analyses (*e.g.* Durig *et al.*, 2005). So far, however, there has been no systematic attempt to correlate modern computational results with experimental information from crystal structure determinations.

In this paper we study the relationship between computed conformational energy profiles and experimental crystal structure geometries for cyclopropyl rings carrying π-acceptor substituents. Our principal objective is to examine the experimental torsion angle (τ) distribution for each π-acceptor substituent, and to compare each distribution with the results of DFT calculations of the torsional energy profile. We also wish to quantify the bond-length asymmetries arising from the orbital interactions, compare these data with the results obtained by Allen (1980), and re-examine the additivity of these effects in explaining bond-length variations in multiply substituted cyclopropane rings. In a later paper we will treat the other two categories of ring–substituent interactions as defined by Clark *et al.* (1984), *i.e.* interactions involving (*a*) σ-acceptor substituents and (*b*) σ- and π-donors.

2. Orbital interactions in substituted cyclopropanes

The bent-bond model for cyclopropane is well documented in major chemistry texts (*e.g.* Vollhardt, 1987; McMurry, 1992; March, 1992) and originates in the work of Coulson & Moffitt (1947) and Walsh (1949). Hoffmann (1964, 1970), Hoffmann & Davidson (1971) and Clark *et al.* (1984) used a molecular orbital approach to cyclopropyl bonding, which then provides a straightforward explanation of the ability of cyclopropane to conjugate with π-acceptor substituents such as $-$COOH, $-CONH_2$, NO_2, vinyl, phenyl *etc*. Illustrations of the relevant orbitals are provided in many textbooks and in the literature by Allen (1980) and Clark *et al.* (1984); they are also available in *The Organic Chemists' Book of Orbitals* (Jorgensen & Salem, 1973), extended and re-presented in electronic form by Clark & Koch (1999).

In the molecular orbital (MO) approach the cyclopropane $3e'$ orbitals have the correct symmetry to interact with π-acceptor substituents, and maximum overlap with low-lying unoccupied orbitals of the π-system occurs when the two orbital systems are parallel. This happens when the π-acceptor bond bisects the ring in projection down the R_1-C_1 bond, as

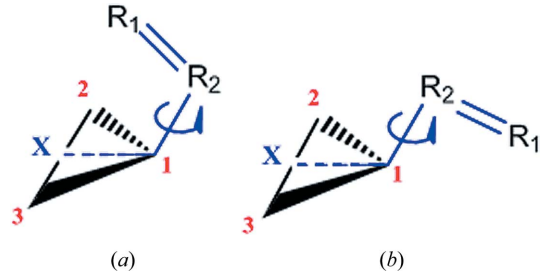


Figure 1
Atomic enumeration and the definition of the torsion angle (τ) for cyclopropane carrying a single π-acceptor substituent; (*a*) shows the *cis*-bisected conformation at $\tau = 0°$ and (*b*) shows the *trans*-bisected conformation at $\tau = 180°$.

shown in Figs. 1(*a*) (*cis*-bisected conformer) and (*b*) (*trans*-bisected), in which the torsion angle τ (R_{11}═R_1—C_1—X, where X is the mid-point of the ring C2—C3 bond) is 0 (*cis*) or 180° (*trans*). Minimum overlap occurs when the two orbital systems are perpendicular ($\tau = \pm 90°$). The effect of orbital mixing is to transfer electron density from the 3e' ring orbital to the π-system. This weakens the cyclopropane ring bonds for which the 3e' orbital has bonding character, *i.e.* the vicinal bonds C1—C2 and C1—C3 which lengthen by δ Å, but strengthens the distal C2—C3 bond for which the 3e' orbital is antibonding, and this bond shortens by δ Å.

3. Methodology

3.1. Database analysis

All searches were carried out using the program *ConQuest* (Bruno *et al.*, 2002) applied to CSD Version 5.31 (November 2009) plus one distributed update, a total of 495 968 entries. Structure visualization made use of *Mercury* (Bruno *et al.*, 2002; Macrae *et al.*, 2006, 2008) and data analysis was carried out using the *Vista* program (Cambridge Structural Database, 2009). Searches for cyclopropane rings used the following secondary search criteria:

(i) single-crystal organic structures with full coordinate data available,

(ii) no residual errors after CSD evaluation,

(iii) no disorder and

(iv) no *catena* bonding;

which yielded 3078, 2820 and 1762 entries with $R < 0.10$, 0.075 and 0.05, respectively. The earlier analysis of cyclopropane bond-length asymmetry (Allen, 1980) was based on only 146 organic structures with $R < 0.10$ retrieved from the 1979 CSD release containing $\sim$28 000 entries. An overall mean ring-bond length of 1.508 (27) Å was reported then (the quantity in parentheses is the sample standard deviation, σ_s). Using current data from 758 non-fused rings in structures having $R <$ 0.05 gives a mean of 1.505 (12) Å – reassuringly close to the 1980 value despite the roughly 20-fold overall increase in data availability.

