Pure Appl. Chem., Vol. 84, No. 7, pp. 1587–1595, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-09-26

Influence of the difluoromethylene group (CF_2) on the conformation and properties of selected organic compounds*

David O'Hagan‡, Yi Wang, Maciej Skibinski, and Alexandra M. Z. Slawin

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK

Abstract: The CF_2 group has found applications as a substituent in all classes of organic chemical products from medicinal products to materials, although it is less frequently encountered than the C–F and CF_3 substituents. In this review, the geometric influence of placing two fluorine atoms on carbon is considered and in particular, deviations from tetrahedral geometry are noted. The incorporation of the CF_2 group into CF_2 phosphonates as phosphate mimics is reviewed and the geometric and steric influences of the CF_2 group are considered when the substituent is placed within aliphatic chains and aliphatic ring (cyclododecane) systems.

Keywords: conformation; fluorochemistry; organic chemistry; organic materials; structure.

INTRODUCTION

Organic bound fluorine is found in all product classes of the organic chemicals industry from pharmaceuticals and agrochemicals to liquid crystals and polymers [1,2]. This is because the C–F bond is the most polar and strongest in organic chemistry, fluorine is the smallest atom after hydrogen that can form covalent bonds to carbon, and fluorine forms only weak interactions with molecules in its environment. Thus, replacing a hydrogen or oxygen atom by electronegative fluorine induces a minimal steric change, but it polarizes the molecule changing its electrostatic surface and conformation, often to advantage during structural optimization programs [3].

In this regard, there are many examples where a single fluorine has replaced a hydrogen atom such as arylfluorines in drug candidates [4]. Also, the CF_3 group has been widely explored as a functionality to improve lipophilicity and alter pharmacokinetic profiles in drug and agrochemicals development [5]. The CF_2 group is intermediate between C–F and CF_3. There are only a few commercial bioactives that contain a CF_2 group such as the well-known anesthetic isoflurane and the anticancer agent pantoprazole [6]. In materials chemistry *poly*-vinylidine fluoride (PVDF) [7], which has the repeat structure ~$(CH_2CF_2)_n$~, is probably the most important CF_2-containing material, apart from perfluorocarbons, which have a distinct set of properties [8]. Some liquid crystals have been developed containing the –CF_2O group. However, more generally, the difluoromethylene functionality has received less attention relative to –F and –CF_3. This review aims to highlight some of the particular properties of the difluoromethylene group.

Pure Appl. Chem.* **84, 1543–1667 (2012). A collection of invited papers based on presentations at the 23rd International Conference on Heterocyclic Chemistry (ICHC-23), Glasgow, UK, 31 July–4 August 2011.
‡Corresponding author: E-mail: do1@st-andrews.ac.uk

GEOMETRY OF THE CF_2 GROUP

The $(sp_3)CF_2$ group has a modified hybridization relative to $(sp_3)CH_2$. The replacement of the two hydrogen atoms of a methylene by fluorine atoms leads to widening of the C-CF_2-C angle and narrowing of the F-C-F angle [9]. This is evident from searches of the crystallographic data [9,10]. Most recently, e.g., when all of the ~$CH_2CF_2CH_2$~ motifs deposited in the Cambridge Crystallographic Database were evaluated for bond angles, then the histograms in Fig. 1 emerged [10]. It can be seen that the average C-CF_2-C angle is around 118º and the average F-C-F angle around 104º.

