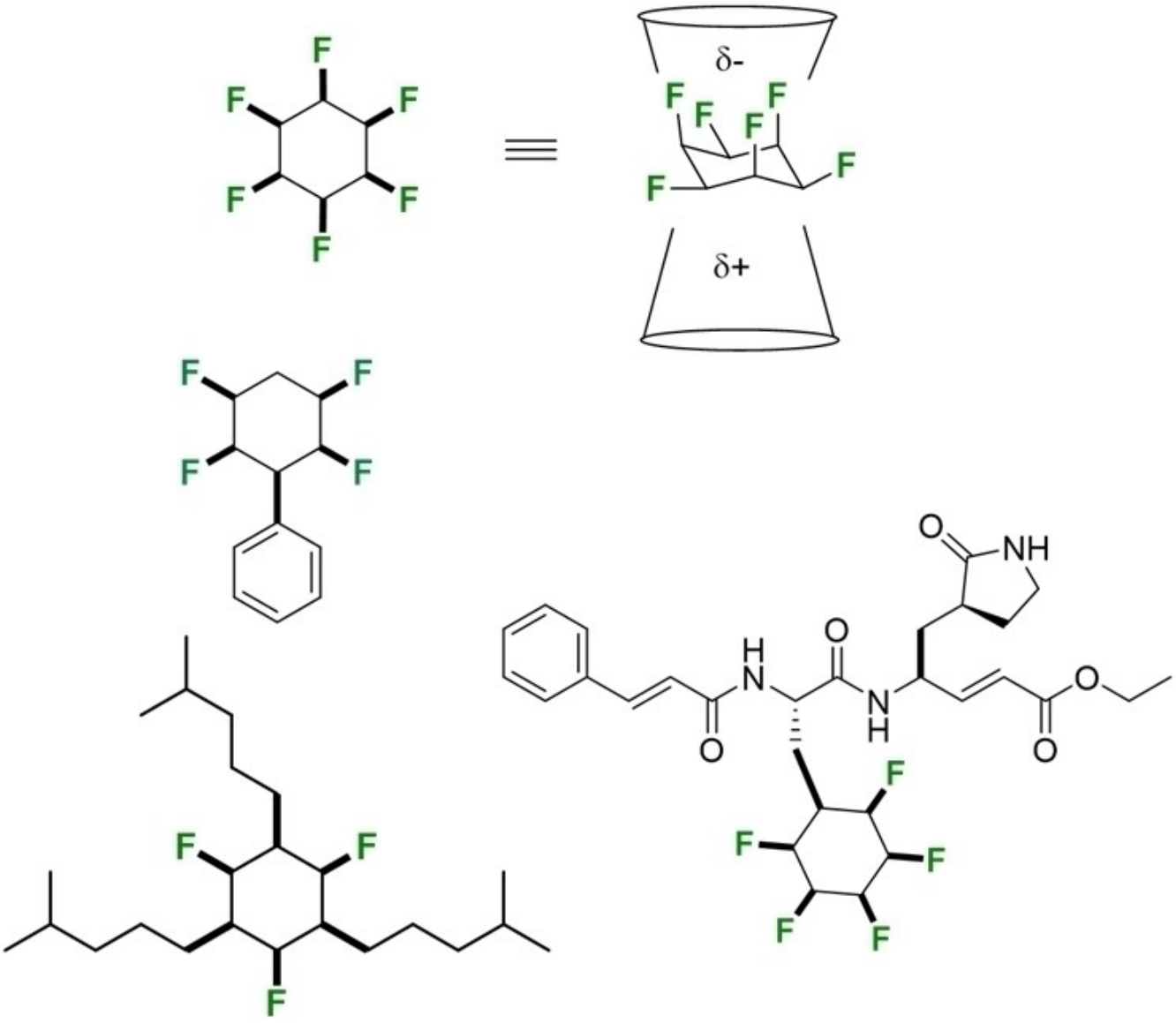
Personal Account

THE CHEMICAL RECORD

doi.org/10.1002/tcr.202300027
tcr.wiley-vch.de

The Emergence and Properties of Selectively Fluorinated 'Janus' Cyclohexanes

David O'Hagan*[a]



Abstract: This account describes the evolution of a research programme that started by linking fluoromethylene (–CHF–) groups along aliphatic chains and then progressing to alicyclic rings with contiguous fluorine atoms. Different stereoisomers of aliphatic chains tend to adopt low polarity conformations. In order to force polar conformations, the programme began to address ring systems and in particular cyclohexanes, to restrain conformational freedom and co-aligned C–F bonds. The flagship molecule, all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane **7**, emerged to be the most polar aliphatic compound recorded. The polarity arises because there are three co-aligned triaxial C–F bonds and the six fluorines occupy one face of the ring. Conversely the electropositive hydrogens occupy the other face. These have been termed Janus face cyclohexanes after the Roman god with two faces. The review outlines progress by our group and others in preparing derivatives of the parent cyclohexane **7**, in order to explore properties and potential applications of these Janus cyclohexanes.

Keywords: Organofluorine compounds, Janus face cyclohexanes, fluorine effects, polar aliphatics, fluorinated building blocks

1. Introduction

Fluorine is the most electronegative element in the Periodic Table, and as a consequence it forms the strongest bonds to carbon due to the increased electrostatic character of the bond ($-C^{\delta+}-F^{d-}$).[1] This strength has resulted in selective fluorinations being widely used to impart attractive properties and behaviours to organic molecules.[2] It is common in the pharmaceuticals industry to replace hydrogens for fluorine atoms as a means to improving the efficacy and pharmacokinetic profile of lead compounds.[3] Similar approaches are taken for the development of other classes of bioactives such as herbicides and insecticides.[4] For organic materials and polymers there has long been a tendency to incorporate perfluoroalkyl chains as they are chemically stable through wide temperature ranges, and they resist interactions with hydrocarbons and water.[5] Historically important products of this class are poly-tetrafluoroethylene **1** (Teflon®) and perfluorooctane sulphonates (PFOS) and perfluoroalkyl sulphonates (PFAS) more generally.[6] Accordingly, perfluoroalkyl substituents have found wide application in the preparation of thermally stable materials which impart surface repellent properties to commercial goods and fabrics. However, there is now a major environmental concern regarding perfluoroalkyls (eg PFAS's) which are persistent in the environment.[7] That concern is extending to other perfluoroalkyl substituents including the CF_3– group, the shortest chain, which despite its wide utility in pharmaceuticals and agrochemicals products, is an increasing focus of environmental concern.[8] Trifluoromethyl containing compounds can metabolize to trifluoroacetic acid (TFA), a compound that accumulates in the water course and is detectable in the oceans. The concern is extending too to modern refrigerant gases which photo-oxidise to TFA.[9] So there are current challenges regarding certain classes of organofluorine substituents used in industrial products, and the next-generation of fluorinated motifs will have to be non-persistent and biodegradable and be conspicuously 'not perfluoro' if they are to be considered as components in commercial products going forward. It is in this context that we have been exploring a new class of organofluorine motifs that sit between hydrocarbons and perfluoro carbons as illustrated in Figure 1.[10] They contain fluoromeths-

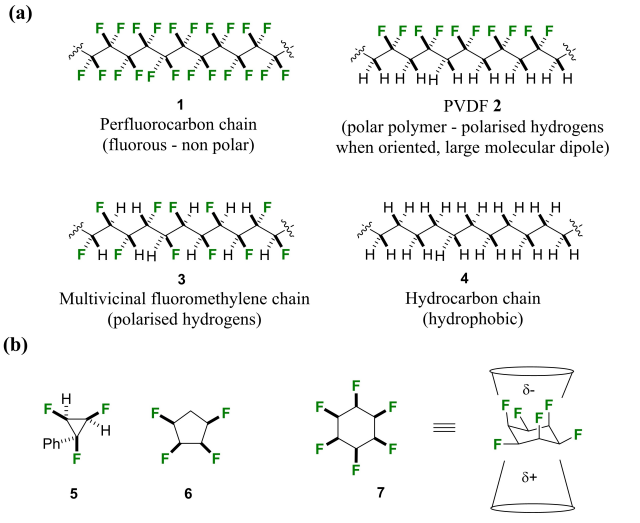


Figure 1. (a) Relationships between non-polar perfluoro (fluorous) **1**, polar partially fluorinated (eg PVDF **2** and multivicinal fluoromethylene chains **3** and lipophilic hydrocarbon chains **4**. (b) Janus face rings **5**–**7** with fluorines on one face and hydrogens on the other are conformationally constrained and become highly polarised cycloalkanes.

[a] *D. O'Hagan*
University of St Andrews
St. Andrews, United Kingdom
E-mail: do1@st-andrews.ac.uk

ylene (−CHF−) substituents, and thus at their core the hydrocarbon chains have only a maximum of 50 % fluorine.

In this class of compounds, the vicinal hydrogens (in PVDF **2**)[11] and the geminal hydrogens in the multi-vicinal fluoromethylene chains **3** are polarised and electropositive because the fluorines are electronegative, relative to common hydrocarbons, and therefore these compounds are polar, unlike fully fluorinated perfluorocarbons eg **1** or aliphatic hydrocarbons eg **4**.[12] When the fluoromethylene substituents are connected along chains (eg –CHF–CHF–CHF– in **3**) then different stereoisomers need to be considered. Molecular conformations are dictated by electrostatic repulsion between 1,3 fluorines and stereoelectronic interactions (*gauche* effects) between vicinal C–F bonds. Linear systems can rotate relatively easily however alicyclic rings containing fluoromethylene carbons have less conformational freedom and polarities can be maximised if the C–F bonds are aligned or are orientated to one face of the alicyclic ring with the C–H bonds to the other face. This has been explored particularly for cyclohexane ring systems such as **7** but it applies also to smaller rings such as cyclopentanes and cyclopropanes too as in **5** and **6** respectively. It is noteworthy in the context of the environmental compatibility that such compounds metabolise[13] and are anticipated not to be persistent as perfluorocarbons. It is early in their development but these fluoromethylene rich compounds impart interesting behaviours, and they have good prospects to be included in the design of the next generation of performance organic molecules and materials. This review gives an account of the evolution of a programme which set out to explore the synthesis and conformations of individual stereoisomers of linear hydrocarbons containing adjacent and skipped –CHF– groups and ended with the development of polar Janus face cyclohexanes, designed very particularly with fluorines on one face of the rings and hydrogens on the other.