Searches for cyclopropane rings having π-acceptor substituents used the secondary search criteria above together with an $R \leq 0.075$ cut-off, except for nitro substituents where $R \leq$ 0.10 was used. Two types of search were performed: *general searches* were used to study the conformational preferences of substituents and *specific searches* were used to locate structures where a given π-acceptor group was the only substituent which would generate asymmetry in the ring bond lengths. In both cases it was necessary to permit additional substitution of the basic π-acceptor unit, *e.g.* by including substituted amides, phenyl rings with any additional substitution *etc*. In the case of vinyl substituents the C═C double bond was specified to be only acyclic. The two types of searches also excluded structures having bond-fusion and spiro-fusion of cyclopropane with other strained three- and four-membered rings; other specific restrictions in general searches will be noted in the text. Specific searches made extensive use of the .NOT. operator in *ConQuest*, as well as subsequent visual inspection, to eliminate additional π-acceptor substituents as well as other substituents (mainly halogen) known to perturb the ring geometry. For each substructure retained two vicinal (C1—C2 and C1—C3) and one distal (C2—C3) ring bond lengths were retrieved from the CSD, together with the torsion angle τ, using the atomic enumeration shown in Fig. 1.

There are two ways to determine the bond-length asymmetry parameter, δ, of Fig. 1:

(i) by comparing the vicinal and distal bond lengths with the mean overall ring-bond length determined from rings which are unaffected by substituent effects, or

(ii) by averaging the two vicinal bonds to give $\langle d_{vic} \rangle = (d_{12} + d_{13})/2$ and then subtracting this quantity from the distal bond length (d_{23}) to give -2δ, *i.e.* a negative δ value is generated for the shortened distal bonds.

Method (ii) is chosen here since it treats each ring individually and takes some account of uncorrected librational and other effects which may vary from ring to ring in CSD structures. The previous work of Allen (1980) used a third method of asymmetry analysis by computing the parameters Δ(distal) as $d_{23} - D$ and Δ(vicinal) = $D - \langle d_{vic} \rangle$, where D is the mean of all three ring-bond lengths in each individual ring. Simple arithmetic shows that Δ(distal) = 2Δ(vicinal), and δ [method (ii)] = 3Δ(distal)/4 or 3Δ(vicinal)/2. In this paper we cite δ values computed using method (ii) and convert the earlier Δ values to provide comparison data throughout.

3.2. *Ab initio* calculations

Starting molecular geometries were generated from molecular sketches using the *ChemBio3D* software (CambridgeSoft Inc., 2009). Molecular models were then geometry optimized using *GAUSSIAN*03 (Frisch *et al.*, 2004) at two different levels of theory:

(i) B3LYP/6–311+G** and

(ii) B3PW91/aug-cc-pVTZ.

The B3LYP method was chosen because of its popularity and for comparison purposes, whilst the B3PW91 method was chosen because of the recent work by Jalkanen *et al.* (2008). This highly detailed theoretical and experimental study concluded that the B3PW91 hybrid functional with the aug-cc-pVTZ basis set reproduced geometrical and vibrational data with high precision for cyano-cyclopropane derivatives.

The geometry-optimized molecular models were then used as starting points in relaxed potential-energy surface (PES) scans of the torsion angle (τ) in cyclopropane–π-acceptor derivatives. The PES scans were performed from $\tau = 0°$ to $\tau =$ 180° in steps of 10° using *GAUSSIAN*03 and the two different levels of theory [see (i) and (ii) above]. Geometry optimizations at level (i) needed just under 1 h of c.p.u. time per molecule whilst level (ii) sometimes required as much as 20 h c.p.u. time per molecule on a 2.6 GHz single processor machine. The relaxed PES scans at level (ii) required up to 10 d of computer time per molecule.

4. Conformational analysis

4.1. *Ab initio* torsional energy profiles

Torsional energy profiles were computed at the B3LYP/6-311+G** and B3PW91/aug-cc-pVTZ levels of theory for the following π-acceptor substituents: (*a*) carboxylic acid $-$COOH, (*b*) amide $-CONH_2$, (*c*) nitro $-NO_2$, (*d*) phenyl $-C_6H_5$ and (*e*) vinyl $-CH{=}CH_2$. The resulting PES profiles were very similar for both functionals and only the B3PW91 results are presented in Fig. 2, since this level of theory reproduced the geometrical parameters with higher accuracy. Key relative energy values are summarized in Table 1. As expected, the global minima for $-$COOH, $-CONH_2$, $-NO_2$ and phenyl substituents occur at $\tau = 0^\circ$ (*cis*-bisected conformation), but the local minima at $\tau = 180^\circ$ (*trans*-bisected conformer) for the unsymmetrical $-$COOH and $-CONH_2$ substituents are rather different at 4.1 and 12.8 kJ mol^{-1}, indicating that the *trans*-bisected conformation is strongly disfavoured for amides. Barriers to rotation about the C_1-R_1 bond (Fig. 1) are highest for $-$COOH (23.8 kJ mol^{-1}), $-NO_2$ (21.9 kJ mol^{-1}) and $-CONH_2$ (18.4 kJ mol^{-1}) at τ values close to 90°. The barrier to phenyl rotation is both low (4.4 kJ mol^{-1}) and broad, being approximately constant across the τ range from 30 to 150°.