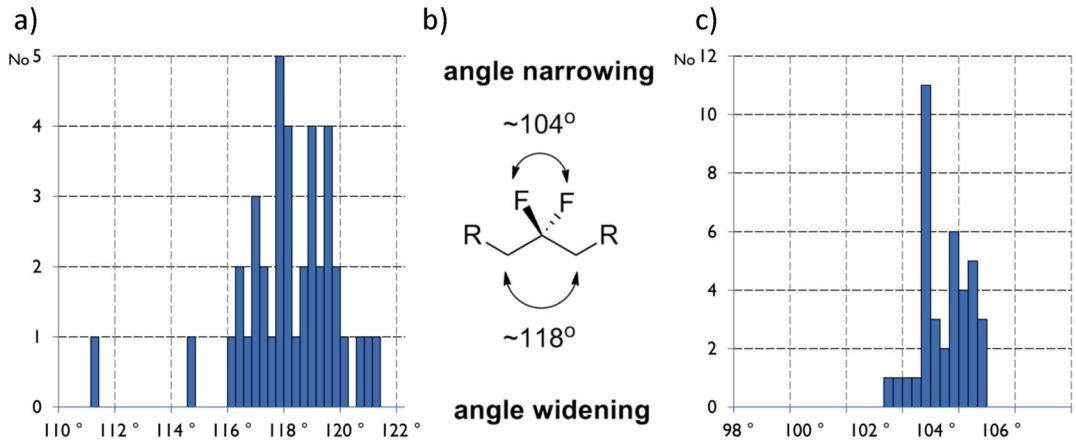


Fig. 1 Illustrates two histograms (a) and (c) which report a range of angles from 24 structures containing 39 ~$CH_2CF_2CH_2$~ motifs within the Cambridge Crystallographic Database. (a) C-CF_2-C angles; (c) F-C-F angles; (b) is an illustrative summary of the average angles in this study [10].

This trend is most straightforwardly observed in going from propane to 2-fluoro and then to 2,2-difluoropropane (Fig. 2). Bond angle data have emerged from a combination of theory and electron spectroscopy data [11,12], and there is a progressive widening of the C-C-C angle as one and two fluorine atoms are introduced onto the central carbon of propane.

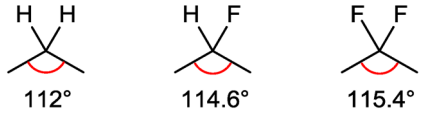


Fig. 2 Progressive angle widening progressing from propane to 2-fluoro and then to 2,2,-difluoropropane.

This trend in angle widening is also apparent in the progressively fluorinated methane series, (CH_4, CH_3F, CH_2F_2, CHF_3, CF_4) (Fig. 3). Methane and tetrafluoromethane are perfectly tetrahederal, however, a distortion in tetrahederal geometry is apparant in each of mono-, di-, and tri- fluoromethane [13,14]. For example, the F-C-F angle (108.4º) in difluoromethane is significantly narrower than tetrahedral, and the H-C-H angle (113.8º) is significantly wider. A similar trend is found in trifluoromethane.

This angle-widening phenomenon has been subject to a range of interpretations. The most straightforward explanation is a valence shell electron pair repulsion (VSEPR) analysis where the relatively electron-rich C–C and C–H bonds repel each other by comparison with the relatively electron-deficient C–F bonds, which then close up on each other, despite the -ve charge density and lone pairs on the fluorine atoms [15]. Other interpretations suggest increased *p*-orbital character for bonding to

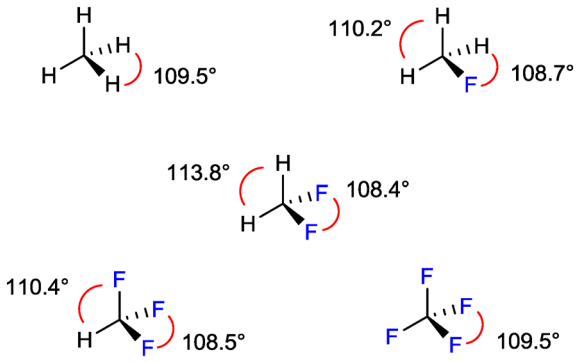


Fig. 3 Bond angles in methane and the fluoromethane series.

fluorinated carbon, owing to a lowering (increased stabilization) of the C_{2s}-orbital energy [16]. This analysis is consistent with a narrowing of the F-C-F angle. Additionally, Donald et al. [14] have proposed that the observed H-C-H angle widening could be accounted for by intramolecular, electrostatic attraction between the polarized $^{\delta+}$H and $^{\delta-}$F atoms in difluoromethane.