2. Linear Multivicinal Fluorinated Motifs

The programme started when we began investigating the synthesis and properties of multivicinal aliphatic alkanes with up to six fluorines along a linear aliphatic chain.[10b,14] This effort in turn was inspired by the stereoelectronic *gauche* effect, as illustrated in Figure 2(a), which recognises that vicinal

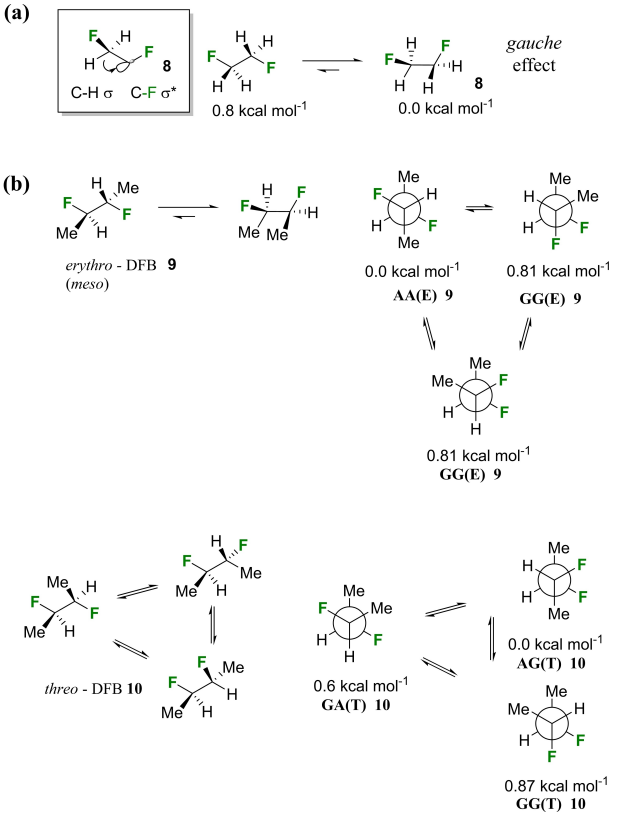


Figure 2. (a) The *gauche* effect in 1,2-difluoroethane **8**; (b) Relative energies of the conformations of *erythro*- **9** and *threo*- **10**, 2,3-difluorobutanes (DFBs).[16a]

fluorines in 1,2-difluoroethane **8** have a tendency to arrange in a conformation such that the fluorine is *anti*-periplanar to a vicinal hydrogen and avoids higher energy conformations where the fluorines align *anti*-periplanar to each other.[15]

Although the *gauche* effect in 1,2-difluoroethane **8** is well known and widely appreciated, it is still an exception in the halogen series where 1,2-dichloro-, bromo- and iodo-ethanes all have lower energy *anti* conformers, whereas 1,2-difluoroethane prefers a *gauche* conformation by about 0.8 kcal mol^{-1} in the gas phase. A significant contributor to *gauche* stabilisation are two hyperconjugative interactions between anti-periplanar σ_{CH} bonding to $^*\sigma_{CF}$ antibonding orbitals, an

Professor David O'Hagan studied chemistry at the University of Glasgow and then Ph.D at the University of Southampton with Prof. J. A. Robinson. He carried out postdoctoral research at the Ohio State University with Prof Heinz G. Floss, before moving to the University of Durham in the UK. At Durham he developed interests in organo-fluorine chemistry. In 2000 he moved to his current location and the University of St Andrews in Scotland. His laboratory is interested in biological fluorination and in the behaviour of selectively fluorinated molecules. They introduced the concept of facially polarised alicyclics, now termed Janus rings, the developments of which form the focus of this review.

interaction that operates in both directions. Extending the carbon chain introduces additional and significant steric factors and their influence competes with the *gauche* effect such that overall conformational preferences are less obvious. The case of 2,3-difluorobutane (DFB) shown in Figure 2(b) illustrates this lack of predictability.[16] There are three isomers of DFB, a *meso* (*erythro*) stereoisomer **9** and two *threo* enantiomers **10**. The two diastereoisomers **9** and **10** are required to be considered independently. In each case three staggered conformers can be considered, each accessed by rotating 120° around the central C–C bond, and in both cases the linear *anti*-zig-zag carbon chain conformer is lowest in energy, avoiding steric clashes between the terminal Me groups. For *threo*-DFB **10** this arrangement accommodates a *gauche* relationship between the fluorines, with C–H bonds lying *anti*-periplanar to the C–F bonds, therefore the favoured conformer AG(T)-**10** might readily be predicted. However for the *erythro* isomer **9** the fluorine *gauche* effect is violated and the *anti*-isomer AA(E)-**9** is preferred over the GG(E)-**9** conformer by 0.81 kcal mol^{-1} (3.43 kJ mol^{-1}),[16a] in no small part due to steric repulsion between the *gauche* Me groups. It should be noted too that the energy differences between these conformers is small, and the value is calculated in the gas phase, which will maximise the difference. In solution in increasingly polar solvents, the energy differences can be expected to narrow as interactions with polar solvents weaken intramolecular dipole-dipole interactions and lower the energy of more polar GG(E) conformers. So what about lining up three and four and five and six vicinal fluorines along an alkyl chain? The situation becomes increasingly complex as the carbon chains get longer as multiple diastereoisomers emerge. With a third vicinal fluorine (−CHFCHFCHF−), a new and important interaction is also introduced, which arises from electrostatic repulsion between alternate 1,3-fluorines. The magnitude of this interaction can be assessed from the energy difference between the four all eclipsing (fluoromethyl groups) conformers of 1,3-difluoropropane **11** and illustrated in Figure 3(a).[17] The lowest energy conformer GG benefits from two eclipsing 1,3-H–F interactions, where there are dipolar compensations, as well as two antiperiplanar C–H$^{\delta+}$ to C–F$^{\delta-}$ bonds to each fluorine. The highest energy (GG ~ 2.86 kcal mol^{-1}) has eclipsing C–F bonds which experience electrostatic repulsion between the fluorines. In the case of 1,2,3-trifluoropropane **12** in Figure 3(b),[18] rotational energy profiles indicate that the eclipsing 1,3 difluoro interaction contributes ~ 3.0 kcal mol^{-1} in the gas phase. This destabilising 1,3-interaction between fluorine atoms emerges as the most significant one in energy terms for multi-vicinal fluoroalkanes. Therefore if extended chains of vicinal fluorines are generated this is expected to be the dominant interaction influencing conformation. It is relatively obvious too that preferred conformations will change for differently defined stereochemistries and consequently properties will vary between the diastereoisomers of a given class of vicinally fluorinated alkanes.

Our programme progressed ultimately to the synthesis of diastereoisomers **13** and **14** of hexa-fluoro aliphatic chains as shown in Figure 4.[19] The peripheral cyclohexyl motifs rendered the isomers crystalline and amenable to X-ray crystallography and their structures are shown in Figure 4. In the case of the all-*syn* isomer **13**, the structure adopts a helical aspect where all of the vicinal fluorines lie *gauche* to each other and rotate with the same sense along the chain. This arrangement avoids any repulsive 1,3-difluoro interactions and it also accommodates stabilising σ_{CH} bonding to $^*\sigma_{CF}$ anti-

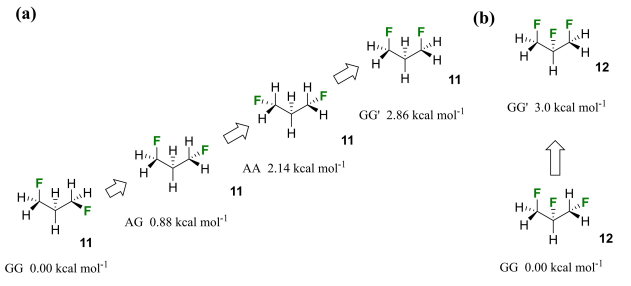


Figure 3. (a) Conformations and relative energies of 1,3-difluorobutane **11** and (b) 1,2,3,–trifluorobutane **12**, indicating that aligned 1,3-C–F bonds are significantly raised in energy above the lowest energy conformers.[17,18]

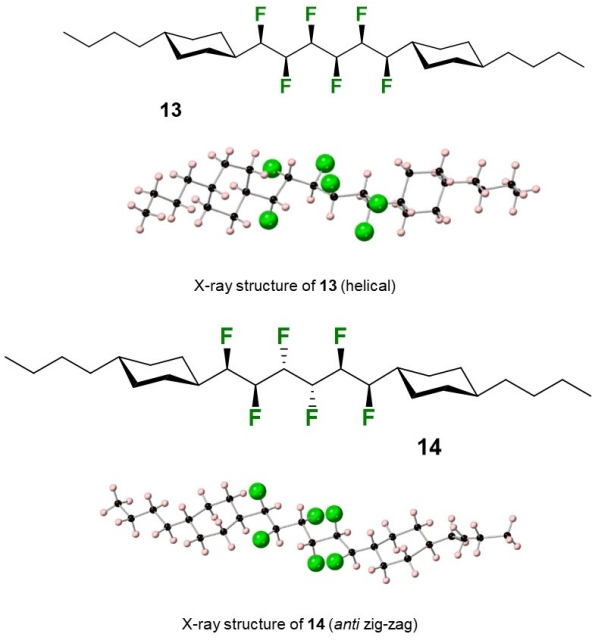


Figure 4. X-ray structures of hexavicinal fluoromethylene chains indicating a helical conformation for the all-*syn* isomer **13** and an *anti* zig-zag conformation in **14** where 1,3 fluorine repulsions are not relevant.[19]

bonding hyperconjugative interactions, important in the classical *gauche* effect. This solid- state structure was also supported in solution (chloroform), after considering the magnitude of $^3J_{HH}$ and $^3J_{HF}$ coupling constants from NMR and appears to be a relatively stable and dominant structure. Large $^3J_{FH}$ vicinal coupling constants (25–30 Hz) indicate *anti*-periplanar relationships and intermediate $^3J_{FH}$ values (15–20 Hz) indicate *gauche* relationships between the vicinal hydrogen and fluorine atoms. In the case of the other diastereoisomer **14**, where the two central fluorine are 'back' relative to the four peripheral fluorines, the structure adopts an extended *anti*-zig-zag conformation. This is now favoured as there are no destabilising 1,3-fluorine interactions in this conformation, and the conformer is supported too by a series of σ_{CH} to $^*\sigma_{CF}$ hyperconjugative interactions, again a structure supported in solution by NMR. A similar situation was observed for the vicinal tetra-fluoro systems illustrated in Figure 5. In that case three ditosylate diastereoisomers **15**–**17** were prepared as shown, and they were also converted to their corresponding hexanes **18**–**20** by reduction with $LiAlH_4$.[21] The X-ray structures of the three ditosylate diastereomers **15**–**17** was solved. The structure of the all-*syn* ditosylate isomer **15** again had a helical aspect where the vicinal C–F bonds arranged ~60° to each other progressing along the chain.

