The difluoromethylene (CF$_2$) group in aliphatic chains: Synthesis and conformational preference of palmitic acids and nonadecane containing CF$_2$ groups

Yi Wang, Ricardo Callejo, Alexandra M. Z. Slawin and David O’Hagan$^*$

Full Research Paper

Address:
EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, Fife KY16 9ST, UK

Email:
David O’Hagan$^*$ - do1@st-andrews.ac.uk

* Corresponding author

Keywords:
difluoromethylene; fatty acids; fluorination; organic fluorine chemistry; organo-fluorine; palmitic acid

Abstract

The syntheses of palmitic acids and a nonadecane are reported with CF$_2$ groups located 1,3 or 1,4 to each other along the aliphatic chain. Specifically 8,8,10,10- and 8,8,11,11-tetrafluorohexadecanoic acids (6b and 6c) are prepared as well as the singly modified analogue 8,8-difluorohexadecanoic acid (6a). Also 8,8,11,11-tetrafluorononadecane (27) is prepared as a pure hydrocarbon containing a 1,4-di-CF$_2$ motif. The modified palmitic acids are characterized by differential scanning calorimetry (DSC) to determine melting points and phase behaviour relative to palmitic acid (62.5 °C). It emerges that 6c, with the CF$_2$ groups placed 1,4- to each other, has a significantly higher melting point (89.9 °C) when compared to the other analogues and palmitic acid itself. It is a crystalline compound and the structure reveals an extended anti-zig-zag chain. Similarly 8,8,11,11-tetrafluorononadecane (27) adopts an extended anti-zig-zag structure. This is rationalized by dipolar relaxation between the two CF$_2$ groups placed 1,4- to each other in the extended anti-zig-zag chain and suggests a design modification for long chain aliphatics which can introduce conformational stability.

Introduction

The selective replacement of hydrogen by fluorine is widely practised in bio-organic and medicinal chemistry [1-4]. It is generally perceived that fluorine exerts only a moderate steric influence relative to hydrogen in organic compounds, but that the electronegativity of fluorine can have significant electronic influences [5]. The difluoromethylene (CF$_2$) functionality has received considerably less attention as a functional group for modifying the properties of organic molecules, relative to –F and –CF$_3$ groups. However we have recently become interested in the CF$_2$ group, and in particular have noticed that the replace-
ment of the two hydrogen atoms of a methylene by two fluo-
rine atoms leads to widening of the C–CF$_2$–C angle (~118°) and
a narrowing of the F–C–F angle (104°) relative to tetrahedral
geometry [6,7]. This deviation of classical sp$^3$ towards sp$^2$
hybridisation, imparts certain properties to the CF$_2$ group in that
it can accommodate angle strain. For example CF$_2$ compounds
display an apparent Thorpe–Ingold effect relative to CH$_2$ in ring
closing metathesis reactions (RCM) to cycloheptene [8]. Com-
parison of the rates of reaction with different substituents at the
C-5 position of the diene precursors 1a–d, revealed that the CF$_2$
substituent in 1c was as effective as the dicarboxylate 1a or
ketal 1b in promoting RCM (Figure 1). This is attributed to
C–CF$_2$–C angle widening, which absorbs angle strain in the
resultant cycloheptene 2c.

In another study we have prepared cyclododecanes 3–5 with
regiospecific placement of two CF$_2$ groups around the ring [6]
(Figure 2). X-ray structures reveal that the CF$_2$ groups only ever
occupy corner locations. This is a result of several factors
including C–CF$_2$–C angle widening, which relaxes 1,4-torsional
strain across corner positions, lengthening the contact distance
between those H(1)–H(4) interactions relative to those with
CH$_2$ at the corner. Also if the CF$_2$ locates at an edge this would
require that a C–F bond project into the middle of the ring. The
larger steric influence of the fluorine, projecting into the tightly
packed arrangement of endo orientated hydrogen atoms, raises
the energy of such conformations. For cyclododecane, placing
the CF$_2$ groups 1,4 (3) or 1,7 (4) to each other, stabilizes the
[3.3.3.3] square like conformation of the ring. However if the

![Figure 1: The CF$_2$ group in 1c accelerates RCM reactions relative to CHF (1d) and CH$_2$ (1e) and with a similar rate to classical or Thorpe–Ingold substituents such as the ketal 1a and dicarboxylate ester 1b [8].](image1.png)

![Figure 2: X-ray structures of a) 1,1,4,4- (3) b) 1,1,7,7- (4) and c) 1,1,6,6- (5) tetrafluorocyclododecanes. The CF$_2$ groups locate at the corners, even for 5 which gives rise to a distorted ring conformation [6,7].](image2.png)
CF₂ groups are placed 1,6 to each other as in 5, this introduces considerable distortion of the ring conformation as shown in Figure 2, because the CF₂ avoids an edge location, which would place a fluorine atom *endo* and unfavourably into the centre of the ring.