The torsional energy profile for the vinyl substituent is rather different, however, showing a global minimum corresponding to the *trans*-bisected conformation at $\tau = 180^\circ$, and a local minimum of 6.6 kJ mol^{-1} corresponding to a *gauche* (*g*) conformation at $\tau \simeq 50^\circ$. Thus there is a symmetry-related *g*′ conformer at $\tau \simeq -50^\circ$, with a *g*–*g*′ rotational barrier of 9.4 kJ mol^{-1} at $\tau = 0^\circ$, so that the *cis*-bisected conformation is significantly disfavoured. These data for vinylcyclopropane agree well with spectroscopic and gas-phase structural studies, and also with the *ab initio* (MP2) and DFT calculations presented by de Meijere & Lüttke (1969), Klahn & Dyczmons (1985), Traetteberg *et al.* (1988), Shen & Traetteberg (2003) and Durig *et al.* (2005). The gas-phase electron diffraction study of Traetteberg *et al.* (1988) reports a mixture of *trans* [77 (3)%] and *gauche* conformers [23 (3)%], while Durig *et al.* (2005) report a 79 (3):21 (3) percentage ratio and a *gauche* local energy minimum of 4.96 kJ mol^{-1} from vibrational spectroscopy. These latter authors also carried out a variety of *ab initio* calculations using MP2 methods (various basis sets) and a number of DFT functionals. They report *gauche* local minima in the ranges 4.3–5.3 (MP2) and 6.8–7.4 kJ mol^{-1} (DFT), and *g*–*g*′ barriers of 6.5–7.4 kJ mol^{-1} (MP2) and 9.6–10.1 kJ mol^{-1} (DFT). Other authors, *e.g.* Klahn & Dyczmons (1985), report very similar results. Our values, computed at the DFT B3PW91/aug-cc-pVTZ level, fit well with these experimental and computational conclusions. Klahn & Dyczmons (1985) interpret the conformational preferences of vinylcyclopropane as a compromise between an attempt to maximize the π-conjugative interaction, which would favour the *cis* conformer, and the avoidance of H$\cdots$H steric interactions, which disfavours the *cis* conformer. Also in our calculations the *gauche* local energy minimum occurs at $\tau = 48.6^\circ$ rather than the archetypal *gauche* torsion angle of 60°. This computed value may be compared with values from gas-phase electron diffraction (Traetteberg *et al.*, 1988), where three least-squares intensity analyses making different geometrical assumptions gave τ values of 56.0 (6.4), 55.4 (6.4) and 51.8 (6.4)°, although *ab initio* values of 62.2 and 61.4° are reported by Klahn & Dyczmons (1985) and Durig *et al.* (2005).

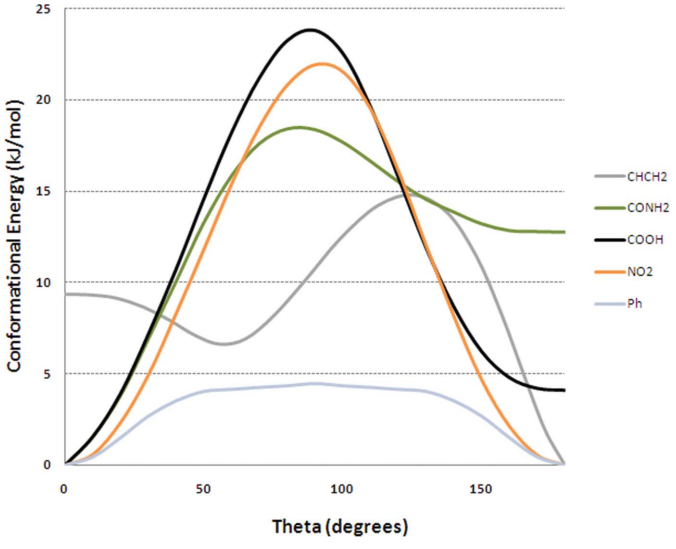


Figure 2
Calculated torsional (τ, Fig. 1) energy profiles for cyclopropane carrying a single π-acceptor substituent. DFT calculations used the B3PW91/aug-cc-pVTZ level of theory.

Table 1
Key relative energy values (kJ mol^{-1}) from the torsional profiles for π-acceptor substituents on cyclopropane rings calculated using DFT at the B3PW91/aug-cc-pVTZ level of theory.

The torsion angle (τ, °) is defined in Fig. 1.