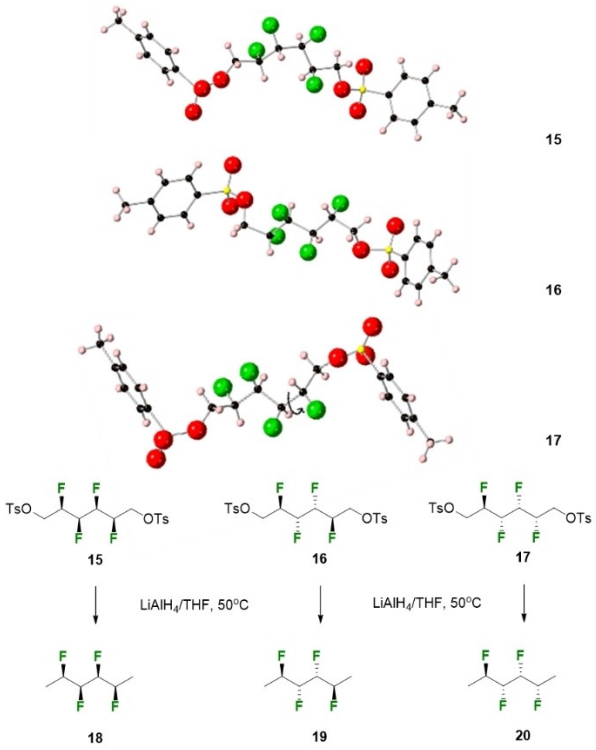


Figure 5. X-Ray structures of diastereoisomers **15**—**17** and their conversions to of 2,3,4,5-tetra-vicinal fluorohexanes **18**—**20**.[20,21]

Diastereoisomer **16** has the two central fluorines 'back' and the peripheral fluorines 'forward'. In that case the ditosylate **16** crystallised in an *anti*-zig-zag conformation. The displayed conformations for both of these solid-state structures and their corresponding hexanes **18** and **19** were reinforced in solution from their $^3J_{HH}$ and $^3J_{HF}$ coupling constants in NMR experiments. However in the case of the third stereochemical arrangement in stereoisomers **17** and **20** there is conformational disorder at one terminus in the X-ray structure, where two of the vicinal fluorines are almost eclipsing each other. Also, NMR indicated an average coupling constant($^3J_{HH}$ and $^3J_{HF}$ Hz) between *anti*- and *gauche*- HC-CF relationships, indicating increased rotational freedom around this bond relative to the rest of the structure. Taking the hexafluoro- and tetrafluoro systems together it was concluded therefore that with extended numbers of fluorines and with judicious choice of stereochemistry, then individual conformations dominate in solution, and these differences in stereochemistry should lead to different properties.

In a more applied example Gilmour and co-workers[22] demonstrated a change in Log P values between the stereoisomers **22** and **23** from 0.4 to 0.6 respectively as illustrated in Figure 6. These are analogues of the rather lipophilic drug Gilenya **21** used to treat multiple sclerosis. Although these Log P values are relatively close indicating only a modest change in polarity with stereochemistry there was a notable change in aqueous solubility (925 μM for **22** vs 563 μM for **23** at pH 4.7) between the stereoisomers suggesting more significant differences in properties due to the individual configurations of these diastereoisomers.

Müller in particular has highlighted the role that aliphatic fluorine can play in the design of drug candidates as conformational adaptors, changing between different optimal conformations as the drug progress through different chemical environments.[23]

It is reasonable to assume that these linear aliphatic chain systems adopt conformations that avoid parallel 1,3-C–F bond alignments. Such alignments are relatively high in energy as the parallel dipoles introduce significant polarity into the conformers, and in a linear aliphatic the fluorines turn away from each other. However given that there are circumstances where polarity is an advantageous property, for example in the design of some classes of liquid crystals and polymers, and

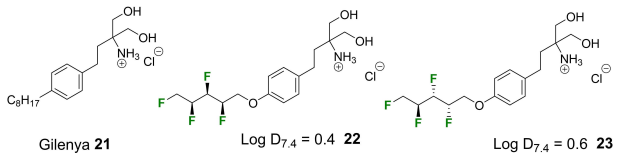


Figure 6. Gilenya **21** and tetravicinal fluoroalkane ether analogues **22** and **23** prepared by Gilmour *et al.*[22]

more generally in organising supramolecular assemblies, then it became an objective of our programme to prepare a series of molecules which proactively align 1,3-C–F bonds to maximise polarity. In order to do this attention turned to cyclic frameworks and in particular cyclohexanes.

3. Let's Make Rings

Cyclohexane has a special place in the history and teaching of organic chemistry in that it is the only alicyclic system that forms a ring without any ring strain.[24] The tetrahedral geometry of sp^3 hybridised carbons readily accommodates a chair conformation as the most favourable arrangement. The chair conformers can invert and the chair dictates that substituents can interconvert between equatorial and axial orientations. For monosubstituted cyclohexanes the equatorial conformer is usually lower in energy as this avoids less favoured 1,3-diaxial interactions with axial hydrogens across the top of the cyclohexane ring, a problem that relaxes when the substituent has an equatorial orientation. The larger the substituent the greater the preference for the equatorial conformer at equilibrium and indeed the free energy difference (ΔG) between axial and equatorial conformers is used as a measure to assess the steric impact of a given substituent (A-values) as illustrated in Figure 7. By this measure the fluorine substituent in cyclohexane **25** is small with a low A-value (ΔG ~ 0.3 kcal mol^{-1}) and it lies next to deuterium in **24** (ΔG ~ 0.006 kcal mol^{-1}) and well below a methyl group in **26** (ΔG ~ 1.75 kcal mol^{-1}).[25]

There is only a very small preference for equatorial over axial fluorine conformers in fluorocyclohexane **25**. The low steric impact of fluorine is one of the reasons it is widely used as a hydrogen surrogate to block metabolism in drug design, as it is the next smallest atom to hydrogen that forms stable bonds to carbon. In the case of *syn*-1,2-difluorocyclohexane **27** then one substituent is axial and the other equatorial, and the interconverted structures are isoenergetic, however as we progress to *syn*-1,3-difluorocyclohexane **28**, then there is a significant energy difference between the ax/ax and eq/eq conformers, favouring the eq/eq conformer, which has been variously measured in the 1.0–2.0 kcal mol^{-1} range.[26] This value is less than that found where there are eclipsing 1,3-C–F bonds in the high energy conformers of the propanes discussed above in Figure 3, however there is additional stabilization from four *anti*-periplanar HC-CF interactions that are associated with the gauche effect.[17,18] The alignment of two di-axial C–F bond in **28** leads to a dipolar repulsion, however the alignment also polarises that conformer ($\mu = 3.85$ D), an effect that is reduced in the di-equatorial conformer ($\mu = 2.88$ D). This situation can be pushed further when all *syn*-1,3,5-trifluorocyclohexane **29** is considered; the ax/ax/ax conformer is 3.85 kcal mol^{-1} higher in energy in the gas phase than the eq/eq/eq conformer, and it has a much higher dipole moment (5.7 D versus 1.7 D).[26,27] For all of the cases discussed so far the higher energy conformers are transient and not relevant in the gas or solution phases as they can easily equilibrate to lower energy non-polar conformers. However an attractive situation presents itself with all *syn*-1,2,3,4,5,6-hexafluorocyclohexane (HFCH) **7**. In that case interconversion of the chair conformers leads to identical iso-energetic structures and with high polarity, because a triaxial arrangement with three C–F bonds is always retained. At the outset of our work this compound was unknown but theory predicted that an extraordinary polarity would be associated with this cyclohexane. Accordingly the synthesis of all-*cis* HFCH **7** became a target compound for preparation and investigation.

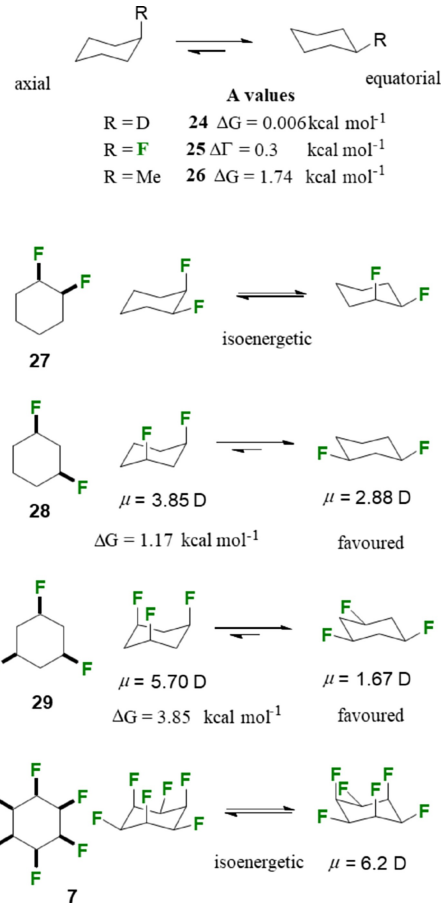


Figure 7. The chair conformations and ring interconversion structures of some selectively fluorinated cyclohexanes.[26]

3.1. The Parent Compound: All Syn-1,2,3,4,5,6-Hexafluorocyclohexane (HFCH)

The synthesis of **7** presented a conceptual challenge as there are 9 (nine) configurational isomers of HFCH **7** including

only one set of enantiomers (i = the enantiomer of i), the rest (ii–viii) have a plane of symmetry and have no enantiomers. Five (ix–xiii) of the ring inverted chair conformers are unique and have different energies to their partners, one (v) generates an enantiomeric chair and two (vii and viii) generate identical structures as summarised in Figure 8. Another two generate an identical enantiomeric conformer after inversion and thus the ring inverted structures for these three conformers are isoenergetic. The relative energies of the 13 non-equivalent chair structures are shown in the bar chart in Figure 8.[26,28]

It is very clear that HFCH **7** (isomer viii) stands out as a particularly high energy conformer. It has around twice the energy of the next nearest conformer, and it is around 16 kcal mol^{-1} higher in energy than the lowest energy conformer of the series, an observation which suggested unique properties. It followed that it may be challenging to synthesise. Our first synthesis of a hexafluorocyclohexane stereoisomer allowed preparation of the significantly lower energy isomer **37**, a stereoisomer which has four fluorines 'up' and two fluorines 'down'.[29] This was prepared as illustrated (isomer v) in Figure 9 and was initiated from a previously reported reaction of benzene and AgF_2.[30]

The reaction generated the tetra-fluorocyclohexene **33** as a major isomer. Isolation and then progression of this cyclohexane by dihydroxylation, cyclic sulfate formation (crystalline intermediate) and then successive fluorinations, each with an inversion of configuration, generated the hexafluorocyclohexane isomer **37**. The structure and stereochemistry of **37** was confirmed by X-ray crystallography and NMR spectroscopy. The successful synthesis of this first stereoisomer of HFCH provided the momentum for a campaign to prepare the HFCH **7**. This was eventually achieved, starting from *myo*-inositol **38**, by the route illustrated in Figure 10.[28] Essentially all of the C–O bonds of inositol were converted either directly of indirectly to C–F bonds in a stereospecific manner in order to secure the desired isomer. The most challenging synthetic step was the final one which introduced the last of the six fluorines. This involved a substitution reaction of triflate **44**. The reluctance of this reaction to go reinforced an awareness that **7** was a particularly high energy conformer. None-the-less a few milligrammes of material was isolated by chromatography for NMR and X-ray structure analysis. HFCH **7** proved to be a very high melting solid (mp 206 °C dec) which actually sublimes rather than melts. This behaviour at high temperature

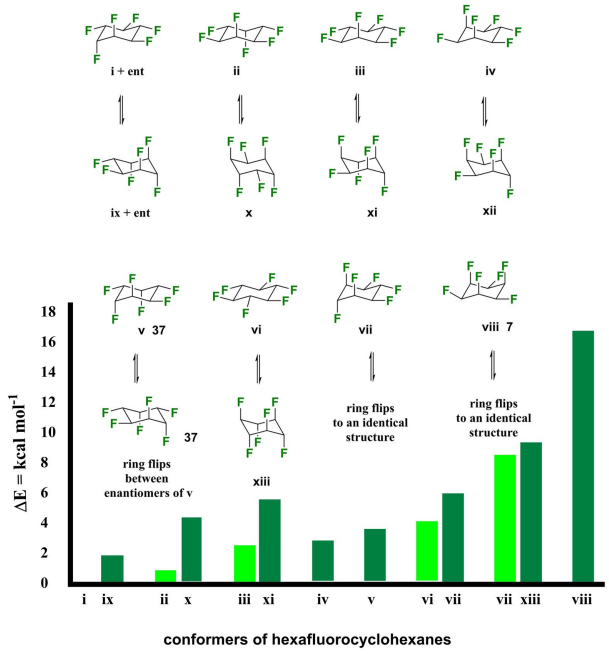


Figure 8. Structures and ring inverted conformers of all possible stereoisomers of 1,2,3,4,5,6-hexafluorocyclohexanes. Relative energies (kcal mol^{-1}) of the chair conformations of all isomers. Light green bars denote the lowest energy and dark green bars the higher energy conformers in each case.[28]