As part of an on-going interest in the behaviour and influence of the CF₂ group we have now explored the effect of locating two CF₂ groups along an extended aliphatic chain. Long chain fatty acids present tractable model systems as they are solid materials and their physical properties are well described [9]. In this study we selected the three palmitic acid analogues 6a–c shown in Figure 3, as targets for synthesis and comparative analysis.

**Results and Discussion**

**Synthesis of the palmitic acids 6a–c**

As a general strategy palmitic acids 6a–c were prepared by aryl oxidation of long chain pentadecabenzenes [10,11]. The introduction of the CF₂ groups was carried out by treatment of the appropriate precursor ketone with diethylaminosulfur trifluoride (DAST) [12,13]. The synthesis of palmitic acid 6a is illustrated in Scheme 1. At the outset aldehyde 8 was condensed with the acetylide of 1-octyne to afford propargylic alcohol 9, an alcohol which was readily oxidized to ketone 10. Treatment with DAST afforded difluoromethyleneacetylene 11 in good yield. The fluorination of propargylic ketones, to generate difluoromethyleneacetylenes, is methodology developed by Grée et al. [14-18] and it proved to be very reliable in our hands. An efficient hydrogenation generated the C-8 substituted difluoromethylenepentadecabenzene 12. Finally biphasic ruthenium tetroxide-catalyzed aryl oxidation gave the palmitic acid 6a in 24% overall yield as illustrated in Scheme 1 [10,11].

For palmitic acid 6b, it was required to introduce the CF₂ groups 1,3 to each other. This was achieved by sequential preparation of appropriate precursor ketones as illustrated in Scheme 2. For the first CF₂ group ketone 14 was treated with DAST. Conversion to the CF₂ group occurred in modest (45%) yield. Generally aliphatic ketones are less efficiently converted...
to CF₂ groups with DAST in comparison to propargylic ketones. Progression of the resultant CF₂-containing olefin 15 by epoxidation, chain extension and then oxidation, to ketone 18, generated the second fluorination substrate of the synthesis. DAST treatment gave pentadecabenzene 19, which was again oxidised by RuO₃ to the corresponding palmitic acid 6b.

Scheme 2: The synthesis of palmitic acid analogues 6b and 6c.
Palmitic acid 6c was prepared again relying on the methodology developed by Grée et al. [14-17] for introduction of the CF₂ groups. Thus treatment of ketone 21 with DAST resulted in an efficient conversion to difluoromethyleneacetylene 22. This terminal acetylene is amenable to acetylide formation on treatment with BuLi [19,20] and condensation with hexaldehyde gave propargylic alcohol 23. The lithium methylenedifluorooacetylide (RCF₂C≡CLi) reaction to form a C–C bond, provides a particularly useful synthon to access this 1,4-di-CF₂ motif. Oxidation and then treatment of the resultant ketone 24, with DAST generated the tetrafluoroacetylene 25. Complete hydrogenation of the triple bond proved efficient and the resultant tetrafluoropentadecabenzene 26 was readily oxidized to palmitic acid 6c as illustrated in Scheme 2. This completed the syntheses of the palmitic acid analogues 6a–c.

Differential scanning calorimetry (DSC) data was then measured for all three of the palmitic acid samples 6a–c over a temperature range of −150 to 400 °C. In this way accurate melting point values were obtained. The melting point of C-8 difluorinated palmitic acid 6a (62.9 °C) was very similar to the natural palmitic acid (62.5 °C), Thus a single CF₂ substitution, certainly at this location, has very little influence on the melting point. For palmitic acid 6b, with the two CF₂-groups placed 1,3 to each other, the melting point (69 °C) is also similar to palmitic acid, but the phase behaviour is more complex as evidenced by the broad DSC profiles. This palmitic acid 6b was amorphous in nature and was not a crystalline solid, unlike the other two analogues 6a and 6c which formed crystals (Figure 4).