POLARITY OF THE CF_2 GROUP

It is interesting to note that for the series of progressively fluorinated methanes (CH_4, CH_3F, CH_2F_2, CHF_3, CF_4), difluoromethane has the largest dipole moment of the series, perhaps unexpectedly larger than trifluoromethane (Fig. 4) [14]. Thus, the CF_2 group emerges as a candidate group for incorporation into molecules that might benefit from high polarity and low viscosity. Indeed, this is the case in organic materials where the CF_2 group finds itself as a useful motif for incorporation into liquid-crystalline scaffolds [17].

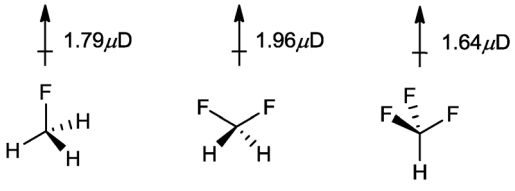


Fig. 4 Dipole moments of fluorinated methanes [14].

Polyvinylidine fluoride is the most important piezo- and pyro-electric polymeric material owing to the CF_2 groups (Fig. 5) [7]. The CF_2 dipoles orient in the same direction when placed under stress (e.g., electric field), and thus the material becomes polarized perpendicular to the carbon chain. The material then expands or contracts as the polarity of the external field direction changes [18].

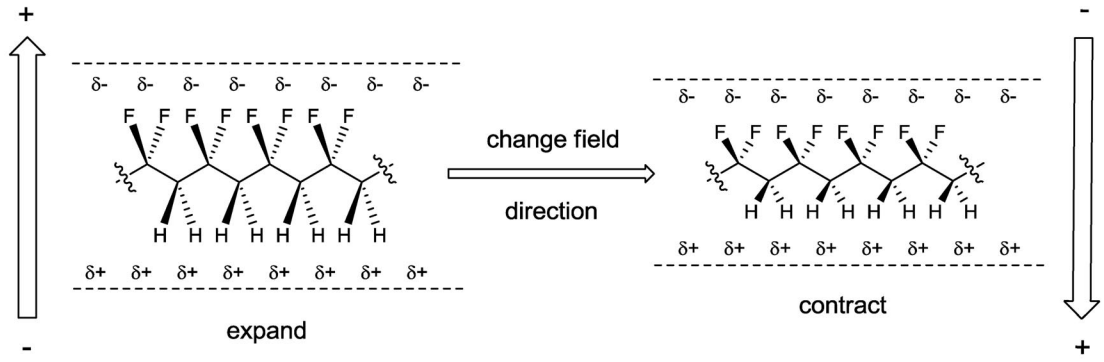
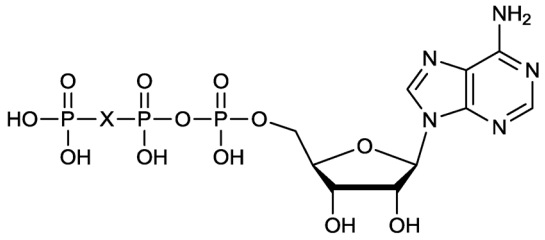


Fig. 5 The piezoelectric response of PVDF in an alternating electric field.

CF_2 PHOSPHONATES

Perhaps the most widely investigated aspect of the CF_2 group has been its replacement for oxygen by CF_2 to generate CF_2 phosphonates as phosphate mimics. This idea was first introduced by Blackburn et al. in the early 1980s (Fig. 6) [19] where they prepared phosphonates including a series of adenosine triphosphate analogues **1**, where the bridging P–O–P bond was replaced by a series of analogues, including NH, S, CH_2, and CF_2 [19a]. This study concluded that the CF_2 analogue **1c** was the most similar to oxygen as an ATP analogue when considering ^{31}P NMR and pK_a data. These observations opened up a new research area, and it was particularly applied to monophosphonates as phosphate mimetics [20,21].



1a X = O
1b X = NH
1c X = CF_2
1d X = CFH
1e X = CCl_2
1f X = C≡C
1g X = O–O
1h X = CH_2

Fig. 6 Blackburn's ATP analogues [19].

Comparisons of the phosphonate pK_a's and the C-X-P geometry of the CF_2-phosphonates relative to its analogues (X = O, CH_2, CHF) became relevant. Appropriate amino phosphonates were prepared and single-crystal structures solved to obtain structural data (R-X-P angles) such that the geometry of selectively fluorinated phosphonates could be compared to the parent monophosphonate (Fig. 7) [22,23].

