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Does Perdeuteration Increase the Polarity of Janus Face Cycloalkanes?

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Dedicated to the memory of Professor *Jack D. Dunitz* whose intellectual curiosity never failed to stimulate additional experiments.

Stimulated by a suggestion of the late Professor *Jack D. Dunitz*, that perdeuterated Janus face cycloalkanes may be more polar than their unlabelled forms, the deuterated isotopologue of all cis-1,2,3,4,5,6-hexafluorocyclohexane ($[^2H_6]$-**1a**) and all cis-1,2,3,4-tetrafluorocyclopentane ($[^2H_6]$-**3a**) were prepared. Computation at the B3LYP–D3 level indicated that $[^2H_6]$-**1a** is not more polar than its protio form **1**, however perdeuterated cyclopentane $[^2H_6]$-**3a** may indeed be more polar than **3**, although the magnitude is predicted to be small. None-the-less retention time analysis on a reverse phase GC/MS column of an add-mix of **3** and $[^2H_6]$-**3a** gave some indication that the per-deuterated isotopologue **3a** was detected marginally before the unlabelled compound consistent with increased polarity associated with perdeuteration.

Keywords: cyclopentane, deuterium, fluorine, Janus face, isotopologues, synthesis.

Introduction

Among Professor *Jack D. Dunitz*'s wide interests throughout his long career, he did focus his attention from time to time on fluorine. Among his most cited papers is *'Organic fluorine hardly ever accepts hydrogen bonds'*[1] published in 1997 and co-authored with *Robin Taylor* of the Cambridge Crystallographic Data Centre (CCDC). They highlighted that given the high number of fluorine containing molecules in the CCDB there were statistically very few containing short contacts between CF···HO and CF···HN. A key conclusion drawn, was that there are usually stronger H-bonding interactions to be found elsewhere than polarised hydrogens linking with fluorine, and essen-

tially these weak interactions are over-ridden by better options. *Dunitz* published[2,3] on the close relationship between F and H in determining molecular crystal packing and he revisited organofluorine compounds in overview in 2004[4] in *'Organic fluorine: Odd man out'* where he summarised his thoughts beyond H-bonding to aryl-to-fluoroaryl ring stacking and he articulated on the nature of key interactions that stabilise (or not) aliphatic perfluorocarbon and hydrocarbon liquids. In exploring the origins of the fluorous effect associated with perfluorocarbons, his analysis emphasised relatively healthy dispersion effects in carbon which offer some electrostatic attraction between chains in hydrocarbon liquids whereas this is not the case for the poor dispersion interactions between fluorines. In perfluorocarbon chains, the steric shielding of the fluorines disallows close proximity of intermolecular C-atom contacts and this results in significantly weaker attraction between the
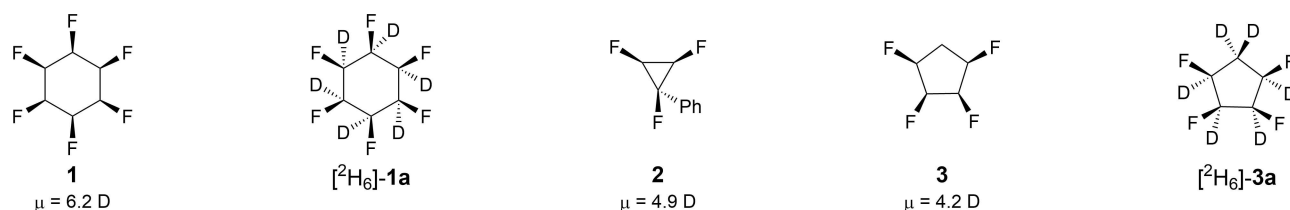
Figure 1. All *cis*-fluorinated cycloalkanes.

perfluorocarbon chains. This appears a very satisfactory analysis however he clearly saw fluorine as an enigmatic element and full of surprises and concludes '*nevertheless, in the absence of better data, better calculations, and better arguments, the above discussion may help throw a hint on the question of why organic fluorine is special and so often behaves as the odd man out*'. Fluorine did seem to intrigue him particularly after formal retirement. It was in this phase of his career that we were lucky enough to interact with him from time to time.