The tetrafluorinated palmitic acid 6c, with the CF₂ groups located 1,4 from each other displays a sharp and significantly higher melting point (89.9 °C) than the other two palmitic acids 6a and 6b.

Palmitic acids 6a and 6c were crystalline solids and single crystal X-ray diffraction data were obtained for these compounds. As described above analogue 6b was amorphous in nature and despite considerable effort a single crystal could not be obtained for 6b. The resultant structures for 6a and 6c are shown in Figure 5 and Figure 6 respectively. In each case two
molecules as they appear within the unit cell are presented in the image, allowing a view from above and to the side of the extended chain. The closest CF···HC contacts are 2.88 Å in 6a and 2.85 Å in 6c, much longer than any meaningful organic fluorine hydrogen bond [21]. The C–CF₂–C angle in 6a (Figure 5) is 117° and as expected, wider than the other C–CH₂–C angles which are typically ~112.5°. For 6c (Figure 6) the C–CF₂–C angles are 115.6° (at C-8) and 116.3° (at C-11) also consistently wider that the aliphatic C–CH₂–C angles. The significantly higher melting point and good crystallinity of 6c can be attributed to the relative orientation of the two CF₂ groups. They are pointing perfectly anti-parallel to each other such that their dipoles cancel out in the extended anti-zig-zag chain conformation. We are currently exploring if this is a special situation whereby CF₂ groups positioned 1,4 from each other can add conformational stability to aliphatic chains in other systems.

It occurred to us that the interactions of the carboxylate groups in palmitic acid 6c, may be dictating overall stability and conformation of the alkyl chain in the solid state. Thus it appeared appropriate to prepare a true hydrocarbon chain to further investigate the conformational preference of the 1,4-di-CF₂ motif. Accordingly we selected to prepare tetrafluorononadecane 27. This is a long chain hydrocarbon with the 1,4-di-CF₂ motif placed centrally. The synthetic route to 27 is illustrated in Scheme 3. The strategy for incorporating the two CF₂ groups followed that used for the preparation of palmitic acid 6c. In this case propargylic ketone 30 was treated with DAST to generate difluoroacetylene 31. The resultant acetylene could then be deprotonated for conjugation to aldehyde 32. Oxidation and then fluorination of ketone 34 with DAST, introduced the second CF₂ group and generated tetrafluoroacetylene 35. Finally hydrogenation of the central acetylene group gave the saturated tetrafluorononadecane 27. This compound proved to
Scheme 3: Synthesis route to the tetrafluorinated alkane 27.

be a crystalline solid (mp 35–37 °C) with a melting point very similar to nonadecane (32–35 °C). A suitable crystal was subject to X-ray structure analysis and the resultant structure is shown in Figure 7. It is clear that the alkyl chain of 27 is extended in a similar conformation to that found in palmitic acid 6c and we conclude that this is the preferred conformation of this motif in a hydrocarbon chain.

Conclusion
In conclusion, we have synthesised three palmitic acid analogues 6a–c carrying regiospecifically located CF$_2$ groups. The tetrafluorononadecane 27 was also prepared as an example of a true hydrocarbon. Relatively efficient synthesis protocols were devised for placing the CF$_2$ groups 1,3 and 1,4 to each other. The CF$_2$ groups of 6b, 6c and 27 were introduced sequentially from appropriate precursor ketones, using DAST. In particular, the methodology of Grée et al., enabled the efficient introduction of CF$_2$ groups from propargylic ketones in the syntheses of 6a, 6c and 27. A useful C–C bond forming reaction involved a lithium methylenedifluoroacetylide (RCF$_2$C≡CLi) condensation with an aldehyde, offers an efficient strategy for the preparation of the 1,4-di-CF$_2$ motif after suitable functional group manipulations.