It is clear from Fig. 7 that the C-X-P angle widens as we progress from the CH_2-P to CHF-P to CF_2-P phosphonate. Thus, increasing the fluorination changes the hybridization at carbon. The angle widening suggests the CF_2 phosphonate most closely mimics the phosphate C-O-P group. Titrations revealed that the second pK_a^2 of the monofluorophosphonate has the closest value to the phosphonate. Nonetheless, when a phosphate is functional as its dianion in vivo then the CF_2 phosphonate mimic will secure full ionization in the dianion form. There have been several examples of selectively fluorinated phosphonates prepared and explored as phosphonate mimics in enzymology. For example, the mono- and di-fluorophosphonate analogues of *sn*-glycerol-3-phosphate are good substrates for the enzyme glycerol-3-phosphate dehydrogenase (Fig. 8) [22].

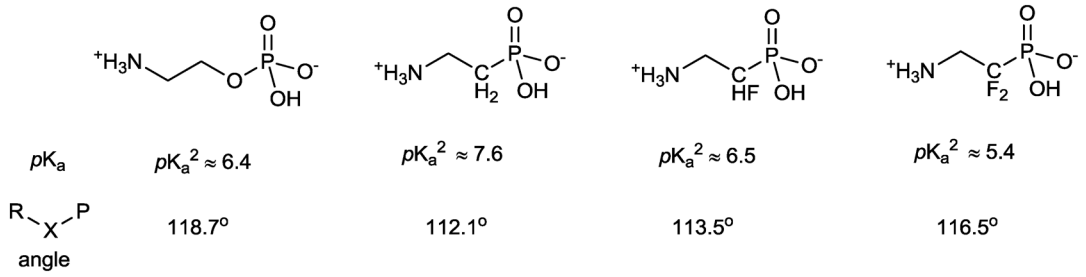


Fig. 7 Comparison of the C-X-P angles and pK_a^2 of phosphate and its phosphonate analogues.

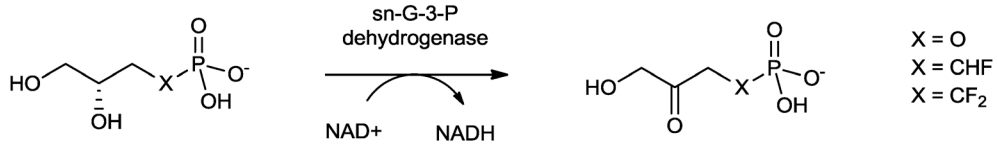


Fig. 8 Fluorophosphonate analogues of *sn*-glycerol-3-phosphate [22].

CF_2 CONTAINING FATTY ACIDS

It is interesting to explore the change in physical properties of a compound where the CH_2 group has been replaced by CF_2 [9]. In this regard, fatty acids present a useful motif for such a functional group conversion because the change can be made remote from the carboxylic acid head group, and thus any changes in physical properties can be attributed primarily to steric and geometric effects, rather than the electronic influence of the CF_2 group. In this context, stearic acids have been prepared with one **2c** and two fluorines **2d** at C-12. The analogue **2b** with fluorine at C-2 was also compared, to illustrate the dramatic effect of placing the fluorine close to the carboxylic acid moiety. These stearic acids were then converted to their corresponding tristearins **3b–d** by esterification with glycerol (Fig. 9).