At St Andrews, we had an interest[5–9] in the synthesis and properties of a range of cycloalkanes containing fluoromethylene (CHF) groups, and a stereochemistry where all fluorines are 'up' or *cis*. These are typified by structures **1**–**3** shown in *Figure 1*. It is a consequence of fluorines on one face and hydrogens on the other that these all-*cis* fluorinated cycloalkanes have electronegative and electropositive faces. Due to their unique properties, these type of aliphatic alicycles have been referred to as 'Janus face' rings.[10] For example, all *cis*-1,2,3,4,5,6-hexafluorocyclohexane (**1**)[9] is an unexpected solid at room temperature with a very high melting point of > 208 °C and a calculated molecular dipole of greater than 6 Debye. This high polarity allows it to associate with both cations and anions with high affinities particularly in the gas phase.[11]

When all *cis*-1,2,3,4,5,6-hexafluorocyclohexane **1** was first prepared,[9] Professor *Dunitz* made the suggestion at Bürgenstock 'Conference on Stereochemistry' in Switzerland in April 2015, that the molecular dipole of **1** might further increase if the molecule was perdeuterated as [²H₆]-**1a**. The increased atomic weight of deuterium induces a reduced vibrational stretching frequency in the C–D compared to C–H bond, and therefore, the C–D bond is estimated to be incrementally shorter on average,[12] an aspect *Dunitz* had also explored in some detail.[13] There may be a measurable change in the molecular dipole of **1** after per-deuteration if the average distance between the electropositive and electronegative faces in [²H₆]-

1a should reduce relative to the nonlabelled compound. We went back to St Andrews to explore this further.

Results and Discussion

In the first instance, we attempted to test this prediction computationally for [²H₆]-**1a** versus **1**. Vibrationally averaged structures were computed (B3LYP–D3/6-311+G(d,p)) from the cubic force field,[1] but the outcome was inconclusive. Even although a slight reduction in C–D *vs.* C–H bond distances was computed, virtually identical dipole moments were predicted for the hydrogenated and deuterated variants of **1** (6.5 D, similar to the equilibrium value for the optimised minimum, *cf. Table S1* in the *Supporting Information*). Also attempts to make [²H₆]-**1** by direct aryl hydrogen[16–18] of hexafluorobenzene with deuterium gas, were only partially successful, as there was a significant presence of hydrogen (> 40 %) in the resultant cyclohexane **1** presumably due to exchange during the process from the hexane solvent. However, extending the computational analysis[6,14] to all-*cis*-tetrafluorocyclopentane (**3**), did suggest an increase in the molecular dipole upon deuteration, albeit only very slightly by *ca.* 0.02 D, (see *Table S2* in the *Supporting Information*). A deeper analysis of the isotopologue structures suggested that it may not be the difference in C–D *vs.* C–H bond distances that is of prime importance here for the change in dipole moment upon deuteration (as these distances are very similar for the cyclopentane and cyclohexane derivatives), but rather the more subtle conformational changes between the cyclopentane isotopomers. Whereas the chair conformation of the six-membered ring in **1** is rather rigid and quite insensitive to vibrational averaging, the dihedral angles along the

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five-membered ring of **3** are more sensitive to this averaging and to the isotopic substitution (some of these dihedral angles are computed to change by up to 0.8° upon deuteration, see θ values in *Tables S1* and *S2* in the *Supporting Information*). It may thus be a slight change in puckering of the five-membered ring upon deuteration that is causing the computed increase in dipole moment of [$^2H_6$]-**3a**. None-the-less this observation was encouraging in the context of the discussion with *Dunitz* and prompted a synthesis of [$^2H_6$]-**3a**.

The synthesis started with dicyclopentadiene **4**, followed by 'cracking' and distillation to acquire pure cyclopentadiene **5**. The perdeuterated isotopologue of cyclopentadiene **5a** has been reported by *Lambert*[19] and therefore the preparation of [$^2H_6$]-cyclopentadiene **5a** was carried out as previously described. The progress of the proton-deuterium exchange towards **5a** (yield 47%) was followed by ^1H-NMR spectroscopy until there were no visible proton signals, indicating that a fully deuterated cyclopentadiene **5a** was formed. The perdeuterated diepoxide **6a** was obtained through a protocol of *Noyori*,[7,20] although the yield in this case was only modest. Since it proved difficult to follow the chemistry by ^1H-NMR, after obtaining diepoxide **6a**, it was decided to proceed through the subsequent fluorination, triflation and fluorination reaction sequence, without intermediate purifications. This proved successful and a sample of **3a** was prepared after a final purification by chromatography. The synthetic route is illustrated in *Scheme 1*.

After purification, [$^2H_6$]-**3a** was isolated as a white crystalline solid and a suitable crystal was subjected to X-ray structure analysis. In the event, the resultant X-ray structure provided an indistinguishable structure to unlabelled **3**[6] and there was no discernible difference between C–C bond lengths or intermolecular C···C distance, and no obvious evidence of a more compact molecule from crystal packing.

