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Alicyclic Ring Structure: Conformational Influence of the CF_2 Group in Cyclododecanes**

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Selective incorporation of fluorine atoms is a proven and powerful method for modulating the properties of organic compounds for the development of performance molecules.[1] For example the selective introduction of fluorine as a replacement for hydrogen or an hydroxy group can confer improved properties in the development of medicinal chemistry products[2] due to the small size and high polarity of the C–F bond,[3] and incorporation of the C/O/S-CF_3 group onto molecular frameworks has been widely adopted as a strategy for modulating pharmacokinetic properties within the medicinal chemistry[4] and agrochemistry industries.[5] Also the dipole moment associated with the C–F bond and its low viscosity modulus has rendered fluoroorganics important entities in organic materials such as liquid crystals.[6] Although selective fluorination and CF_3 incorporation have been widely explored, the CF_2 group has received relatively limited attention despite having unique properties as a functional group.[3,7] For example H_2CF_2 has the highest dipole moment (1.97 D) relative to H_3CF (1.87 D) or HCF_3 (1.65 D) progressing along the fluoromethane series from methane to tetrafluoromethane.[8] Here we have focused on the role of the CF_2 group as a CH_2 replacement, and as a case study have selected the alicyclic ring, cyclododecane (**1**) as a molecular framework to explore its steric and structural influence. At the outset a screen of all structures deposited in the Cambridge Crystallographic Data Centre (CCDC) containing the $\sim CH_2CF_2CH_2 \sim$ motif were explored to assess trends in the F-C-F and C-C(F_2)-C bond angles.[9] The search revealed that from 23 compounds and 38 motifs, satisfying this criterion, the average C-CF_2-C angle was 118° and the average F-C-F angle was 104° (Figure 1), significantly wider and narrower, respectively, than the tetrahedral angle and consistent with the earlier predictions from Wiberg's theory analyses.[10] These geometric changes can be rationalized by valence shell electron pair repulsion theory (VSEPR) analysis of the central carbon atom.[3,11] To a first approximation this indicates that the difluoromethyl group will relax strained alicyclic rings as it can accommodate a much wider C-C(F_2)-C angle relative to C-C(H_2)-C.

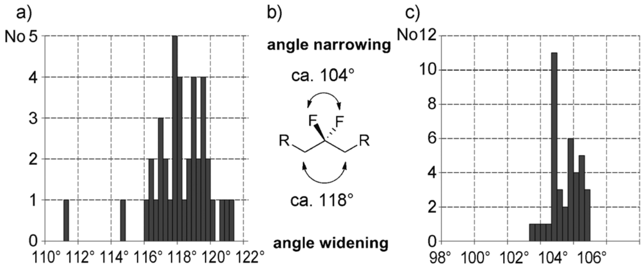

Figure 1. a,c) Histograms reporting the range of angles from 23 structures containing 38 $\sim CH_2CF_2CH_2 \sim$ motifs within the Cambridge Crystallographic Data Base. a) C-C(CF_2)-C angles; c) F-C-F angles. b) Summary of the average angles in this study.

Cyclododecane (**1**) has a melting point (m.p.) of 64 °C and is the first of the alicyclic rings which is a solid at room temperature. In a landmark paper in 1960 Dunitz and Shearer[12] solved the structure of cyclododecane by single-crystal X-ray diffraction, although the molecule was highly disordered with large thermal parameters. Their best solution concluded that in the solid state, **1** is essentially a square [3333][13] structure with the four-carbon chain edges arranged in an *anti* zig-zag manner, as shown in Figure 2 a. Subsequent theory[14] and electron diffraction[15] studies supported this D_4 structure. Anet et al. determined an experimental (NMR) conformational energy barrier of 7.3 $kcal\,mol^{-1}$ for the cyclododecane ring interconversion.[14,16] This is several $kcal\,mol^{-1}$ lower than e.g. cyclohexane (10.5 $kcal\,mol^{-1}$)[13b] indicative of significant conformational flexibility and consistent with the difficulty of resolving the solid-state structure by X-ray diffraction. It follows from the [3333] structure that there are eight *endo* hydrogen atoms pointing into the molecule, four above and four below the plane of the ring, each quartet arranged in a square. The 1,4-H,H transannular contacts are at van der Waals proximities (2.10–2.25 Å), and are a significant feature adding to the ring strain. Also the [3333] structure clearly distinguishes edge and corner methylene (CH_2) groups. The ring offers an interesting framework in which to explore the nature of the CF_2 group and in particular to establish the preferred location of CF_2. Will it prefer to locate at a corner or an edge?