	Torsion angle (τ)				
Substituent	0	60	90	120	180
-Carboxylic acid (COOH)	0.0	18.2	23.8	15.8	4.1
-Amide ($CONH_2$)	0.0	15.8	18.4	15.5	12.8
-Nitro (NO_2)	0.0	16.1	21.9	Symmetric	Symmetric
-Phenyl (C_6H_5)	0.0	4.1	4.4	Symmetric	Symmetric
-Vinyl ($CH{=}CH_2$)	9.4	6.6	10.1	14.8	0.0

4.2. CSD torsional distributions

Fig. 3 shows the τ distributions from the CSD for the π-acceptor substituents studied in the DFT analysis above and for which sufficient crystal structure data are available. A statistical summary of these and other CSD τ distributions is given in Table 2. There is generally excellent correspondence between the τ-distributions observed experimentally in crystal structures and the global and local energy minima calculated using DFT.

For $-$COO*R* substituents in the CSD (Figs. 3*a* and *b*) the *cis*-bisected conformer is dominant (>70%, Table 2) over the *trans*-bisected conformer ($\sim$15%, Table 2). Although it is inappropriate to use experimental torsional distributions from

e.g. the CSD to derive quantitative energy relationships (Bürgi & Dunitz, 1988), it is relevant to note that the experimental conformer ratios are well aligned with the 80:20 *cis*:*trans* percentage ratio expected from a room-temperature Boltzmann distribution for an energy difference of ~ 4 kJ mol^{-1} (Table 1). Nevertheless, the —COO*R* distribution (Fig. 3*a*) resulting from the general CSD search shows a significant population in the energetically disfavoured τ range from 30 to 150°, in particular around $\tau = 60°$. These higher-energy conformers arise from steric effects in highly substituted rings, particularly those involving additional large substituents *gem* to the —COO*R*. The cluster around $\tau = 60°$ arises from multi-fragment contributions from a rather small number of structures which are multiply substituted by up to six —COOEt or —COOMe groups. The effect of these contributions is to lower the *cis*:*trans* conformer ratio for this CSD subset. When substitution is further restricted to only —COOH, or to the presence of just a single —COO*R* or —COOH substituent, the CSD τ distributions (Fig. 3*b*, Table 2) reflect the calculated *cis*:*trans* energy difference very well.

For —CONR_2 substituents (Figs. 3*c* and *d*, Table 2) there is a complete absence of *trans* conformers, as expected from the 12.8 kJ mol^{-1} energy difference (Table 1). This is true even for the general search (Fig. 3*c*), but as with the general —COO*R* distribution (Fig. 3*a*) steric effects in a few highly substituted rings force energetically disfavoured —CONR_2 conformations. Again, the distribution from the specific search for single —CONR_2 substituents (Fig. 3*d*) more closely reflects the energy profiles of Fig. 2 with rather few examples showing serious steric hindrance. In five of the six examples having $\tau >$ 30° there is additional substitution *gem* to the —CONR_2, while in the sixth example both *R* groups are bulky cyclohexyl units which must minimize steric interactions with a *vic* methyl group. Unfortunately, there are too few CSD examples of unsubstituted —CONH$_2$ substituents for a meaningful torsional analysis.

The clear preference for —C═O substituents to adopt the *cis*-bisected conformation is also reflected in CSD data for cyclopropyl ketones (for which DFT calculations were not performed). In the general search (Table 2) 49.1% of the 108 CSD examples are *cis*-bisected, while only 2.8% are *trans*-bisected. The remaining 48.1% occupy the τ range from 30 to 150°, but in this case the observed range actually lies within the much narrower range 30–94°, and the conformers can be described as *cisoid* rather than *transoid*. As with the —COO*R* subset this sample of non-conjugated intermediate conformations is dominated by fragments involving multiply substituted rings. Despite the rather low number (31) of cyclopropyl fragments having the ketone as the sole strong electron-acceptor or electron-donor substituent in the specific search (Table 2), the proportion of $\tau = 30$–150° conformers decreases to just 6.5%, while the proportion of *cis*-bisected conformers rises to 83.9%.

For phenyl substituents Figs. 3(*e*) and (*f*) show conformational density across the complete symmetrized torsional range from 0 to 90°, a situation which arises from the low phenyl rotational barrier of 4.4 kJ mol^{-1} and the bulky nature of generalized phenyl substituents retrieved in both the general and specific CSD searches.