For all-*cis*-1,2,3,4-tetrafluorocyclopentane **3**, its polar aspect was investigated by comparative NMR experiments, recorded in CDCl₃ and the aromatic solvent, C₇D₈ (toluene). Due to an interaction between the aromatic ring of toluene and the electropositive hydrogen face of **3**, these hydrogens experience an anisotropic upfield shift induced by the aromatic ring current. Therefore, the same comparative ^2H-NMR experiments for [$^2H_6$]-**3a** was conducted in these two solvents, and a similar effect to that observed for **3** was found. For the ^2H-NMR recorded in toluene, all of the deuterium signals experienced a significant upfield shift, compared with the ^2H-NMR spectrum recorded
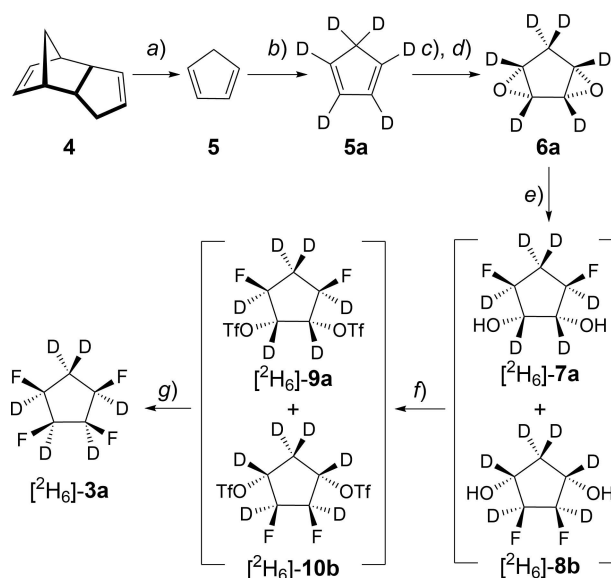
Scheme 1. Synthesis of [$^2H_6$]-tetrafluorocyclopentane **3a**. Reagents and conditions: *a*) Δ, 78%. *b*) NaOD, D₂O, Me₂SO, 0 °C, 44%. *c*) O₃, P(OPh)₃, CH₂Cl₂, −78→−30 °C. *d*) Ru(PPh₃)₃Cl₂, CH₂Cl₂, −78 °C, 1 h; −40 °C, 0.5 h; −25 °C, 1 h, 13%. *e*) Et₃N·3HF, 120 °C, 24 h. *f*) Tf₂O, pyridine, r.t., 24 h. *g*) Et₃N·3HF, 100 °C, 48 h.

in chloroform. The least shifted deuterium (D$_a$) is assigned to that on the upper (fluorine rich) face of the ring, associated with the CD₂ methylene group.[6] These significant upfield-shifted signals, compared to the experiment in chloroform, suggest a C–D/π electrostatic interaction between toluene and the deuterium face of [$^2H_6$]-**3a**. Another characteristic aspect of cyclopentane [$^2H_6$]-**3a** is the magnitude of the isotope induced chemical-shifts, which are demonstrated by $^{19}F\{^1H\}$-NMR. Due to the heavy atoms the two fluorine signals of [$^2H_6$]-**3a** are shifted up-field by around 1.5 ppm and 1.1 ppm respectively compared to the protio compound **3** as shown in *Figure 2*. These values are consistent with the magnitude of previously reported F/D geminal and vicinal isotopically induced shifts.[21]