At the outset a sample of 1,1-difluorocyclododecane (**2**) was prepared by treatment of cyclododecanone with HF/SF_4.[17] This gave a low-melting gel-like solid (m.p. 44 °C as determined by DSC; see Supporting Information). Similar to **1**, cyclododecane **2** proved very difficult to obtain good X-ray

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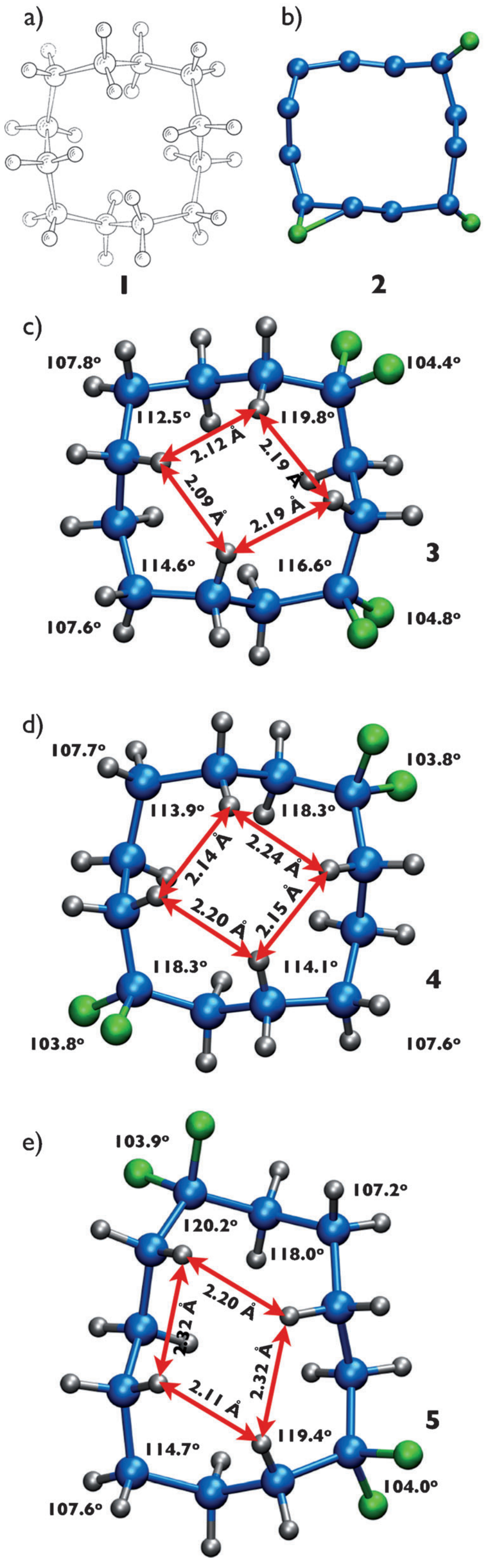


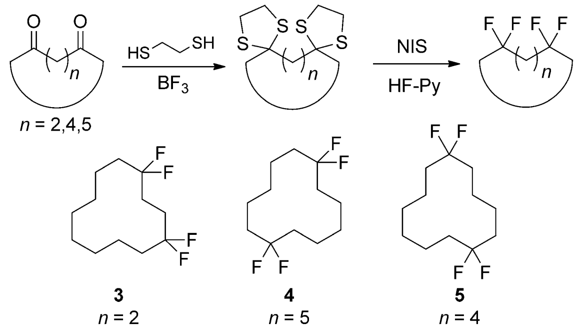
Figure 2. X-Ray crystal structures of cyclododecanes. a) The Dunitz & Shearer [3333] structure of cyclododecane (**1**). b) Disordered structure of 1,1-difluorocyclododecane (**2**). The fluorines were randomly located at corners and the hydrogen atoms were insufficiently resolved. c) The structure of 1,1,4,4-cyclododecane (**3**). d) The structure of 1,1,7,7-cyclododecane (**4**). e) The distorted [4332] structure of 1,1,6,6-cyclododecane (**5**).