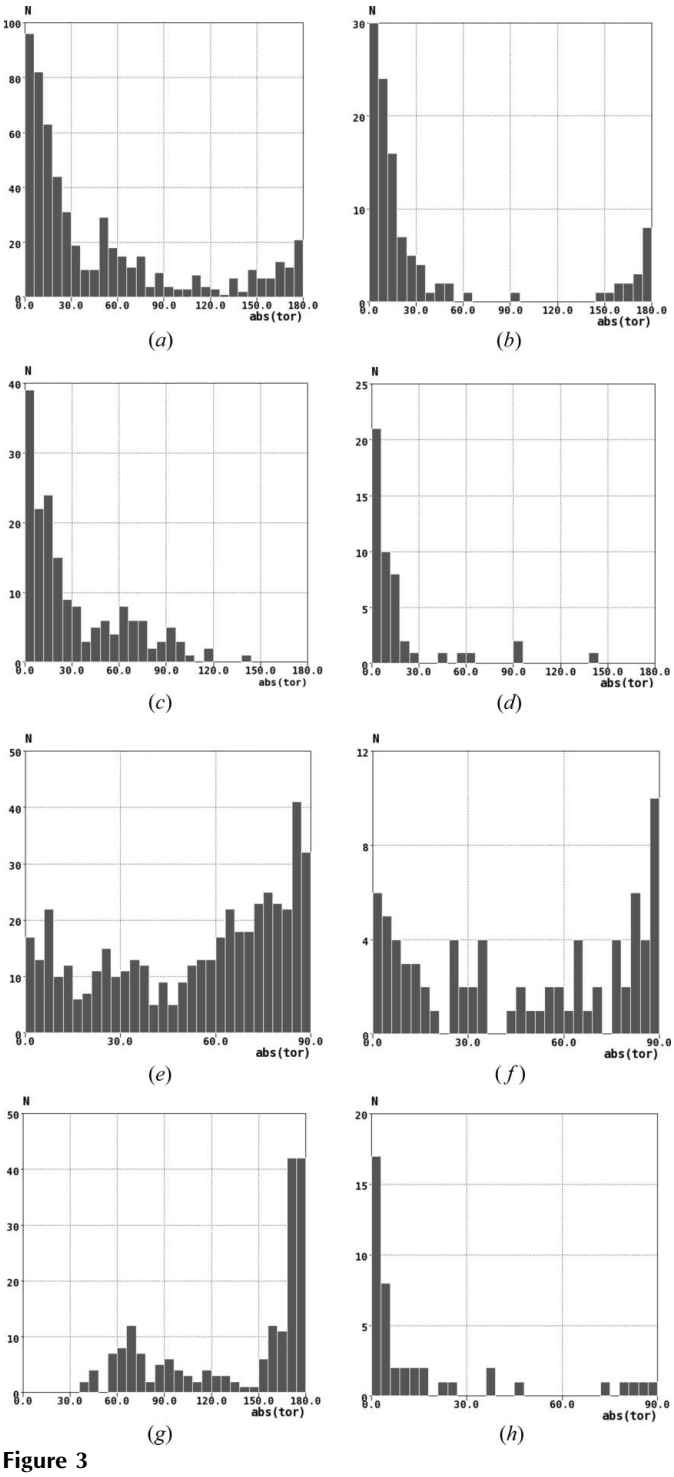


Figure 3
Torsional distributions from the CSD for π-acceptor substituents on cyclopropane arising from: (*a*) and (*b*) general and specific —COO*R* substructures, (*c*) and (*d*) general and specific CONR_2 substructures, (*e*) and (*f*) general and specific -phenyl substructures, (*g*) general -vinyl substructures, and (*h*) general NO$_2$ substructures, where general substructures permit any substitution additional to the π-acceptor stated, and specific substructures require the stated substituent to be the only π-acceptor or δ-donor substituent on the ring (although non-acceptor and non-donor substituents are permitted).

Table 2
Summary of experimental torsional distributions for π-acceptor substituents on cyclopropane rings determined from crystal structures in the CSD.

N_f is the total number of substructures in each distribution, and N (%) records the number and percentage of these substructures within the specified τ range, where τ is defined in Fig. 1. Substituent R is C or H and data are given for both general (G) and specific (S) searches of the CSD as described in §3.

			N (%) values for τ ranges		
Substituent	Search	N_f	τ = 0–30°	τ = 30–150°	τ = 150–180°
Acids and					
—C(═O)O*R*	G	560	316 (56.4)	185 (33.0)	59 (10.5)
—C(═O)OH	G	126	89 (70.6)	16 (12.7)	21 (16.7)
—C(═O)O*R*	S	110	82 (74.5)	12 (10.9)	16 (14.5)
—C(═O)OH	S	25	19 (76.0)	2 (8.0)	4 (16.0)
Amides					
—C(═O)NR_2	G	172	109 (63.4)	36 (36.6)	0 (0.0)
—C(═O)NH_2	G	25	15 (60.0)	10 (40.0)	0 (0.0)
—C(═O)NR_2	S	48	42 (87.5)	6 (12.5)	0 (0.0)
Ketones					
—C(═O)*R*	G	108	53 (49.1)	52 (48.1)	3 (2.8)
—C(═O)*R*	S	31	26 (83.9)	2 (6.5)	2 (9.7)

			τ = 0–30	τ = 30–90	τ = 90–150	τ = 150–180
-Vinyl	G	189	0 (0.0)	47 (24.9)	29 (15.3)	113 (59.8)
-Vinyl	S	53	0 (0.0)	21 (39.6)	10 (18.9)	22 (41.5)
-Phenyl	G	466	123 (26.4)	343 (73.6)	Symmetric	Symmetric
-Phenyl	S	79	30 (38.0)	49 (62.0)	Symmetric	Symmetric
—NO_2	G	43	35 (81.4)	8 (18.6)	Symmetric	Symmetric