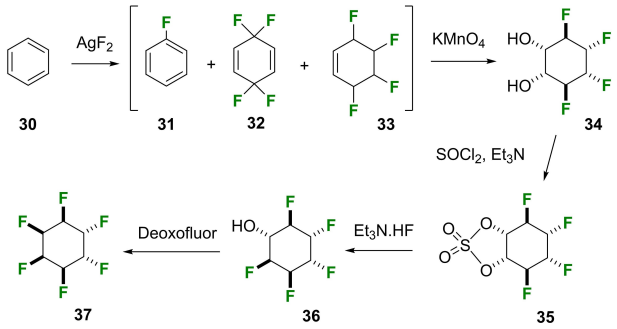


Figure 9. First synthesis of a 1,2,3,4,5,6-hexafluorocyclohexane diastereoisomer, which started from benzene.[29]

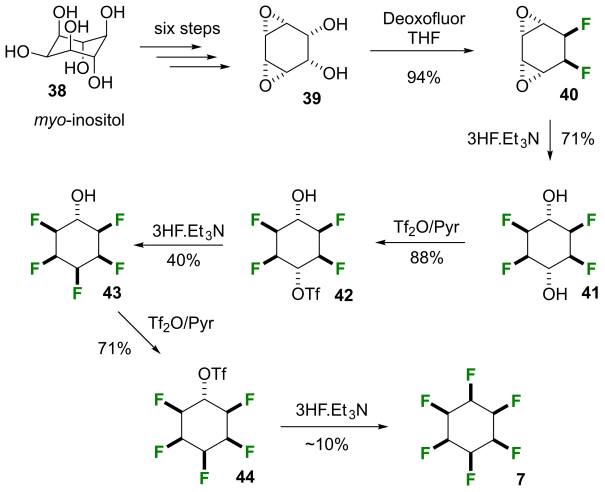


Figure 10. Original 12-step synthetic route to all-cis HFCH **7** starting from *myo*-inositol **38**.[28]

is much more characteristic of an ionic organic material such as an amino acid and was unexpected for a cyclohexane carrying only fluorine atoms. The X-ray structure gave some insight into the properties of HFCH **7**. The rings stack with the hydrogens making contact with fluorine faces, clearly stabilised by electrostatic interactions between the polarised faces of the ring. There is no sense that the solid state structure is stabilised through fluorous-fluorous or hydrogen face - hydrogen face interactions. The structure has perhaps a tangential relationship to the co-crystals formed from mixing equal amounts of benzene **30** and hexafluorobenzene **45** as described in the early 1960's by Patrick and Prosser as illustrated in Figure 11b.[31] In that case the two liquids (**30** and **45**) when mixed, generate a white solid (mp 24 °C) the structure of which alternates benzene **30** and hexafluorobenzene **45** rings. This arrangement is stabilised because the benzene core is electronegative and the hydrogens are electropositive, whereas the reverse is true for hexafluorobenzene where the ring core is electropositive and the fluorines are electronegative. Janus cyclohexane rings can be considered a fusion of this arrangement, where the hydrogen face is electropositive and the fluorine face is electronegative.

The polar nature of these rings is reinforced also by the ability of the fluorine face of **7** to complex to cations (eg Na^+), and the hydrogen face to complex to anions (eg Cl^-) in the gas phase and in solution. This was demonstrated experimentally by the isolation of charged ion complexes to sodium ions (Na^+) and separately to chloride ions (Cl^-) in a mass spectrometer ion chamber.[32] The isolated ions were then interrogated within the ion chamber with a free electron laser (FEL) in order to carry out infra-red (IR) spectroscopy. Theory and experiment were unified by iterative modelling and this allowed structures of the ion complexes to be proposed and their complexation energies in the gas phase to be calculated as illustrated in Figure 12. The complexation energies are remarkably large for these cations and anions (−41 kcal mol^{-1} for Na^+ and −37 kcal mol^{-1} for Cl^-). The sodium cations (Na^+) complexed to the fluorine face of cyclohexane **7** and chloride ions (Cl^-) to the hydrogen face of **7**, both in 1 : 1 and 1 : 2 ion : cyclohexane complexes, each of which could be independently isolated in the ion chamber and interrogated with the laser to record infra-red (IR) spectra. Subtle changes in the bond lengths relative to the neutral cyclohexane were observed. Sodium ion (Na^+) complexation lengthened the axial C–F bonds and shortened the equatorial C–F bonds of **7** consistent with the modelled structures. On the other hand chloride ion (Cl^-) complexation resulted in a lengthening of both the C-F_{ax} and C–F_{eq} bonds of ligand **7**, consistent with pushing electron density into the ring through complexation with the hydrogen face. Solution complexation of the methoxy-cyclohexane **46** was explored in acetone, a solvent of high dielectric constant, and the affinity, in this case for potassium ion (K^+) was significantly reduced from the gas phase experiments with association constants of ~ 400 M.[33] These outcomes are summarised in Figure 12. HFCH **7** also interacts strongly with the traditionally non-coordinating ion $B_{12}F_{12}^{2-}$

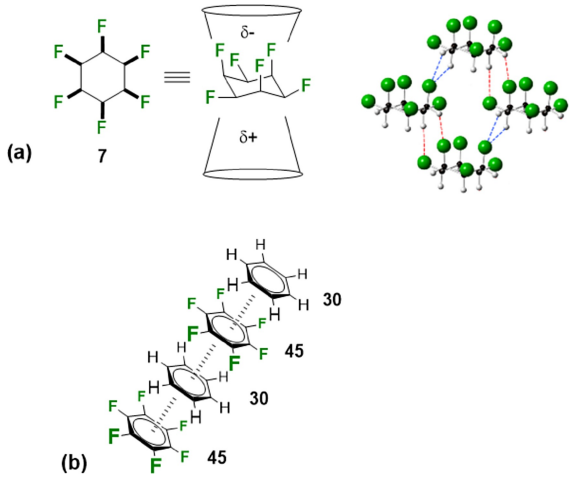


Figure 11. (a) Janus face representation and the molecular arrangement in the X-ray structure of HFCH **7**.[28] (b) Stacking representation of benzene **30** -hexafluorobenzene **45**.[31]

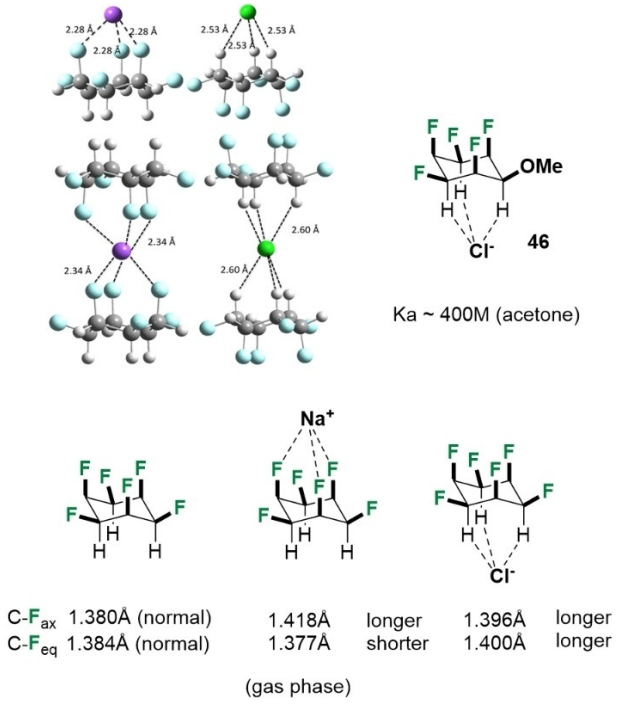


Figure 12. Structures of complexes of HFCH **7** with sodium (Na^+) and chloride (Cl^-) ions observed by mass spectroscopy and calculated bond lengths as they deviate from non-complexed HFCH **7**.[32] Methoxy-HFCH **46** complexes with Cl^- in solution.[33]

47, where 1 : 1, 1 : 2 and 1 : 3 complexes were also detectable in mass spectrometry ion chamber experiments, indicating that the large surface areas of these interacting species led to strong face to face associations.[34] There is good symmetry in the associations between the electropositive axial hydrogens of the cyclohexane and the electronegative fluorines on the borane cage as illustrated in Figure 13.

3.2. Aryl Hydrogenation

The synthesis of all-*syn* HFCH **7** was spectacularly improved by the lab of Frank Glorius in Műnster in 2017 through direct aryl hydrogenation of hexafluorobenzene.[35] Although this approach is relatively obvious in concept, attempts over many years at direct hydrogenations or fluoroaryls to fluorocyclohexanes had met with limited success and were essentially restricted to mono-fluorocyclohexane from fluorobenzene using Pt, Pd and Ni catalysts.[36] Higher levels of fluorination only ever resulted in fluoride ion eliminations.

However, Glorius's lab investigated the Rh-(CAAC) carbene catalyst **48** which had been developed by Zeng *et al.*, for aryl hydrogens more generally.[37] This proved very successful and for example HFCH **7** was prepared from hexafluorobenzene **45** in an 88 % yield, with low catalyst loading (2 %) and around 50 bar H_2, as illustrated in Figure 14.[35] Many substituted fluoroaryls and also fluoropyridines[38] are good substrates for this transformation and the chemistry has opened up access to a diversity of Janus face cyclohexanes with a range of substituents attached, as well as selectively fluorinated piperidines.