diffraction data due to considerable molecular disorder within the unit cell. However, after many attempts a disordered structure was solved, with electron density from the fluorine atoms poorly resolved, but located only at the corner positions of a [3333] structure, as shown in Figure 2b. It appears the molecules pack rather randomly with respect to which corner the CF_2 occupies relative to neighboring molecules. The best we could conclude from this structure was that there was a preference for CF_2 to occupy corner rather than edge locations.

A quantum chemical study (MP2/6-311+G(2d,p)//B3LYP/6-311+G(2d,p)+ZPE)[18] was carried out to determine the relative energies of minimized 1,1-difluorocyclododecane (**2**) structures with the CF_2 placed either at an edge or at a corner position. The structure with CF_2 at the corner was calculated to be 2.86 kcal mol^{-1} lower in energy relative to an edge location, consistent with the developing experimental observations (see Supporting Information). In order to improve the molecular order, two CF_2 groups were placed within the cyclododecane ring, with a spacing designed to occupy adjacent or opposite corner locations of the [3333] structure. Accordingly 1,1,4,4- (**3**) and 1,1,7,7-tetrafluorocyclododecanes (**4**) became synthesis targets.

Tetrafluoroclodododecanes **3** and **4** were prepared as summarized in Scheme 1. In each case they were accessed by fluorination of their respective 1,4- and 1,7-dithiane precursors, following the methodology of Sondej and Katzenellenbogen[19] for CF_2 preparations from ketones. 1,1,4,4-Tetrafluoroclodododecane (**3**) is a crystalline solid (m.p. 83 °C) and X-ray analysis of a suitable crystal generated the structure in Figure 2c. This was a well behaved structure and there was now no problem in obtaining good diffraction data. The CF_2 groups do indeed occupy corner locations and this leads to a significantly improved solid-state order relative to **2**.

A low-temperature (CD_2Cl_2, 200 K) ^{19}F NMR experiment on **3** allowed resolution of the fluorine atoms into an AB-system distinguishing pseudo-axial and pseudo-equatorial fluorines at the corners of the ring (see Supporting Information). Rate constants for the ring interconversion were determined by complete lineshape analysis of the ^{19}F NMR spectra recorded across the temperature range 190–295 K.



Scheme 1. Synthesis approach to cyclododecanes carrying two CF_2 groups by fluorination of bisdithiane precursors.[16] Cyclododecanes **3** and **4** are designed to locate the CF_2 groups at adjacent and opposite corners of the [3333] ring structure, respectively, and cyclododecane **5** is designed as a mismatched structure.

Fitting the Eyring equation[20] to the experimental data allowed determination of the activation parameters: $\Delta G^{\neq} = 9.54\ \text{kcal mol}^{-1}$, $\Delta H^{\neq} = 9.16\ \text{kcal mol}^{-1}$, and $\Delta S^{\neq} = -1.26\ \text{cal K}^{-1}\text{mol}^{-1}$ (see Supporting Information). Thus, cyclododecane **3** has a conformational energier barrier $3.0\ \text{kcal mol}^{-1}$ higher than cyclododecane itself indicating that the CF_2 groups introduce conformational stability.