The CSD torsional distribution from the general search for vinyl substituents (Fig. 3*g*) is in excellent overall agreement with the DFT results, and with the gas-phase electron diffraction and spectroscopic results discussed in the previous section. There is zero density close to $\tau = 0°$, maximum density close to 180° and a definite smaller peak in the 30–90° range. Again, the 29 substructures in the energetically disfavoured region, τ = 90–150° are all examples of multiply substituted rings, and often have additional R substituents in vinyl groups of the form —C(R or H)═C(R or H)$_2$, which must then compete sterically with other *gem* or *vic* substituents on the cyclopropane ring. If we eliminate these 29 substructures from the calculation of the *trans*:*gauche* percentage ratio, then 71% of the remaining 160 general vinyl substituents are *trans*, and 29% are *gauche*: a result which is comparable to the 77:23% ratio indicated by gas-phase electron diffraction (Traetteberg *et al.*, 1988) and to the 79 (3):21 (3)% ratio from vibrational spectroscopy (Durig *et al.*, 2005).

For the nitro group (Fig. 3*h*, Table 2) 35 of the 43 examples from the general CSD search adopt a bisected conformation, which is unsurprising given the 21.9 kJ mol^{-1} energy barrier in the perpendicular form (Table 1). Nevertheless, eight substructures lie in the energetically disfavoured region with $\tau > 30°$ and all of these experience steric crowding owing to multiply substituted rings. Five of the substructures have τ approaching 90° and all have *gem*-C═O substituents from keto or carboxylic acid groups, resulting in competition for the favoured bisected conformation. However, in two other cases of *gem*-(nitro,carbonyl) substitution, it is the —C═O that is forced to adopt the unfavourable perpendicular conformation.

4.3. Using *Mogul* to identify conformational preferences in substituted cyclopropanes

Mogul (Bruno *et al.*, 2004), a searchable library of intramolecular geometry derived from the CSD and distributed as part of the CSD system, is frequently used in molecular modelling to assess the experimentally observed conformational preferences of chemical fragments in crystal structures. Two *Mogul* torsional distributions for cyclopropane rings having π-acceptor substituents are presented in Fig. 4, (*a*) for —COOH and (*b*) for —CONH$_2$ substituents.

While both *Mogul* and *ConQuest* searches use the CSD as their data source, there are differences in the search methodologies. In *ConQuest* the environment of a search fragment

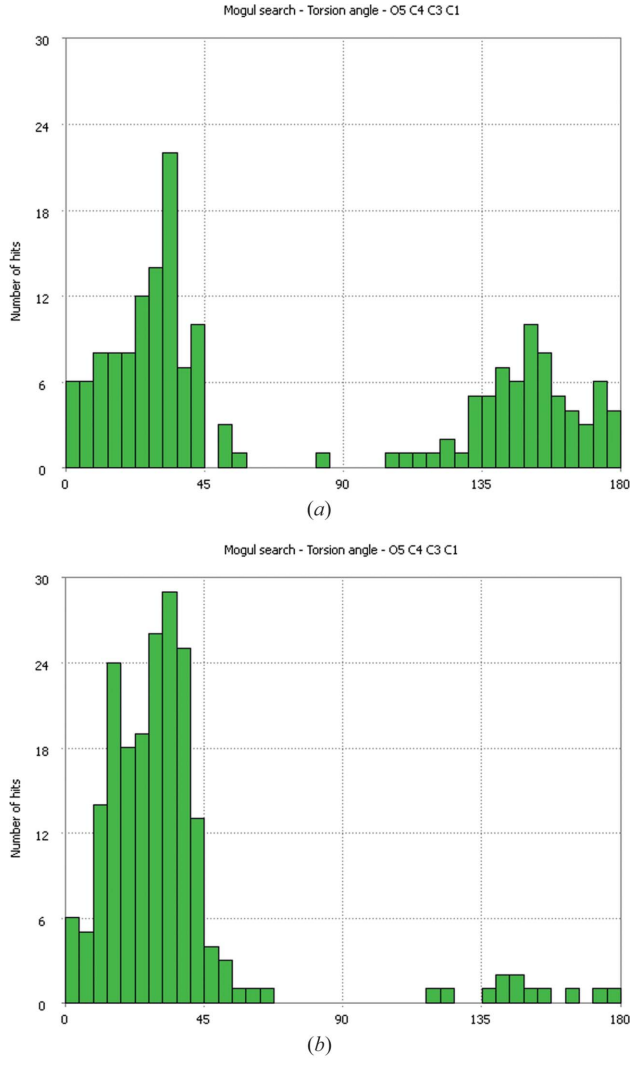


Figure 4
Torsional distributions for π-acceptor substituents on cyclopropane from the intermolecular geometry library *Mogul* (*a*) for —COOH substituents and (*b*) for —CONC$_2$ substituents. See text for notes on differences between CSD searches with *ConQuest* and the *Mogul* search methodology.

Table 3
Optimized cyclopropane ring bond lengths (Å) from DFT calculations at the B3PW91/aug-cc-pVTZ level of theory compared with mean experimental values (Å) from the CSD.