The non-crystalline nature of 6b presumably arises due to chain disorder from linear 1,3-repulsions between the fluorines, so the preferred conformation of this motif could not be determined in this study. The melting point of palmitic acid 6c (89.9 °C) was

Figure 7: The X-ray structure of 8,8,11,11-tetrafluorononadecane (27).
Figure 8: Conformational interconversion of 1,4-di-CF₂ motif.

notable in that it was significantly higher than that of the two other analogues 6a and 6b, and also of palmitic acid itself. The solid state structure of 6c and 27 show that the 1,4-di-CF₂ motif prefers an anti-zig-zag conformation. We attribute this preference to intramolecular dipole–dipole relaxation which is maximised in the extended anti-zig-zag chain conformation (Figure 8). Also repulsive through space 1,4-F···F interactions will be disfavoured if the chain undergoes gauche conformational disorder. These contributing factors suggest that the 1,4-di-CF₂ motif (R–CF₂CH₂CH₂CF₂–R) will be useful for adding conformational stability to aliphatic chains.

Supporting Information
Supporting Information File 1
Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-4-S1.pdf]

Acknowledgements
D.O’H. thanks the ERC for an Advanced Investigator Grant to support this research and Mrs S. Williamson (University of St Andrews) for DSC analyses.

References
1. Müller, K.; Faeh, C.; Diederich, F. Science 2007, 317, 1881–1886. doi:10.1126/science.1131943
2. Liu, W.; Huang, W.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. Science 2012, 337, 1322–1325. doi:10.1126/science.1222327
3. Jarchow-Choy, S. K.; Sjuvarsson, E.; Sintim, H. O.; Eriksson, S.; Kool, E. T. J. Am. Chem. Soc. 2009, 131, 5488–5494. doi:10.1021/ja808244t
4. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. 2008, 37, 320–330. doi:10.1039/b610213c
5. O’Hagan, D. Chem. Soc. Rev. 2008, 37, 308–319. doi:10.1039/b711844a
6. Skibinski, M.; Wang, Y.; Slawin, A. M. Z.; Lebl, T.; Kirsch, P.; O’Hagan, D. Angew. Chem., Int. Ed. 2011, 50, 10581–10584. doi:10.1002/anie.201105060
7. O’Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. Pure Appl. Chem. 2012, 84, 1587–1595. doi:10.1351/PAC-CON-11-09-26
8. Urbina-Blanco, C. A.; Skibinski, M.; O’Hagan, D.; Nolan, S. P. Chem. Commun. 2013, 49, 7201–7203. doi:10.1039/c3cc44312d
9. Dasaradhi, L.; O’Hagan, D.; Petty, M. C.; Pearson, C. J. Chem. Soc., Perkin Trans. 2 1995, 221–225. doi:10.1039/p9950000221
10. Carlsten, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936–3938. doi:10.1021/jo00332a045
11. O’Hagan, D. J. Fluorine Chem. 1989, 43, 371–377. doi:10.1016/0022-1139(89)82723-2
12. Middleton, W. J. J. Org. Chem. 1975, 40, 574–578. doi:10.1021/jo00893a007
13. O’Hagan, D.; Al-Maharik, N. Aldrichimica Acta 2011, 44, 65–75.
14. Prakesch, M.; Keroueredan, E.; Grée, D.; Grée, R.; DeChancie, J.; Houk, K. N. J. Fluorine Chem. 2004, 125, 537–541. doi:10.1016/S0022-1139(03)82723-2
15. Khalaf, A.; Grée, D.; Abdallah, H.; Jaber, N.; Hachem, A.; Grée, R. Tetrahedron 2011, 67, 3881–3886. doi:10.1016/j.tet.2011.03.073
16. Bannwarth, P.; Valleeix, A.; Grée, D.; Grée, R. J. Org. Chem. 2009, 74, 4646–4649. doi:10.1021/jo900674u
17. Bannwarth, P.; Grée, D.; Grée, R. Tetrahedron Lett. 2010, 51, 2413–2415. doi:10.1016/j.tetlet.2010.02.116
18. Pazeco, M. C.; Purser, S.; Gouverneur, V. Chem. Rev. 2008, 108, 1943–1981. doi:10.1021/cr068410e
19. Pajkert, R.; Rüschendorf, G.-V. J. Org. Chem. 2013, 78, 3697–3708. doi:10.1021/jo400198a
20. Drakesmith, F. G.; Stewart, O. J.; Tarrant, P. J. Org. Chem. 1968, 33, 280–285. doi:10.1021/jo01265a005
21. Howard, J. A. K.; Hoy, V. J.; O’Hagan, D.; Smith, G. T. Tetrahedron 1996, 52, 12613–12622. doi:10.1016/0040-4020(96)00749-1

License and Terms
This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.10.4