1,1,7,7-Tetrafluorocyclododecane (**4**) resulted in a much higher melting solid (143 °C) which was also readily amenable to X-ray structure analysis, and the resultant structure is shown in Figure 2 d. A quantum chemical study (MP2/6-311 + G(2d,p)//B3LYP/6-311 + G(2d,p) + ZPE)[17] on **4**, similar to that carried out for **2**, indicated that the corner/corner structure was more stable than the alternative edge/edge [3333] structure by $5.91\ \text{kcal mol}^{-1}$ (see Supporting Information). The fluorine of the CF_2 groups at the corner locations are *exo* to the ring and they provide conformational stability to the ring structure. This corner/corner structure has C_2 symmetry, and unlike **3** low-temperature ^{19}F NMR spectroscopy did not resolve these fluorines. However, ^{1}H NMR lineshape analysis and coalescence of *exo* and *endo* edge CH_2 groups of **4** allowed evaluation of the free-energy barrier ($\Delta G^{\neq} = 10.6\ \text{kcal mol}^{-1}$) at the coalescence temperature (233 K), which is significantly higher than for cyclododecane ($7.3\ \text{kcal mol}^{-1}$) and 1,1,4,4-tetrafluoroclododecane (**3**) ($9.54\ \text{kcal mol}^{-1}$). This increased stability to ring interconversion for **4** relative to **3** may be due to its zero dipole moment.

Analysis of the structures of cyclododecanes **3** and **4** reveal that the CH_2-C(F_2)-CH_2 angles are wide, ranging from 115–118° consistent with the CCDC survey described in Figure 1.[9] This presumably relieves some angle strain relative to the native cyclododecane structure **1**. The angle widening also has the consequence of relaxing 1,4-H,H transannular interactions above and below the face of the ring. These non-covalent interactions are lengthened by the presence of the CF_2 group at a corner position relative to those interactions with CH_2 at the corner (e.g. 2.24 Å/2.20 Å versus 2.14 Å/2.15 Å in **4**). Thus there are two effects, angle widening and transannular relaxation, favoring the corner location of the CF_2 group. Additionally, if CF_2 were located at an edge, the 1,4-H,F interaction of the *endo* fluorines would be raised in energy relative to the corresponding 1,4-H,H interaction due to the slighly larger steric influence of fluorine.

In order to gain further insight into the influence of CF_2 groups within the cyclododecane motif a synthesis of 1,1,6,6-tetrafluorocyclododecane (**5**) was carried out. This molecule was selected because one of the CF_2 groups is forced to an edge position, if the cyclododecane maintains a square [3333] structure. Tetrafluoroclododecane **5** was prepared by the route illustrated in Scheme 1. This compound has the lowest melting point (40 °C) of the series **1**–**5**, and it was significantly more amorphous in nature than **3** and **4**. Accordingly it proved very difficult to find a suitable crystal for X-ray analysis. After extended trials a small crystal of **5** was identified which diffracted X-rays, and the resultant structure is shown in Figure 2 e. It is clear that the ring conformation has changed significantly from the [3333] square type conformation to a distorted [4332] pseudo-rectangular structure. The 1,6-CF_2 groups force this conformational change such that they avoid edge positions, presumably due to unfavorable 1,4-H,F steric interactions which would arise if a fluorine atom was located at one of the four transannular positions above (or below) the plane of a [3333] ring. Features of the structure of **5** suggest substantial ring strain. The C-C(CF_2)-C angles are 119.4° and 120.2° the widest observed in this family of structures so far. Nonetheless, the CF_2 groups organize the ring in such a manner that they maintain corner locations.

In summary, we have used cyclododecane as a molecular framework to explore the steric and geometric influence of the CF_2 group. It emerges from this study that there is a very strong geometric preference for the CF_2 to locate at corner positions of the ring, to relieve both angle strain and relax 1,4-H,H transannular interactions. The cyclododecane [3333] conformation is particularly tensioned due to transannular H–H interactions and the system avoids 1,4-H,F transannular interactions due to the small but increased van der Waals/steric influence of fluorine. Judicious spacing of two CF_2 groups can lead to relatively stable ring conformations, for example, in the case of structures **3** and **4**. It follows that strategic incorporation of one or more CF_2 groups could stabilize larger alicyclic rings. The polar nature and conformational preference of the CF_2 group offers potential as a strategy in the design of performance aliphatic compounds which require both molecular order and polarity, such as organic liquid crystals and polymer chains.

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