CSD results are given in the form $d(\sigma_s,n)$, where σ_s is the sample e.s.d., and n is the number of contributors to the sample. The two vicinal bonds, d_1 and d_2, are averaged together. Asymmetry parameters (δ, in Å) are given in each case and are compared with δ(1980) values recomputed from the data of Allen (1980), as described in §3.

	DFT results				CSD results			
Substituent	*d*1	*d*2	*d*3	δ	*d*1,*d*2	*d*3	δ	δ(1980)
−COOH	1.513	1.513	1.483	−0.015	1.516 (9,46)	1.482 (15,23)	−0.016	−0.019†
$-CONH_2$	1.510	1.510	1.485	−0.012	1.518 (13,274)	1.489 (20,137)	−0.014	−0.019†
-Vinyl	1.511	1.511	1.492	−0.010	1.513 (8,56)	1.489 (18,28)	−0.012	−0.016
-Phenyl	1.509	1.509	1.493	−0.008	1.514 (9,52)	1.496 (12,26)	−0.009	−0.014
$-NO_2$	1.501	1.501	1.489	−0.006	1.515 (9,16)	1.492 (9,8)	−0.011	–
−CN	1.512	1.512	1.490	−0.011	1.520 (9,42)	1.492 (9,21)	−0.014	−0.013

† Allen (1980) presented data for a generic −C═O acceptor arising from both carboxylic acid and amido substituents taken together. Here crystal structure data are given for −COOH alone, and for $-CONR_2$; there are insufficient pure amides $-CONH_2$, for a viable analysis.

is defined in the connectivity query using specific element definitions, or it can be generalized:

(*a*) through the use of free points of substitution, *i.e.* any element is accepted, or

(*b*) by using generalized element definitions such as C,H only, halogen only, or a user-specified list of permitted elements.

Mogul uses a hierarchical tree structure to record details of bond, angle and torsion fragments together with their exact local environment. The numerical distributions displayed can be restricted to exact matches or generalized to include information from fragments with high chemical similarity to the search fragment (bond, angle or torsion). The default similarity cut-off is 0.75 (Bruno *et al.*, 2004), but can be set higher or lower by the user. Given that carboxylic acid and amide substituents are quite similar in *Mogul* terms (similarity coefficient of *ca* 0.80), *Mogul* hits should be inspected to ensure that suitable similarity cut-offs are used to retrieve appropriate torsional distributions. Once this is done (see Fig. 4) then distributions that closely mirror those in Figs. 3(*a*) and (*c*) are obtained. [Torsions in *Mogul* use chemical bonds (the vicinal bonds in Fig. 1) not bond midpoints, and absolute torsions are reported. Hence, *cis*- and *trans*-bisected π-acceptor conformers occur at $\tau(Mogul) \simeq 30$ or $\simeq 150^\circ$.]

5. Bond length asymmetry

5.1. *Ab initio* geometry and CSD data

Table 3 compares optimized ring geometry from the DFT calculations with the mean ring bond lengths obtained from distributions obtained in the specific searches of the CSD. Also included in Table 3 are asymmetry parameters δ, obtained by both theory and experiment. These δ values are compared with the earlier δ(1980) values re-computed from Allen (1980) as described in §3. There is excellent overall agreement between the DFT and CSD results in Table 3, with CSD values being slightly larger than the *ab initio* results for each of the substituents. This consistency is remarkable, given the very small values of δ, and particularly bearing in mind the typical level of bond length e.s.d.s in crystal structures. The largest difference between the calculated and experimental results occurs for the nitro substituent. However, only eight CSD examples are retrieved in the specific search, where nitro is the only substituent interacting with the ring, and this CSD analysis is less reliable than for the other substituents.

5.2. Additivity of asymmetry parameters

Allen (1980) carried out a detailed analysis of bond lengths in cyclopropane rings that were multiply substituted with π-acceptor substituents and concluded that substituent effects on ring bond lengths were additive. Thus, with two π-acceptor substituents, *X* and *Y*, on the same ring carbon, the distal bond should shorten by $\delta(X) + \delta(Y)$, while the vicinal bonds should lengthen by the same amount, hence $\Delta = d(\text{distal} - d(\text{vicinal}) = 2[\delta(X) + \delta(Y)]$. If $Y = X$ either chemically or by virtue of identical individual δ values then $\Delta = 4\delta(X)$. There are rather few CSD structures that:

(i) have two chemically identical π-acceptor substituents on the same ring carbon, with

(ii) both adopting a bisected conformation (or being −CN), and

(iii) with no other strong electron donor or acceptor substituents on the ring.

However, if we regard $-COOR$, $-CONR_2$ and −CN substituents as 'equivalent' in light of their closely similar δ values (Table 3), 17 chemical fragments can be located in the CSD that fulfil criteria (i)–(iii) above. The mean value of *d*(distal) is 1.471 (12) Å, and the mean *d*(vicinal) is 1.531 (9) Å, where σ(sample) is given in parentheses. In this case $\Delta = 4\delta = -0.060$ Å, and $\delta = -0.015$ Å, a value which is almost identical to the δ values (Table 3) for each individual substituent included in the search.