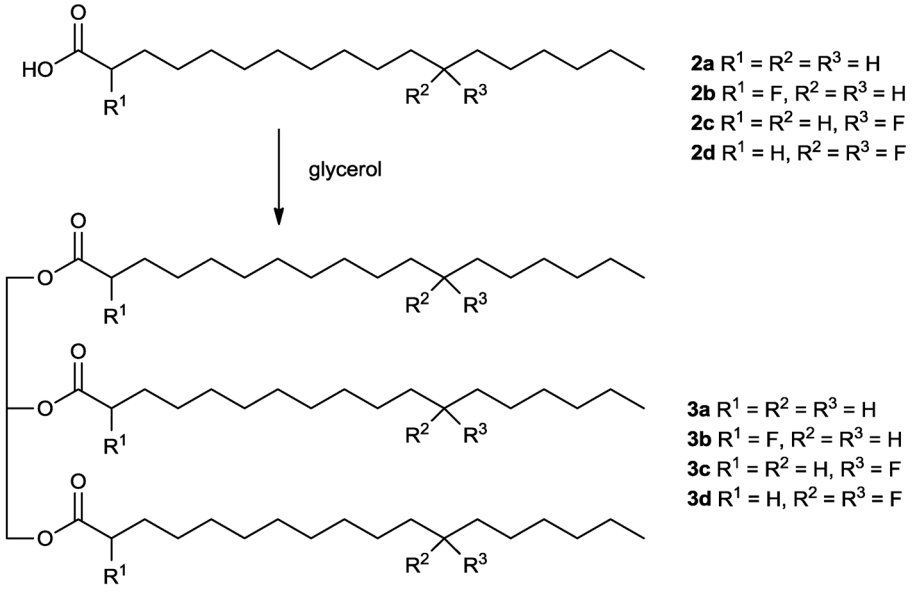


Fig. 9 Preparation of selectively fluorinated tristearins by condensation of stearic acids and glycerol.

Tristerin **3a** has a very well defined polymorphism, and the polymorphic behavior of the selectively fluorinated analogues was compared directly with tristearin by differential scanning calorimetry (DSC) over a 100 °C temperature range. Also, their relative melting points were compared. The data are presented in Fig. 10. The 2-fluoro analogue **3b** is a white amorphous solid with the lowest melting point, and as expected had the least similarity to tristearin. It is clear that tristearin and 12-fluorotristearin are very similar, both regarding their melting points and their polymorphism profile, suggesting that a single fluorine in the middle of the chain does not significantly change the overall physical properties of the material. However, the 12,12-difluoroanalogue has a lower a to b transition and a lower overall melting point. Thus, the CF_2 appears to be increasing chain disorder relative to –CHF and –CH_2.

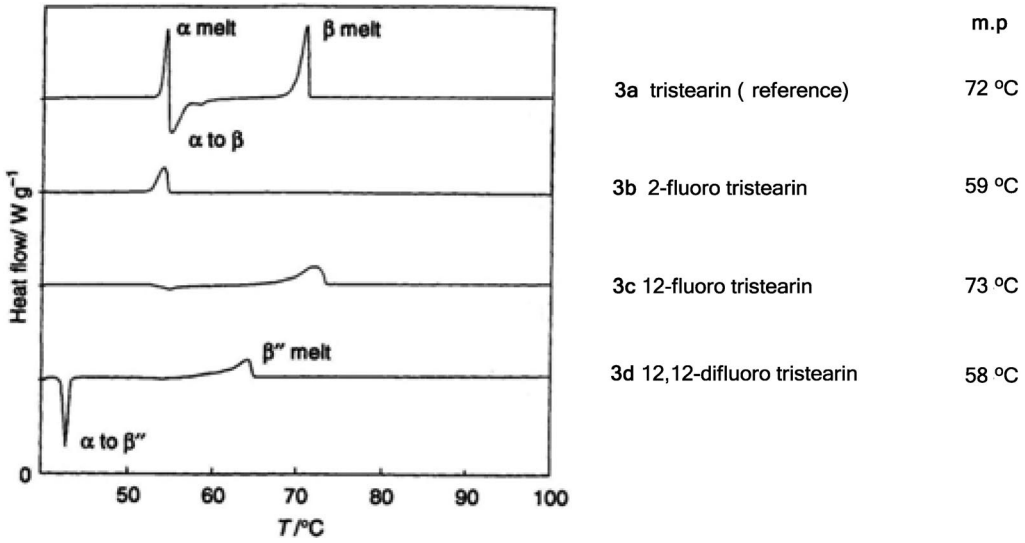


Fig. 10 DSC thermogram of tristearin **3a** and fluorinated tristearins **3b–d** [9].