3.3. Janus Face Cyclohexane Building Blocks

In order to explore the properties of the pentafluorocyclohexyl motif in a range of performance molecules, access to appropriate building blocks is required, and this became possible with the developments in direct fluoro-aryl hydrogenation. Suitably protected amino acids are attractive building blocks and such a compound **50** is readily accessed after hydrogenation of the NBoc methyl ester of pentafluoroarylphenylalanine **49** as illustrated in Figure 15.[39] This transformation is relatively straightforward and the amino acid was used to prepare a series of candidate coronavirus protease inhibitors such as **51–54**, where the all-*cis* pentafluorocyclo-

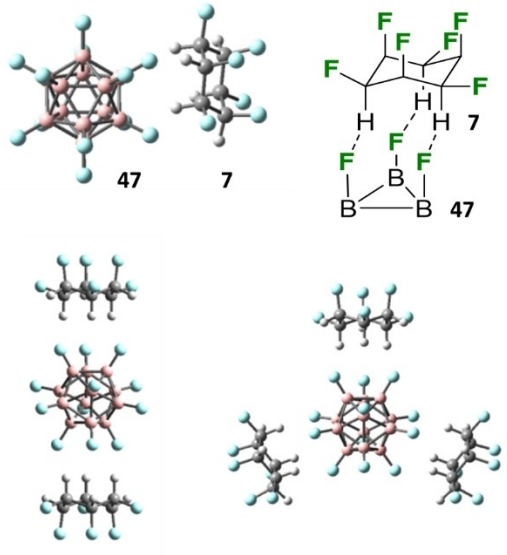


Figure 13. Various complexes of HFCH **7** interacting with the weakly coordinating ion $B_{12}F_{12}^{2-}$ **47** as observed by mass spectroscopy, with structures refined by computation.[34]

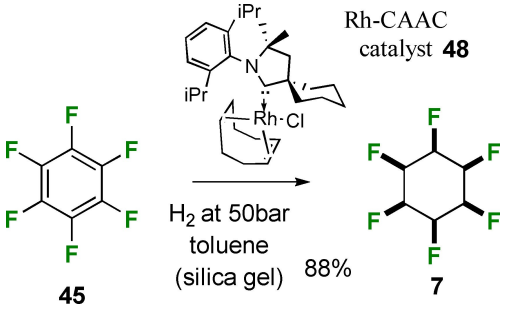


Figure 14. Single step aryl hydrogenation of hexafluorobenzene **45** with a Rh-CAAC catalyst **48** generates HFCH **7** as a single stereoisomer.[35]

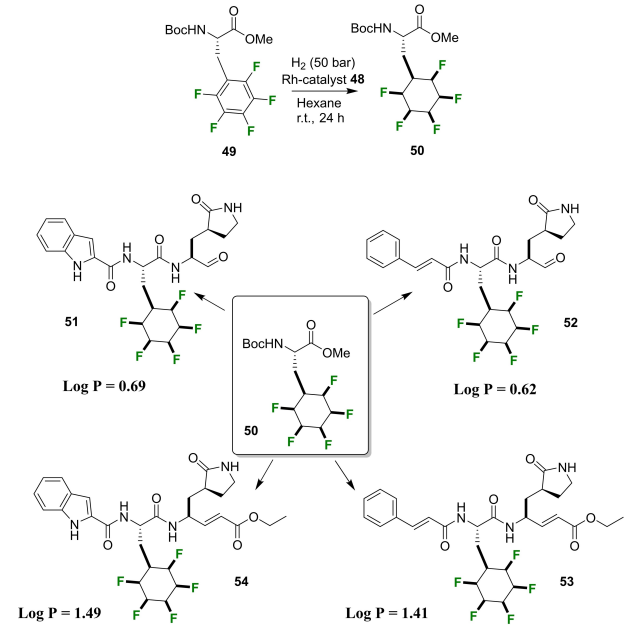


Figure 15. The structures and Log P values of candidate viral protease inhibitors **51–54** prepared from the protected amino acid **50**.[39]

hexyl side chain replaced the benzyl moiety of phenylalanine in the active compounds. In the event these compounds did not display anti-viral activity, indicating, not surprisingly that the Janus ring is not a straightforward bio-isostere of the aryl or cyclohexyl ring. It was notable however that the Log P values of the drug analogues remained low (Log P ~ 0–2) and in a very acceptable range for pharmaceutical development. Thus this motif remains a candidate for exploration in drug discovery. Pentafluorophenyl acetate ester **55** emerged as a very accessible precursor to useful building blocks carrying the Janus cyclohexane. Direct aryl hydrogenation of **55** generates cyclohexane **56**, which was progressed to alcohol **57**, aldehyde **58** (Figure 16), alkyl bromide **65** and then azide **66** (Figure 17), all useful building blocks. Aldehyde **58** has proven to be an excellent constituent in Ugi multi-component reactions as illustrated in Figure 16.[39] Azide **66** also proved useful for introducing this motive into triazoles as candidate bioactives as illustrated in Figure 17.[39]

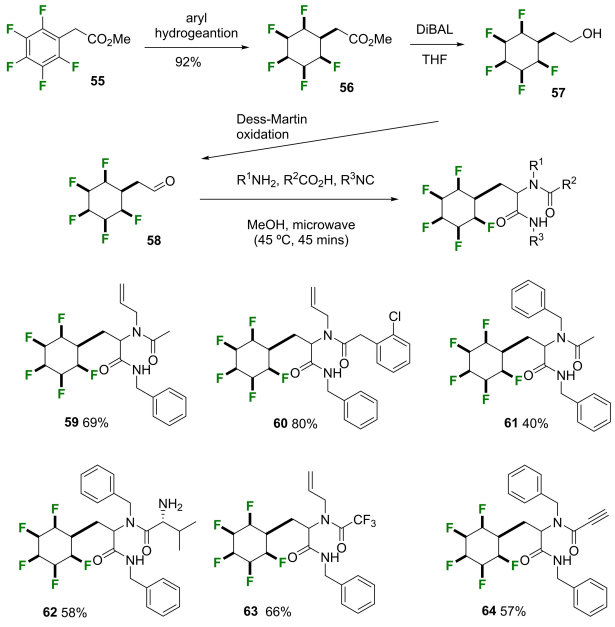


Figure 16. All-*cis* pentafluorocyclohexyl building blocks **56**–**58** and products of Ugi multi-component reaction products **59**–**64** from aldehyde **58**.[39]

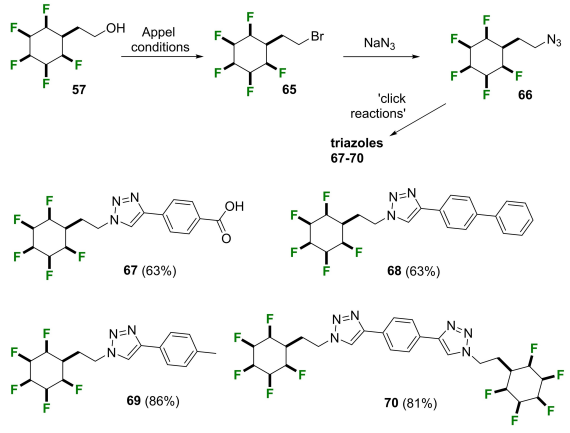


Figure 17. Triazole products **67**–**70** of azide-acetylene 'click' reactions using azide **66**.[39]

3.4. Supramolecular Assembly

Another starting material that can be usefully used to access Janus face cyclohexanes is phosphonate **71** illustrated in Figure 18. Horner-Wardsworth-Emmons chemistry allowed long chain extension, and the resultant aryl olefin was fully hydrogenated using the Rh-carbene catalyst **48** to generate long chain alkyls with a terminal all *cis*-pentafluorocyclohexane motif. The pentafluoro fatty acid **74** was prepared in this way after ester hydrolysis.[40] It is notable that the long chain fatty acid **74** has a melting point approximately 100 °C higher than its hydrocarbon (cyclohexyl-) counterpart **75** indicative of electrostatic packing between the Janus rings. Fatty acid **74** was used to explore monolayer behaviour on an aqueous subphase on a Langmuir trough, relative to hydrocarbon fatty acid analogue **75**.[40] These compounds behave very differently on the aqueous subphase. Hydrocarbon fatty acid **75** assembled into a well organised monolayer as anticipated for a classical fatty acid such as steric acid, whereas the pentafluoro fatty acid **74** immediately formed a multilayer aggregation, with no evidence at all of coherent monolayer assembly. Pre-aggregated bilayer domains were generated on the water surface, and this molecular arrangement progressed directly to a bilayer on the first compression in the Langmuir trough. The Langmuir isotherms illustrating this are shown in Figure 19. This indicates extensive pre-aggregation on the water surface through self-association of the polar fluorocyclohexyl rings, an

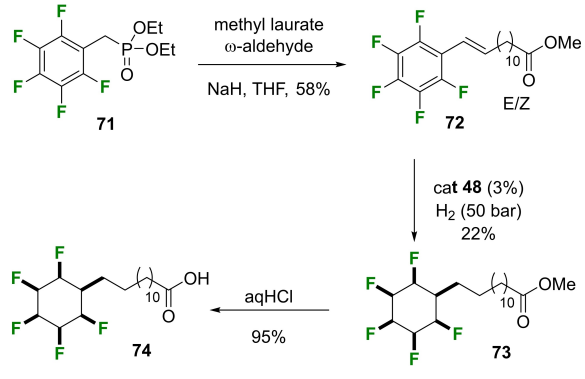


Figure 18. Synthesis of fatty acid **74** containing a terminal all-*cis* pentafluorocyclohexyl moiety. i NaH, THF, lauric ester-ω-aldehyde, 58%; ii **48** (3 mol%), H_2 (50 bar), 22%; iii $_{aq}$HCl, 95%.[40]

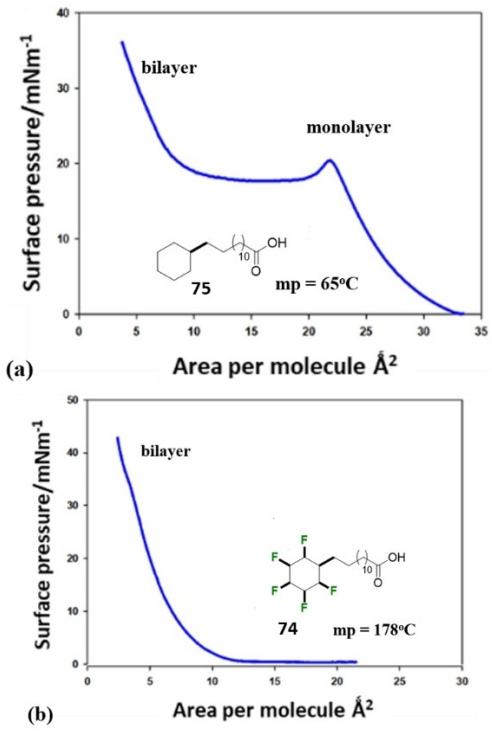


Figure 19. (a) Langmuir isotherm of **75** indicating a classical pressure/area isotherm progressing through a monolayer, and then with increased pressure to a bilayer. (b) Langmuir isotherm of the Janus ring containing fatty acid **74** indicates pre-aggregation and results in direct formation of a bilayer at full compression, indicating that fatty acid Y does not form classical monolayers.[40]

interaction which energetically competes with the interaction of the carboxylate groups with the water surface.