There are a number of CSD examples of cyclopropane rings having two π-acceptor substituents on adjacent C atoms, with no other electron-withdrawing or -donating substituents on the ring. Seventeen of these examples have identical vicinal $-COOR$ or $-CONR_2$ (hereafter 'carbonyl' substituents for which the δ values are almost identical (Table 3), while five

examples have dicyano substitution. For equivalent substituents, two of the ring bonds are distal to one substituent and vicinal to the other (*dv* bonds), and the asymmetry effects cancel out. However, the bond between the substituents is vicinal to both (*vv* bond), and its length should increase by 2δ. Using the $d(\sigma(\text{sample}))$ format, the 17 vicinal dicarbonyls have 34 *dv* bonds with a mean length of 1.495 (11) Å, while the mean *vv* bond is 1.532 (12) Å; the difference of 0.037 Å gives a carbonyl δ value of −0.019 Å closely comparable to the values for −COO*R* or −CONR_2 in Table 3. The five vicinal dicyanocyclopropanes have mean *dv* = 1.494 (9) Å, and mean *vv* = 1.526 (15) Å, giving a cyano δ value of −0.016 Å, again close to the single substituent value in Table 3.

In the case of 1,2,3-trisubstitution by identical π-acceptors in bisected conformations (or −CN), all three ring bond lengths should be equal, but asymmetry effects should increase individual and mean ring-bond lengths over values for unsubstituted rings. Thus, each ring bond is distal to one of the substituents, but is vicinal to two of them, leading to an increase in each bond length by δ Å. There are only three suitable examples in the CSD, for which the mean ring-bond length is 1.516 (3) Å, longer by 0.011 Å than the mean ring bond over all CSD examples [1.505 (12) Å, see above]. This overall lengthening effect is doubled, to 2δ Å, for rings that are hexa-substituted by an effective π-acceptor. In the CSD five rings are hexa-substituted by conjugated carbonyl or cyano groups, and the 15 ring bonds average to 1.538 (5) Å, longer by 0.033 Å than the CSD global mean noted above and giving a δ value of −0.017 Å for these substituents, in close accordance with data in Table 3.

Recognition of the quite obvious effects of π-acceptor substituents on cyclopropane ring bond lengths, even in cases of symmetrical substitution, calls into question the derivation of the mean C—C bond length in cyclopropane when it is determined from crystal structure data that exhibit a wide variety of electron-withdrawing and -donating substituents. We will return to this topic in more detail elsewhere (Cruz-Cabeza & Allen, 2011) in a discussion of cyclopropane rings that carry electron-donating substituents.

6. Conclusions

The crystal structure data and DFT calculations described here clearly illustrate the conformational importance of conjugative interactions between cyclopropane rings and π-acceptor substituents. Where steric hindrance is not an issue, substituents prefer to adopt a bisected arrangement with respect to the ring, and where the substituent is asymmetric (*e.g.* −COOH, vinyl *etc.*), strong preferences exist for either *cis*- or *trans*-bisected conformations. Thus, where conjugation is with a −C═O acceptor (acids, esters, amides and ketones), the strong DFT energetic preference for *cis*-bisected conformers is clearly reflected in the crystal structure data, with limited occurrence of *trans*-bisected forms, reducing to a zero occurrence of the *trans* form for amide −C═O acceptors. For the vinyl −C═C acceptor the DFT energetic preference is for the *trans*-conformer, again clearly reflected in crystal structures, but with a local *gauche* energy minimum at $\tau \simeq 60^\circ$ which is also represented in crystal structures with a *trans*:*gauche* ratio close to that observed in the gas phase.

Importantly, we have also illustrated the conformational variation that occurs in cyclopropane derivatives in which the ring is multiply substituted by even quite small groups, such as −COO*R*, −CONR_2, −CO*R*, phenyl, nitro *etc.*, especially when pairs of substituents are bonded to the same ring carbon. In modelling cyclopropyl compounds having multiple ring substituents, the CSD is an indispensible resource for indicating the likely conformational outcomes of steric interactions between substituents, information that can be obtained through CSD searches and data analyses for specific ring-substitution patterns.

This work has again shown the excellent correspondence between torsional distributions obtained from experimental crystal structures and conformational energy profiles computed using *ab initio* methods. The work complements other similar studies (*e.g.* Allen *et al.*, 1996; Weng *et al.*, 2008) and reinforces the value of crystal structure conformations in applications such as drug discovery (Brameld *et al.*, 2008), structure solution using powder diffraction data (Pidcock *et al.*, 2007), and to obtain conformation(s) for use in crystal structure prediction (Cooper *et al.*, 2007; Kazantsev *et al.*, 2011). We have shown that the overall conformational preferences of cyclopropyl derivatives can be rapidly assessed through simple CSD searches and data analyses, or through the use of the *Mogul* library of intramolecular geometry. These two procedures are normally quicker and far less c.p.u.-intensive than computational techniques.

AJCC thanks the Pfizer Institute for Pharmaceutical Materials Sciences for funding.

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