The nature of the free stearic acids **2a–d**, carrying CH_2, CHF, and CF_2 at C-12 was explored with respect to their ability to form monolayers on the surface of water by recording pressure-area isotherms in a Langmuir trough. Again, stearic acid **2a** and the mono-fluoro analogue **2c** displayed similar behavior, however, the introduction of a second fluorine (CF_2) at C-12 led to increased disorder and generated a far less stable monolayer (Fig. 11). These observations are rooted in the change in hybridization at the difluoromethylene carbon. The C-CF_2-C angle widens to ~116–118°. This angle widening relaxes the steric interaction between 1,4 hydrogens, which now allows the chain to twist and deviate from the more generally favored *anti*-zig-zag conformation commonly associated with hydrocarbon chains. Thus, replacement of a CH_2 by two fluorines (CF_2 group) in an aliphatic chain increases conformational disorder and lowers melting points.

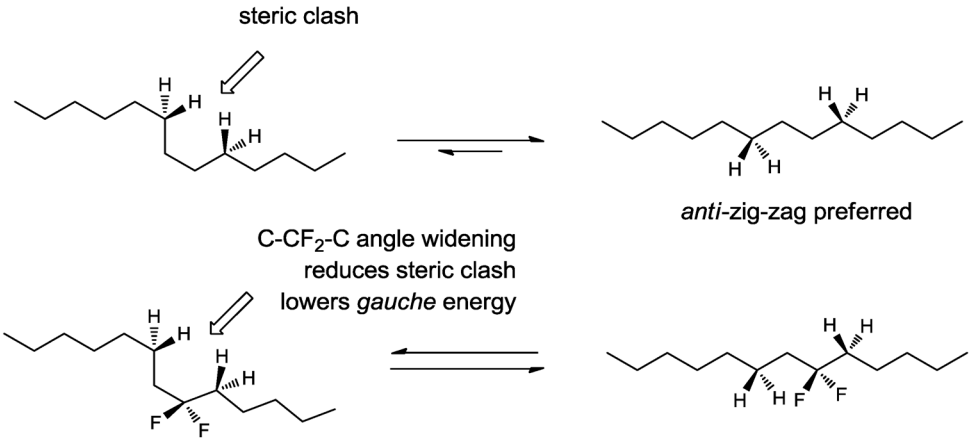


Fig. 11 CF_2-functionalized aliphatic chain introduce increased conformational disorder.

CYCLODODECANES AS A FRAMEWORK FOR CF_2 INCORPORATION

In 1960 Dunitz and Shearer solved the structure of cyclododecane by a combination of X-ray diffraction and computational analysis [24]. Their deduced structure is shown in Fig. 12. Cyclododecane is the first of the cycloalkanes that is a solid at room temperature (mp 64 °C), and unlike many medium-sized rings, it has structural integrity. It is a square [3333] type structure, with nonequilvalent edge and corner CH_2 groups. The structure also reveals *endo* and *exo* hydrogens, with eight *endo* hydrogens, four above and four below the ring plane arranged in a square relationship. These hydrogens tension the structure with transannular interactions because they are at van der Waals contact distances.

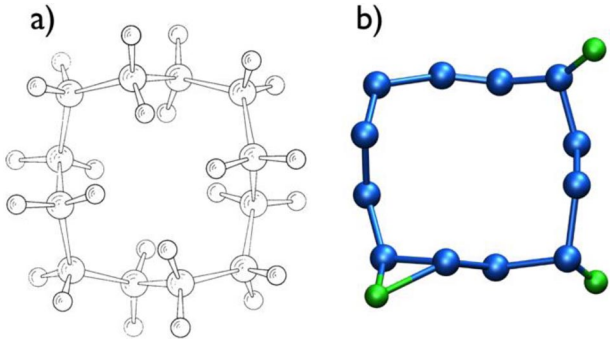


Fig. 12 (a) Dunitz and Shearer cyclododecane X-ray derived structure [24]. (b) Disordered 1,1-difluorocyclododecane structure [10].

The question arises as to what will happen with a CF_2 group. Will it occupy a corner or an edge location if incorporated into cyclododecane?