A study by Shyshov *et al.*,[41] explored Janus rings as motifs incorporated into monomers for living (dynamic) supramolecular polymerisations. Gallic acid derivatives, including chiral enantiomerically pure variants exemplified by **76** were predisposed towards a folded form, stabilised through intramolecular hydrogen bonding. These were used as 'dormant' monomers. These monomers readily formed gels and fibres at the liquid-air interface in solutions of chloroform, and particularly so when the monomers were seeded with fibrous precursors prepared by sonication. These fibres acted as templates for further living polymerisation dictated by electrostatic attraction between the Janus rings as illustrated in Figure 20. Blocks of various lengths could be prepared by controlled additions. In these studies AFM images of the fibres formed indicated that several one dimensional filaments entwine to form the stable fibre. TEM indicated that the molecular packing (Janus ring stacks) ran parallel to the direction of fibre elongation. Molecular dynamics (MD) simulations indicated that the fibres are formed from two antiparallel stacks of monomers combining to form a helical

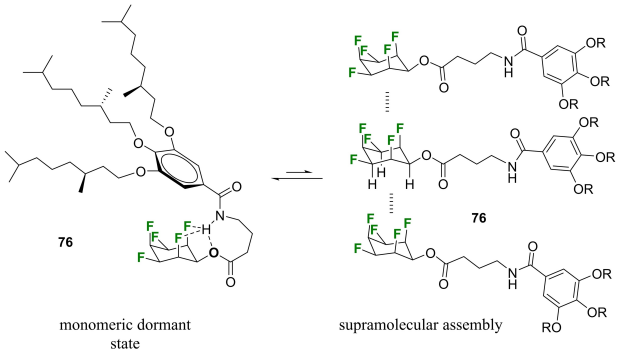


Figure 20. Living non-covalent polymerisation of **76** for the controlled supramolecular assembly of nano-fibres reported by Shyshov *et al.*[41]

superstructure (fibre). The study concluded that these simple Janus face building blocks, which lack extended π-systems or metals, offer a very attractive approach for the preparation of functional materials by living supramolecular assembly.

3.5. Log P and Metabolism

In the course of our programme we have prepared a range of Janus face cyclohexanes with an early focus on aryl tetrafluorocyclohexanes as well as substituted pentafluorocyclohexanes.[13,42] Direct Log P comparisons of tetrafluorocyclohexyl- benzoic acids and anilines as illustrated in Figure 21a with cyclohexane as a control substituent, illustrates dramatic reductions in Log P with progressive fluorination.[13] This observation also extended to cyclopropanes in Figure 21c, where aryl all-*cis* 1,2,3-trifluorocyclopropane **5** has a significantly lower Log P when compared stereoisomer **78**, indicating that these affects are also influenced by stereochemistry as well as the degree of fluorination in comparisons with cyclopropanes **79** and **80**.[43] The difluoromethylene cyclopropane **79** is less polar, with the nonfluorinated aryl-cyclopropane **80** being the most lipophilic.

In the case of aryl-tetrafluorocyclohexane **77**, a molecular mechanics study[13] explored how a water molecule interacts with these Janus rings as illustrated in Figure 21b. The study revealed a most favourable association between water and the hydrogen face of the cyclohexane ring, and with no particular affinity of water for the fluorine face. This can be accounted for by polarisation of the hydrogens by the geminal fluorine atoms, rendering these hydrogens electropositive and thus they pick up hydrogen bonds to the oxygen atoms in water through electrostatic attraction.

This study[13] extended to exploring the metabolism of aryl-tetrafluorocyclohexane **77** and lesser fluorinated rings such as **82** as illustrated in Figure 22. When compound **77** was added to incubations of the fungus *Cunninghamella elegans*, the cyclohexane ring was readily metabolised to the benzylic

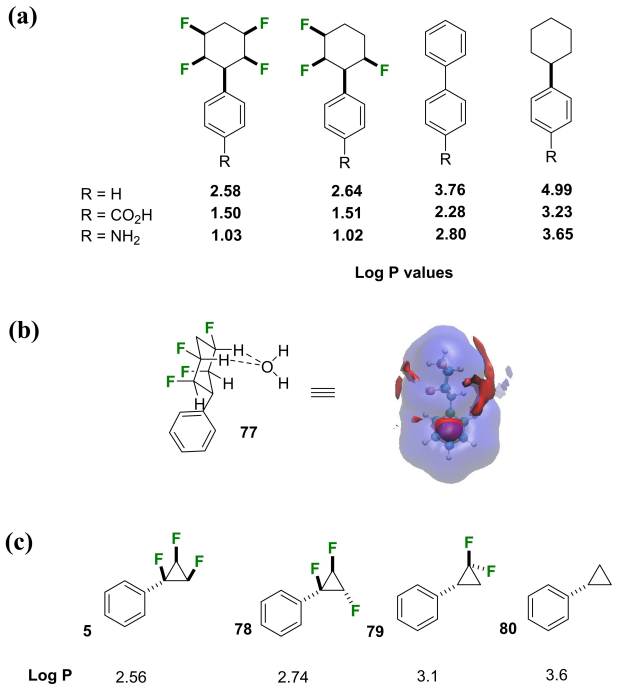


Figure 21. (a) Log P values of selectively fluorinated cyclohexyl benxoic acid and aniline derivatives; (b) the interaction of water with a Janus face cyclohexane **77** as determined by molecular mechanics;[13] (c) Log P values of phenyl fluorocyclopropanes **5**, **78** and **79** relative to phenylcyclopropane **80**.[43]

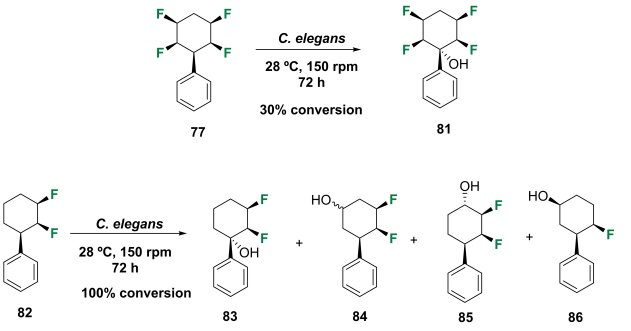


Figure 22. Examples of the metabolism of selectively fluorinated cyclohexanes **82** and **87**.[13]

alcohol **81**. *C. elegans* is used as a model for human metabolism as it is rich in P-450 enzyme activity. Difluorocyclohexane **82** incubations with *C. elegans* resulted in a rapid metabolism and generated a range of oxygenated metabolites **83**–**86** and including the defluorinated product **86**. The rate of metabolism may vary depending on the degree of fluorination, however these studies are a positive indicator that this class of selectively fluorinated cyclohexanes will be biodegradable and that they should not be persistant in the environment unlike perfluorinated hydrocarbons and PFASs, a situation of current concern.

A research group from Genentech Ltd. have recently explored the medicinal chemistry profile of the aryl tetrafluorocyclohexane motif exemplified by parent compound **77**.[44] In particular they investigated the performance of this ring system relative to cyclohexane in a wide range of matched pairs, exploring important pharmacokinetic parameters such as relative changes in Log P, solubility, cell permeability and metabolism. There was a consistent reduction in Log P of between 1 and 2 Log units (orders of magnitude). Other factors were more ambiguous such as the relative solubility of matched pairs, where it was difficult to predict when the fluorines offered a solubility advantage and when they did not depending on other substituents. In general cell permeability (the ability to cross lipid membranes) was poorer for the Janus face moiety in matched pairs, although there were some exceptions. When these pharmacokinetic parameters were considered in overview, the Janus ring system was considered to have an overall profile that matched the morpholine ring as a substituent quite closely eg relating the pharamacokinetic profiles of **87** and **88** as illustrated in Figure 23. The morpholine moiety is a widely used substituent in medicinal chemistry and the study concluded that the Janus ring cyclohexane motif possessed related characteristics and may have potential as a substituent for bio-actives discovery.

In another related medicinal chemistry study[45] a significant lowering in Log P was observed in exploring analogues of the HIF-2α inhibitor, Belzutifan **90** and particularly in comparison with the isomer **89** where vicinal fluorines have been placed geminal in a difluoromethylene group as illustrated in Figure 24.

This demonstrates again the dramatic effects of fluorine in polarizing geminal hydrogens by the incorporation of fluoromethylene groups (–CHF–).

4. Deleting Equatorial Fluorines

The polar nature of the Janus face cyclohexanes is very specifically associated with the alignment of axial C–F bonds in the chair conformation. In this context all-*cis*-1,3,5,-trifluorocyclohexane **29** offers an intriguing case. In the gas

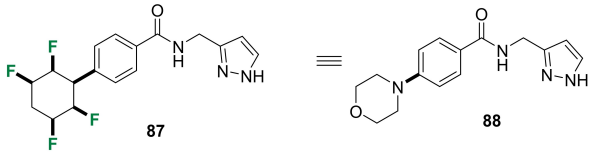


Figure 23. Medicinal chemistry analysis revealed a similar pharmacokinetic chemistry profile between the all-*cis* tetrafluorocyclohexane motif in **87** and a morpholine ring as a substituent in **88**.[44]

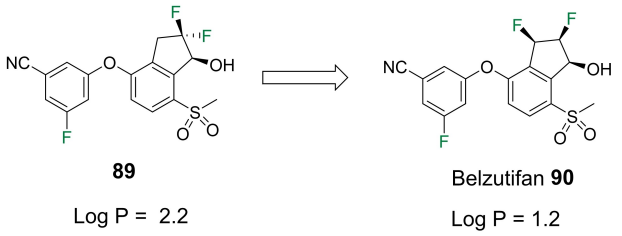


Figure 24. HIF-2α inhibitor Belzutifan **90** with vicinal fluorines, is more polar than the isomer **89** with geminal fluorines.[45]

phase the tri-equatorial conformation is very strongly favoured by ~3.5 kcal mol^{-1} as illustrated in Figure 25.[27]

This is also the case in solution where NMR coupling constants indicate a tri-equatorial conformation due to the obvious repulsion in aligning three triaxial C–F bonds and generating a highly polar arrangement ($\mu = 5.12$ D). Thus when the conformers are free to interconvert, the equilibrium shifts to the all equatorial conformer of **29** as would be expected. It was an intriguing observation therefore to find that cyclohexane **29** crystallises in the triaxial conformation. Molecular packing in the solid state is arranged such that the triaxial conformers stack one on top of another. Computation was used in order to rationalise this observation. The study explored the energy gained (interaction energy) in bringing three tri-axial conformers together in the gas phase and compared that to bringing three tri-equatorial conformers

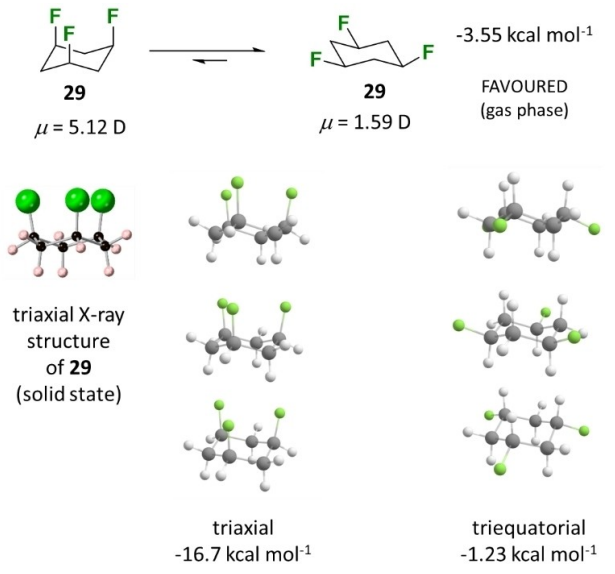


Figure 25. A reversal of the conformational preference for all-*cis* 1,3,5-trifluorocyclohexane **29** is observed between the gas phase (triequatorial) and the solid phase (triaxial). Electrostatic interactions between the more polar triaxial conformers are much stronger than that between triequatorial conformers in the condensed (solid) state.[27]

together. The outcome revealed a very substantial energy gain for condensing tri-axial over tri-equatorial conformers, and particularly in the packing geometry observed in the X-ray structure. The face-to-face association in bringing two polar tri-axial conformers together results in an energy gain of ~8.0 kcal mol^{-1} for each face-to-face interaction and can be compared to only ~1.5 kcal mol^{-1} in bringing two tri-equatorial conformers together. This difference in energy gain is greater than that lost (~3.5 kcal mol^{-1}) by interconverting an equatorial to a triaxial conformer. Larger gains are made in condensing three triaxial conformers and so on. Clearly if such stabilising interactions between the more polar conformers of **29** are translated through the infinite molecular packing array then the observed outcome emerges as inevitable. The ability of these ring systems to change polarity in going from solution to a condensed phase offers an advantage in the design of soft materials where soluble (less polar) constituents can then become ordered into condensed phases in more stable polar arrangements. The dynamic supramolecular polymerisation discussed above and illustrated in Figure 20 exemplifies this point.