In order to explore further if compound [$^2H_6$]-**3a** is measurably more polar than non-deuterated **3**, retention times by GC/MS were explored (see *Supporting Information* for more details). Isotopologues **3** and [$^2H_6$]-**3a** were add-mixed and the mixture was injected into a GC instrument with a reverse phase column to explore their separation. The isotopologues **3** and [$^2H_6$]-**3a** are both cleaved into various fragment ions in the mass-detector. Among these fragments, the two most abundant peaks, with recorded masses of 77 amu and 80 amu, correspond to ions of C₃F₂H₃$^+$ and C₃F₂D₃$^+$, respectively. The relative retention times of
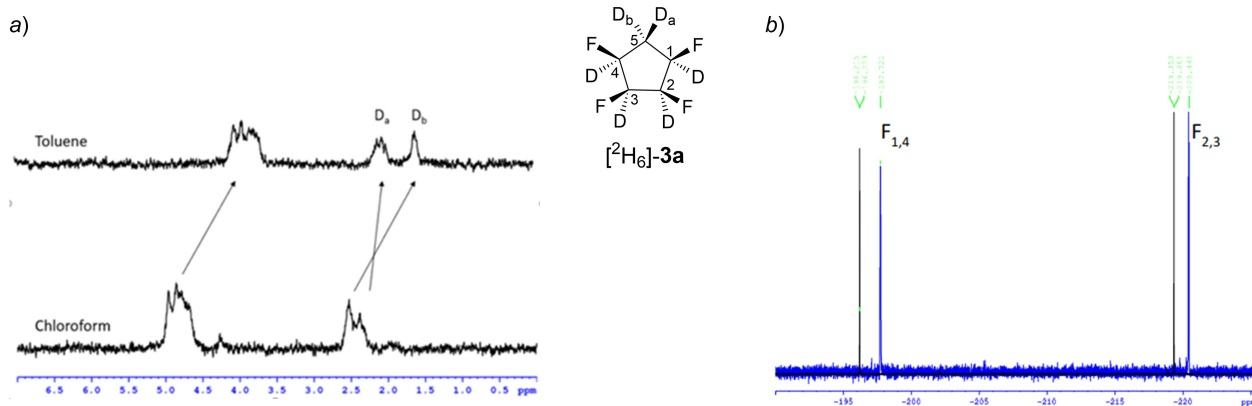
Figure 2. *a*) Comparison of the ^{2}H-NMR of cyclopentane $[^2H_6]$-**3a** in toluene and chloroform at r.t. *b*) ^{19}F{^{1}H}-NMR of compounds **3** and $[^2H_6]$-**3a**; the blue traces are the upfield signals for $[^2H_6]$-**3a**, the black traces are the signals for **3**.

the compounds delivering these ions were determined by monitoring the molecular ions at 77 amu and 80 amu (*Figure 3*). From the data, it can be seen that although the time difference between peak 77 amu (red) and 80 amu (blue) is very small (8.44 min versus 8.46 min), the deuterated ion ($C_3F_2D_3^+$) emerged from the reverse phase GC column ahead of the protic ion ($C_3F_2H_3^+$). This analysis was conducted in six separate runs and in each case the intensity of the perdeuterated ion was recorded in the detector ahead of the protic ion (See *Supporting Information*). The outcome is indicative of an increased polarity for **3** *versus* $[^2H_6]$-**3a** on the reverse phase column, the magnitude of which is difficult to quantify, but appears to be small and consistent with the predicted difference in molecular dipole from computation.
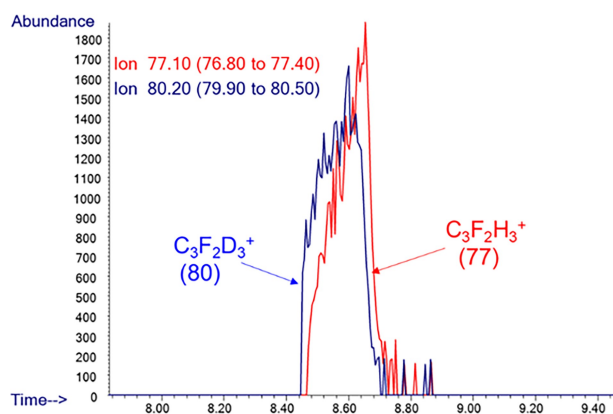
Conclusions

In summary, there does not appear to be evidence of an increased polarity through per-deuteration of all-*cis* hexafluorocyclohexane $[^2H_6]$-**1a** as determined computationally, however, in the case of cyclopentane $[^2H_6]$-**3a**, a measurable polarity difference was recorded relative to **3** by GC/MS, a polarity difference predicted by computation. Perhaps however the problem is not conclusively solved, – *Jack liked problems, puzzles and mysteries* –[22] as the effect is small and its origin unclear. None-the-less to have Professor *Dunitz* take an interest in our molecules, and to be the recipient of his intellectual curiosity, was a particular delight.

Supporting Information

Detailed research data, experimental procedures, characterization data, copies of ^{1}H, ^{13}C and ^{19}F-NMR spectra. This material is available free of charge through the Internet at https://doi.org/10.1002/hlca.202200177.

Figure 3. Typical GC/MS retention time [min] profiles of molecular ions 77 amu and 80 amu derived from injections of **3** and $[^2H_6]$-**3a**. The blue traces are the $C_3F_2D_3^+$, while the red traces are $C_3F_2H_3^+$.

Notes

The authors declare no competing financial interest.

Acknowledgements

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Author Contribution Statement

Z. F. and *C. Y.* carried out the synthesis and analysis protocols, *M. B.* carried out the computational chemistry and *D.O'H.* conceived the experiments. *D.O'H.* and *Z. F.* analysed the data and wrote the paper.

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