Cyclododecane containing one CF_2 was prepared and is a nice crystalline solid, however, it proved difficult to obtain a good single-crystal X-ray crystal structure. Diffraction analyses indicated a square structure with significant disorder, similar to the original cyclododecane structure examined by Dunitz and Shearer. However, there is clear diffraction density at the corner locations associated with the fluorine atoms, despite the considerable molecular disorder in this pseudo C_4 system. In order to achieve higher order in the cyclododecane structure, two CF_2 groups were incorporated, and they were

designed with a regiochemistry such that they would locate at corner positions of the [3333] structure. Thus, 1,1,4,4,- and 1,1,7,7-tetrafluorocyclododecanes were prepared. These were nice crystalline solids, and the resultant X-ray derived structures confirmed that the CF_2 groups were securely located at the corners. A closer analysis of these structures reveals that the C-CF_2-C angles are wider than the C-CH_2-C angles within each ring (Fig. 13). This has the effect of increasing the distance between pairs of 1,4-hydrogens traversing the CF_2 corners relative to that distance traversing the CH_2 corners, in a similar manner to that discussed for stearic acid and the tristearins above (Fig. 11). Thus, the angle widening with the concomitant relaxation of 1,4-H,H distance releases angle strain and stabilizes these structures. If a CF_2 was located at an edge, this would have the effect of projecting one fluorine atom into an *endo* orientation across the top of the ring. Although the size of the fluorine is small, and the smallest available substituent after hydrogen in organic chemistry, the increased size of the fluorine will clearly add to the transannular strain in this highly tensioned ring system. Thus, there are mutually exclusive factors influencing the preference for CF_2 to locate at the corner of the cyclododecane ring systems. In this study, a 1,1,6,6-tetrafluorocyclododecane was also prepared to test the system. This molecule was designed to force a CF_2 to the edge if the ring persisted to adopt a [3333] square-type structure. However, this material, which was a crystalline solid, gave rise to a solid-state structure that had now puckered to a [4332] conformation as shown in Fig. 13. Thus, the CF_2 forces a new corner for itself, presumably to avoid projecting fluorine into the ring in an *endo* orientation.

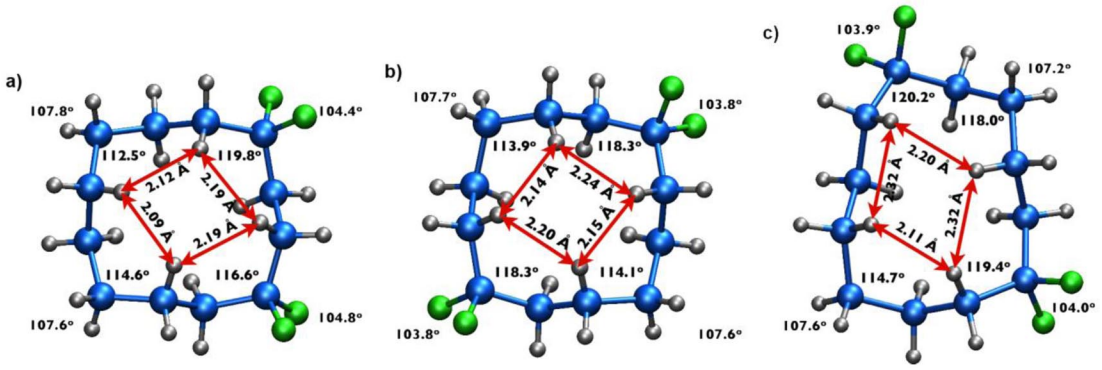


Fig. 13 (a) 1,1,4,4-, (b) 1,1,7,7-, and (c) 1,1,6,6-tetrafluorocyclododecanes [10]. The CF_2 groups occupy corner locations and will distort the ring to achieve this.