It is clear that the polarity of the Janus rings arises from the triaxial arrangement of the C–F bonds, when these polar bonds co-align. It became attractive therefore to design molecules where this arrangement could be achieved by heavily biasing the conformational equilibrium in favour of the triaxial arrangement. This led to the preparation of alternating all-*cis* 1,3,5-trialkyl-2,4,6-trifluoro cyclohexanes exemplified by cyclohexane **92** as illustrated in Figure 26. It follows from the comparative equatorial preferences for substituents on cyclohexane (A-values) in progressing from **26** to **91** and then **92** in Figure 26, that there is a greater tendency for the Me or alkyl groups more generally, to lie equatorial relative to a fluorine substituent, thus in competition Me/alkyl should outcompete F on sterics, and the equatorial bias should increase with increasing Me/alkyl groups. The calculated equilibrium energies of the progressively methylated fluorocyclohexanes are illustrated in Figure 26.[45] Placing methyl groups alternately at the 1,3 and finally the 5 position leads to an increasing tendency towards stabilising the trifluoro-triaxial conformation, and in the case of three Me groups in **92**, then the equilibrium energy of ~7.08 kcal mol^{-1} indicates a very high conformational energy preference for the triaxial (C–F) conformer, overcoming electrostatic repulsions between the fluorines. This conformer is the more polar of the two chair structures by a significant margin, and thus 1,3,5-trialkylation is anticipated to generate polar Janus face cyclohexanes. In order to explore this a series of compounds was prepared as illustrated in Figure 27.

The synthesis approach exploited a threefold Sonogashira reaction on trifluoro-tri-iodobenzene **93**, to generate the arylacetylenes **94 a–f** as illustrated in Figure 27. These products

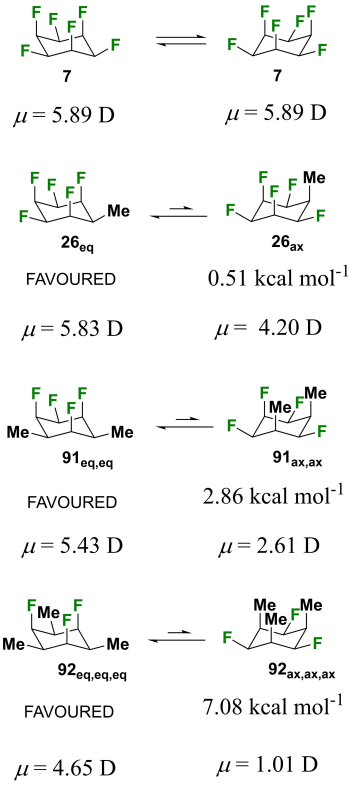


Figure 26. Relative energies of ring interconverted conformers progressively replacing F for Me at alternate carbons from HFCH **7**. Trifluoro cyclohexane **92** has a strong preference to orient the Me groups equatorial and thus forcing a polar triaxial fluorine arrangement.[46]

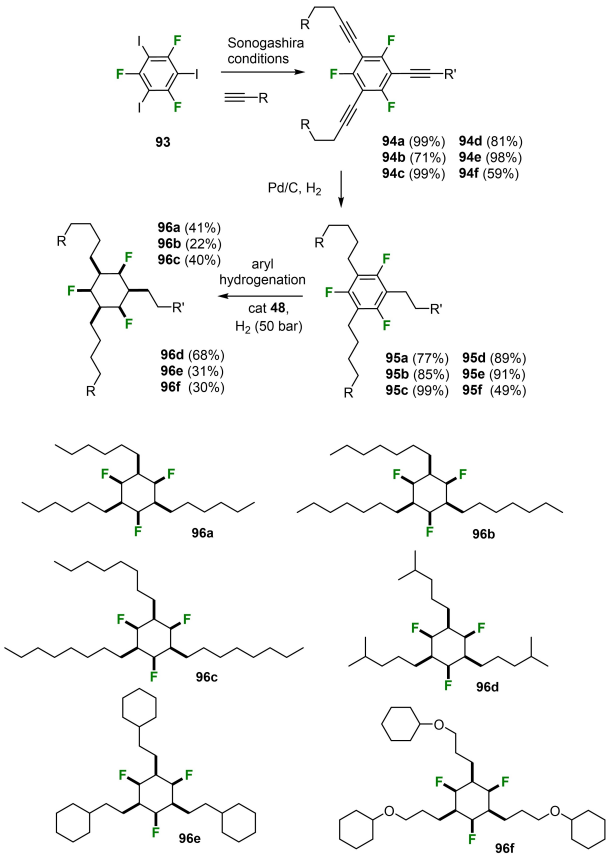


Figure 27. General synthesis route to alternately trialkylated, all-*cis* trifluorocyclohexanes **96a–f**.[46]

were only partially hydrogenated to the aryl alkanes **95a–f** under standard atmospheric hydrogenation conditions. This was then followed by high pressure (~50 bar) aryl hydrogenation reactions using Zeng's catalyst **48** to generate trifluorocyclohexanes **96a–f**. Products **96** are highly crystalline and the X-ray structures of representative product **96e** are illustrated in Figure 28. It is clear that the alkyl groups adopt equatorial orientations and that the rings are perfectly stacked in the solid state, one on top of another and consistent with maximal electrostatic attraction between the fluorine and hydrogen faces of the cyclohexane rings. Interestingly too the ring stacks are insulated from each other, with no lateral contact, each stack surrounded entirely by laterally packed hydrocarbon groups supporting the triaxial arrangement of the C–F bonds.

This phenomenon is not observed when only one or two alkyl chains are attached and there is lateral contact between ring stacks. This ability to order the alternately trialkylated Janus ring compounds, with a highly oriented polarity, opens up new prospects for supramolecular assembly for example for the preparation of discotic liquid crystals. Such applications are currently under investigation in our laboratory.

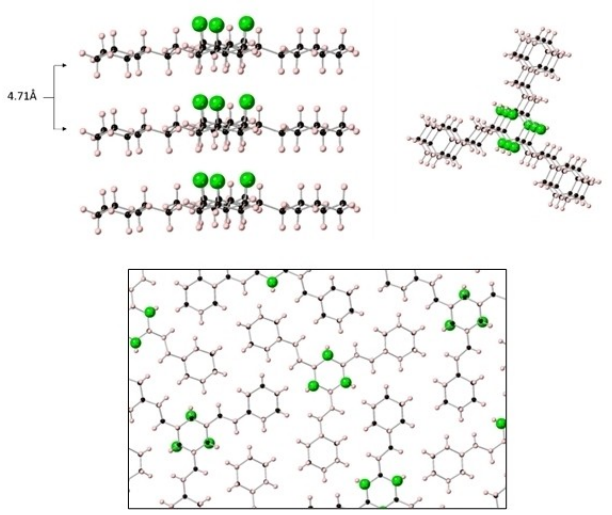


Figure 28. Cyclohexane **96e** forms supramolecular stacks stabilised by interaction between the alternate faces of the polarised triaxial-trifluoro conformers of the cyclohexane rings. The equatorial alkyl groups insulate the ring stacks from each other in the solid state.[46]

5. Concluding Remarks

The emergence of selectively fluorinated facially polarised cyclohexyl ring systems is a recent phenomenon and these systems remain to be explored in different areas of molecular science discovery. The review set out to demonstrate how this class of compounds emerged from studies on linear (acyclic) multi-vicinally fluorinated aliphatic chains, and recognising that individual stereoisomers possessed different properties. The remarkable polarities of the alicyclic rings, when fluorines are arranged on one face and hydrogens on the other, sets them apart and they already have demonstrated potential to modulate paharmacokinetic properties in medicinal chemistry or become key substituents in the supramolecular organisation of, or in imparting properties to, organic materials. The early challenges of preparing these compounds, an in particular Janus face cyclohexanes has been overcome, although challenges remain for example in efficiently preparing other aliphatic ring sizes such as all-*syn* trifluorocyclopropane motifs. However given the ingenuity of organic chemists as a community, such challenges will be overcome in due course, particularly if the properties prove attractive.

Acknowledgements

The author thanks many Ph.Ds and postdoctoral workers who have worked creatively on this project in the laboratory, with notable contributions from Luke Hunter, Marcello Nicoletti, Denis Bouvet, Alastair J. Durie, Neil S. Keddie, Tanja Bykova, Nawaf Al Maharik, Andrea Rodil, Rifa Neyyappadath, Fang Zeguo, Joshua Clark, Cihang Yu and Tommy Poskin. A long collaboration with Alexandra Slawin and David Cordes is gratefully acknowledged for crystallography support, and Rodrigo Cormanich and Bruno Piscelli of the University of Campinas in Brazil are gratefully acknowledged for their ongoing support with computation and theory.

References

[1] a) S. Swallow, *Prog. Med. Chem.* **2015**, *54*, 65–133; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chemie. Int Ed.* **2013**, *52*, 8214–8264; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[2] a) O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem.* **2022**, *17*, e20220036; b) K. Müller, *Chimia* **2019**, *73*, 417.

[3] a) J. R. He, Z, Y, Z. Y. Li, G. Dhawan, W. Zhang, A. E. Sorochinsky, G. Butler, V. A. Soloshonok, J. L. Han, *Chinese. Chem. Lett.* **2023**, *34*, 107578; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[4] a) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; b) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29.

[5] a) J. Lv, Y. Y. Cheng, *Chem. Soc. Rev.* **2021**, *50*, 5435–5467; b) R Berger, G. Resnati, P. Metrangolo, E. Weber, J Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.

[6] J. Gluge, M. Scheringer, I. T. Cousins, J. C. DeWitt, G. Goldenman, D. Herzke, R. Lohmann, C. A. Ng, X. Trier, Z. Y. Wang, *Environ. Sci. Process. Impacts* **2020**, *22*, 2345–2373.

[7] a) R. Lohmann, I. T. Cousins, J. C. DeWitt, J. Gluge, G. Goldenman, D. Herzke, A. B. Lindstrom, M. F. Miller, C. A. Ng, S. Patton, M. Scheringer, X. Trier, Z. Y. Wang, *Environ. Sci. Technol.* **2020**, *54*,12820–12828.

[8] a) T. M. Cahill, *Environ. Sci. Technol.* **2022**, *56*, 9428–9434; b) H. M. Pickard, A. S. Criscitiello, D. Persaud, C. Spencer, D. C. G. Muir, I. Lehnherr, M. J. Sharp, A. O. De Silva, C. J. Young, *Geophys. Res. Lett.* **2020**, *47*, e2020GL087535.

[9] a) R. Holland, M. A. H. Khan, I. Driscoll, R. Chhantyal-Pun, R. G. Derwent, C. A. Taatjes, A. J. Orr-Ewing, C. J. Percival, D. E. Shallcross, *ACS Earth Space Chem.* **2021**, *5*, 849–857; b) S. Henne, D. E. Shallcross, S. Reimann, P. Xiao, D. Brunner, S. O'Doherty, B. Buchmann, *Environ. Sci. Technol.* **2012**, *46*, 1650–1658.

[10] a) D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7981–7997; b) D. O'Hagan, *J. Org. Chem.* **2012**, *77*, 3689–3699.

[11] Y. Li, C. Liao, S. C. Tjong, *Nanomaterials* **2019**, *9*, 952.

[12] B. U. Emenike, A. Farshadmand, M. Zeller, A. J. Roman, A. Sevimler, D. W. Shinn, *Chem. Eur. J.* **2022**, e202203139.

[13] A. Rodil, S. Bosisio, M. S. Ayoup, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.

[14] a) D. Farran, A. M. Z. Slawin, P. Kirsch, P, D. O'Hagan, *J. Org. Chem.* **2009**, *74*, 7168–7171; b) L. Hunter, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 2843–2848; c) M. Nicoletti, D' O'Hagan, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2005**, *127*, 482–483.

[15] a) V. C. Port, R. A. Cormanich, *Phys. Chem. Chem. Phys.* **2021**, *23*, 17329–17337; b) M. Aufiero, R. Gilmour, *Acc. Chem. Res.* **2018**, *51*, 1701–1710; c) C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem.* **2017**, *57*, 92–100; d) I. Yamamoto, M. J. T. Jordan, N. Gavande, M. R. Doddareddy, M. Chebib, L. Hunter, *Chem. Commun.* **2012**, *48*, 829–831.

[16] a) N. Hayashi, T. Ujihara, H. Ikeda, *Tetrahedron* **2019**, *75*, 527–532; b) S. J. Fox, S. Gourdain, A. Coulthurst, C. Fox, I. Kuprov, J. W. Essex, C.-K. Skylaris, B. Linclau, *Chem. Eur. J.* **2015**, *21*, 1682–1691.

[17] a) T. Lu, J. Zhang, J. Chen, Q. Gou, Z. Xia, G. Fenga, *J. Chem. Phys.* **2019**, *150*, 064305; b) K. M. Marstokk, H. Møllendal, *Acta. Chemica. Scand.* **1997**, *51*, 1058–1065.

[18] N. Díaz, F. Jiménez-Grávalos, D. Suárez, E. Francisco, Á. Martín-Pendás, *Phys. Chem. Chem. Phys.* **2019**, *21*, 25258–25275.

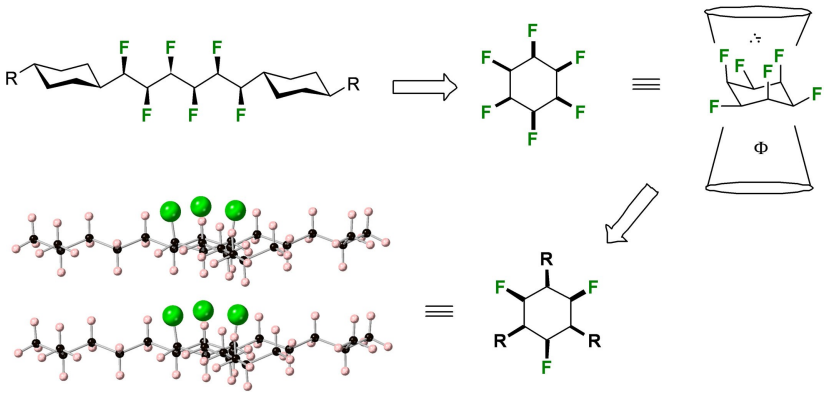
[19] L. Hunter, P. Kirsch, A. M. Z. Slawin, D. O'Hagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 5457–5460; *Angew. Chem.* **2009**, *121*, 5565–5568.

[20] a) L. Hunter, D. O'Hagan, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423; b) L. Hunter, D. O'Hagan, *Angew.*

Chem. Int. Ed. **2007**, *46*,7887–7890; *Angew. Chem.* **2007**, *119*, 8033–8036.
[21] L. Hunter, P. Kirsch, J. T. G. Hamilton, D. O'Hagan, *Org. Biomol. Chem.* **2008**, *6*, 3105–3108.
[22] P. Bentler, N. Erdeljac, K. Bussmann, M. Ahlqvist, L. Knerr, K. Bergander, C. G. Daniliuc, R. Gilmour, *Org. Lett.* **2019**, *21*, 7741–7745.
[23] Q. A. Huchet, N. Trapp, B. Kuhn, B. Wagner, H. Fischer, N. A. Kratochwil, E. M. Carreira, Klaus Müller, *J. Fluorine Chem.* **2017**, *198*, 34–46.
[24] a) E. F. Warnhoff, *J. Chem. Ed.* **1996**, *73*, 494–497; b) D. H. R. Barton, *J. Chem. Soc.* **1953**, 1027–1040; c) O. Hassel, B. Ottar, *Acta. Chemica. Scand.* **1947**, *1*, 929–943.
[25] a) E. L. Eliel. S. H. Wilen. S. H. Stereochemistry of organic compounds. John Wiley & Sons, Inc. New York, NY. **1994**; b) S. Winstein. N. J. Holness. *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578.
[26] a) V. Umadevi, N. Santhanamoorthi, L. Senthilkumar, *Comp. Theor. Chem.* **2014**, *1049*, 55–61; b) Q. Luo, K. R. Randall, H. F. Schaefer, *RSC Adv.* **2013**, *3*, 6572–6585. (c) K. B. Wiberg, *J. Org. Chem.* **1999**, *64*, 6387-6393
[27] C. Yu, B. A. Piscelli, N. Al-Maharik, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, D. O'Hagan, *Chem. Commun.* **2022**, *58*, 12855–12858.
[28] N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, *Nat. Chem.* **2015**, *7*, 483–488.
[29] A. J. Durie, A. M. Z. Slawin, T. Lebl, D. O'Hagan, *Angew. Chem. Int. Ed.* **2012**, *51*, 10086–10088; *Angew. Chem.* **2012**, *124*, 10233–10235.
[30] Z. Zweig, R. G. Fischer, J. E. Lancaster, *J. Org. Chem.* **1980**, *45*, 3597–3603.
[31] a) C. R. Patrick, G. S. Prosser, *Nature* **1960**, *187*,102; b) J. H. Williams, *Acc. Chem. Res.* **1993**, *26*, 593–598; c) C. E. Smith, P. S. Smith, R.L Thomas, E. G. Robins, J. C. Collings, C. Dai, A. J. Scott, S. Borwick, A. S. Batsanov, S. W. Watt, S. J. Clark, C. Viney, J. A. K. Howard, W. Clegg, T. B. Marder, *J. Mater. Chem.* **2004**, *14*, 413–420.
[32] B. E. Ziegler, M. Lecours, R. A. Marta, J. Featherstone, E. Fillion, W. S. Hopkins, V. Steinmetz, N. S. Keddie, D. O'Hagan, T. B. McMahon, *J. Am. Chem. Soc.* **2016**, *138*, 7460–7463.
[33] O. Shyshov, K. A. Siewerth, M. von Delius, *Chem. Commun.* **2018**, *54*, 4353–4355.
[34] M. J. Lecours, R. A. Marta, V. Steinmetz, N. S. Keddie, E. Fillion, D. O'Hagan, T. B. McMahon, W. S. Hopkins, *J. Phys. Chem. Lett.* **2017**, *8*, 109–113.
[35] a) Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264–270; b) M. P. Wiesenfeldt, T. Knecht, C. Schlepphorst, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 8297–8300; *Angew. Chem.* **2018**, *130*, 8429–8432; c) M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908–912.
[36] a) S. Kacem, M. Emondts, A. Bordet, W. Leitner, *Catal. Sci. Technol.* **2020**,*10*, 8120–1826; b) K. J. Stanger, R. J. Angelici, *J. Mol. Catal.* **2004**, *207*, 59–68.
[37] a) X. Zhang, L. Ling, M. Luo, X. Zeng, *Angew. Chem. Int. Ed.* **2019**, *58*, 16785–16789; *Angew. Chem.* **2019**, *131*, 16941–16945; b) Y. Wei, B. Rao, X. Cong, X. Zeng, *J. Am. Chem. Soc.* **2015**, *137*, 9250–9253.
[38] Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nature. Chem.* **2020**,*11*, 264–270.
[39] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.
[40] J. L. Clark, A. Taylor, A. Geddis, R. M. Neyyappadath, B. A. Piscelli, C. Yu, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Guldin, D. O'Hagan, *Chem. Sci.* **2021**, *12*, 9712–9719.
[41] O. Shyshov, S. V. Haridas, L. Pesce, H. Qi, A. Gardin, D. Bochicchio, U. Kaiser, G. M. Pavan, M. von Delius, *Nat. Commun.* **2021**, *12*, 3134.
[42] a) T. Bykova, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, T. Lebl, D. O' Hagan, *Chem. Eur. J.* **2018**, *24*, 13290–13296; b) T. Bykova, N. Al-Maharik, A. M. Z. Slawin, D. O'Hagan, *Beilstein J. Org. Chem.* **2017**, *13*, 728–733; c) T. Bykova, N. Al-Maharik, A. M. Z. Slawin, D. O'Hagan *Org. Biolmol. Chem.* **2016**, *14*, 1117–1123; d) M. Salah Ayoup, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Beilstein J. Org. Chem.* **2015**, *11*, 2671–2676; e) A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z. Slawin, D. O'Hagan, *Chem. Eur. J.* **2014**, *20*, 6259–6263.
[43] a) Z. Fang, N. Al-Maharik, P. Kirsch, M. Bremer, A. M. Z. Slawin, D. O'Hagan, *Beilstein J. Org. Chem.* **2020**, *16*, 674–680; b) Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.
[44] Y. Wang, W. Lee, Y.-C Chen, Y. Zhou, E. Plise, M. Migliozzi, J. J. Crawford, *ACS Med. Chem. Lett.* **2022**, *13*, 1517–1523.
[45] a) B. M. Johnson, Y.-Z Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*, 6315–6386; b) C. Xie, X. Gao, D. Sun, Y. Zhang, K. W. Krausz, X. Qin, *Drug Metab. Dispos.* **2018**, *46*, 336–345.
[46] T. J. Poskin, B. A. Piscelli, K. Yoshida, D. B. Cordes, A. M. Z. Sla win, R. A. Cormanich, S. Yamada, D. O'Hagan, *Chem. Commun.* **2022**, *58*,7968–7971.

Manuscript received: January 26, 2023
Revised manuscript received: March 14, 2023
Version of record online: ■■ ■■, ■■■■

PERSONAL ACCOUNT



*D. O'Hagan**

Janus face cyclohexanes offer a novel motif in organic chemistry that demonstrate the unexpectedly high polarity of partially fluorinated alkyl substituents. In the form of cyclohexane rings they offer new options for low Log P substituents in medicinal chemistry and they present exciting options for supramolecular assembly.