In conclusion, examples are highlighted to outline the comparative geometric and electronic influence of replacing difluoromethylene for methylene or oxygen in selected molecules. It is the most polar form of fluorine at carbon and is attractive in the design of polar organic materials. An enduring characteristic of the CF_2 group is the significant change in hybridization at carbon relative to CH_2, with a widening of the C-CF_2-C angle greater than tetrahedral and perhaps a counter-intuitive narrowing of the F-C-F angle. This is general for aliphatic CF_2 groups, but it is also evident in CF_2 phosphonates, providing them with both a geometric and electronic similarity to the phosphate group. This geometric change (angle widening) has been shown to confer stability when judiciously placed at the corner of cyclododecane rings, to relieve transannular strain, but more generally CF_2 incorporation leads to increased conformational disorder in aliphatic chains, as the angle widening accommodates conformational disorder.

REFERENCES

1. P. Kirsch. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim (2004).
2. A. Tressaud, G. Haufe. *Fluorine in Health, Molecular Imaging, Biomedical Materials and Pharmaceuticals*, Elsevier, Amsterdam (2008).
3. (a) D. O'Hagan. *Chem. Soc. Rev.* **37**, 308 (2008); (b) L. Hunter. *Beilstein J. Org. Chem*. **6**, 38 (2010).
4. K. Müller, C. Faeh, F. Diederich. *Science* **317**, 1881 (2007).
5 (a) M. Martinelli, T. Milcent, S. Ongeri, B. Crousse. *Beilstein J. Org. Chem.* **4**, 19 (2008); (b) M. Zanda. *New J. Chem.* **28**, 1401 (2004).
6. I. Ojima. *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, UK (2009).
7 J. J. Li, Q. J. Meng, W. J. Li, Z. C. Zhang. *J. Appl. Poly. Sci.* **122**, 1659 (2011).
8. J. A. Gladysz, D. P. Curran, I. T. Horvath. *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim (2004).
9. L. Dasaradhi, D. O'Hagan, M. C. Petty, C. Pearson. *J. Chem. Soc., Perkin. Trans. 2* 221 (1995).
10. M. Skibinski, Y. Wang, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan. *Angew. Chem., Int. Ed.* **50**, 10581 (2011).
11. H.-G. Mack, M. Dakkouri, H. Oberhammer. *J. Phys. Chem.* **95**, 3136 (1991).
12. J. R. Durig, C. Zheng, G. A. Guirgis, H. Nanaie. *J. Mol. Struct.* **742**, 191 (2005).
13. P.-Y. Lien, R.-M. You, W.-P. Hu. *J. Phys. Chem., A* **105**, 2391 (2001).
14. J. D. Kelling, M. C. Böhm, H. J. Lindner. *J. Mol. Struct. (Theo. Chem.)* **710**, 1 (2004).
15. R. J. Gillespie, E. A. Robinson. *Chem. Soc. Rev.* **34**, 396 (2005).
16. K. B. Wiberg, P. R. Rabelen. *J. Am. Chem. Soc.* **115**, 614 (1993).
17. P. Kirsch, M. Bremer. *ChemPhysChem* **11**, 357 (2010).
18. (a) Z. Zhang, T. C. M. Chung. *Macromolecules* **40**, 9391 (2007); (b) A. J. Lovinger. *Science* **220**, 1115 (1983).
19. (a) G. M. Blackburn, D. E. Kent, F. Kolkmann. *J. Chem. Soc., Perkin. Trans. 1* 1119 (1984); (b) G. M. Blackburn, D. E. Kent. *J. Chem. Soc., Chem. Commun*. 511 (1981).
20. (a) D. B. Berkowitz, M. Bose, T. J. Pfannensteil, T. Dovkov. *J. Org. Chem.* **65**, 4498 (2000); (b) D. B. Berkowitz, M. Eggen, Q. R. Shen, R. K. Shoemaker. *J. Org. Chem.* **61**, 4666 (1996).
21. D. B. Berkowitz, M. Bose. *J. Fluor. Chem.* **112**, 13 (2001).
22. J. Nieschalk, A. S. Batsanov, D. O'Hagan, J. A. K. Howard. *Tetrahedron* **52**, 165 (1996).
23. R. D. Chambers, D. O'Hagan, B. Lamont, S. C. Jain. *J. Chem. Soc., Chem. Commun.* 1053 (1990).
24. J. D. Dunitz, H. M. M. Shearer. *Helv. Chim. Acta* **43**, 18 (1960).

