Janus Face All-cis 1,2,4,5-tetrakis(trifluoromethyl)- and All-cis 1,2,3,4,5,6-hexakis(trifluoromethyl)- Cyclohexanes

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Abstract: We report the synthesis of all-cis 1,2,4,5-tetrakis (trifluoromethyl)- and all-cis 1,2,3,4,5,6-hexakis (trifluoromethyl)- cyclohexanes by direct hydrogenation of precursor tetrakis- or hexakis- (trifluoromethyl)benzenes. The resultant cyclohexanes have a stereochemistry such that all the CF3 groups are on the same face of the cyclohexyl ring. All-cis 1,2,3,4,5,6-hexakis(trifluoromethyl)cyclohexane is the most sterically demanding of the all-cis hexakis substituted cyclohexanes prepared to date, with a barrier (ΔG) to ring inversion calculated at 27 kcalmol⁻¹. The X-ray structure of all-cis 1,2,3,4,5,6-hexakis(trifluoromethyl)cyclohexane displays a flattened chair conformation and the electrostatic profile of this compound reveals a large diffuse negative density on the fluorine face and a focused positive density on the hydrogen face. The electropositive hydrogen face can co-ordinate fluoride ion acting as a base.

To measure and teach relative steric impacts (A-values) [3] of individual substituents and higher levels of substitution generate interconverting chair conformations which can have equivalent or non-equivalent energies, depending on relative stereochemistry. There is a certain impulse, driven largely by aesthetics to consider cyclohexanes with six identical substituents on each ring. Such compounds have nine configurational isomers (and thirteen conformational isomers),[10] but a special situation arises when all six substituents have a syn or cis stereochemistry as these isomers have the highest energy chair conformers due to steric interactions between three axial substituents. Only a small collection of such cis- compounds have been prepared as illustrated in Figure 1. These are where the hexa-substituents are hydroxyl [1] as well as the corresponding peracetate [2] and perbenzoyl [3] esters, the hexa-carboxylic acid [4] and its permethyl [5] esters, the hexamethyl [6] esters, the hexamethyl [7] and most recently hexafluoro cyclohexane [8] [11] The sterically most demanding case so far is all-cis 1,2,3,4,5,6-hexamethylcyclohexane 7, [10] where the minimum energy chair structure is a splayed chair. An X-ray structure of this compound reveals an average splay angle of 105.5° where the triaxial methyl groups are approximately 15.5° from parallel. The barrier (ΔG) to ring inversion was experimentally evaluated at 17.6 kcalmol⁻¹ and can be compared to the significantly lower barrier for cyclohexane at ≈11.0 kcalmol⁻¹ [3b].

Figure 1. Structures 1–8 represent the known examples of all-cis-1,2,3,4,5,6-hexakis substituted cyclohexanes. Cyclohexane 8 is accessible by direct aryl hydrogenation with catalyst 10a, [13] a process recently extended to the direct hydrogenation of trifluoromethyl aryls such as 11 to generate 12. [15] Cyclohexanes 13 and 14 emerged as target compounds for this study.
The preparation of all cis-1,2,3,4,5,6-hexafluorocyclohexane 8 was reported in 2015.[13] This molecule proved to be high melting (208 °C dec) and an extraordinarily polar aliphatic with the capacity to coordinate to both cations (through the fluorine face) and anions (through the hydrogen face) in the gas phase[12] and in solution.[13] The difference in facial polarity led to the term “Janus face” rings being coined[14] for this type of ring system. The original stepwise synthesis of 8 was recently superseded by a direct heterogeneous hydrogenation approach developed by Glorius,[15] where 8 was prepared by aryl hydrogenation of hexafluorobenzene 6 under pressure (50 bar H2) using the cyclic (alkyl)-(amino)carbene (CAAC)/Rh catalyst 10a developed by Zeng.[16] Most recently Zeng’s lab has extended[17] the approach to the preparation of aryl-CF3 and heteroaryl-CF3 compounds using the closely related catalyst 10b to generate cyclohexanes and aliphatic heterocycles carrying up to three aliphatic-CF3 substituents such as 12, by direct hydrogenation of aryl 11.

In light of the recent developments in direct aryl hydrogenation chemistry[15–17] we decided to explore a preparation of all-cis tetrakis(trifluoromethyl)cyclohexane 13 and all-cis hexa-kis(trifluoromethyl)cyclohexane 14, by direct hydrogenation of the corresponding benzenes 15 and 16 respectively (Figure 2a and Figure 3a). These cyclohexanes are the first in the all-cis series that can be expected to display a “Janus face” polarity as a consequence of always possessing diaxial -CF3 groups, if the rings adopt ground state chair conformations. This can be contrasted with tris(trifluoromethyl) cyclohexane 12 which will predominantly exist in the all equatorial conformation in the ground state. In the case of 14, such a cyclohexane would represent the most sterically demanding member of the all-cis hexakis family of cyclohexanes so far and it was unclear if the steric crowding of the triaxial -CF3 groups would allow such a stereoisomer to emerge from the hydrogenation reaction. The preparation of these cyclohexanes and an evaluation of some of their properties are reported below.

Results and Discussion: The direct hydrogenation of 1,2,4,5-tetrakis(trifluoromethyl)benzene 15 was explored with the Zeng catalyst Rh(CAAC) 10a (H2, 50 bar), for conversion to the resultant all-cis 1,2,4,5-tetrakis(trifluoromethyl)cyclohexane 13. This proved to be a relatively straightforward transformation and the desired all-cis isomer 13 was isolated in a 60% yield as the only significant product. This compound was a crystalline solid (mp 73 °C) and was amenable to X-ray structure analysis. An image of the resultant structure of 13 is shown in Figure 2a. The solid state structure is a chair and this conformation dictates that there are two 1,3-diaxial, and two 1,3-diequatorial CF3 groups. Steric and electrostatic repulsion between the two diaxial CF3 groups is apparent from the 1,3-diaxial splay angle (CF3-C=C(CF3) = 107.5 °C) which deviates significantly from an ideal angle of 90°. A variable temperature (VT) 19F{1H}-NMR study of 13 reveals an equivalence of the -CF3 groups at 25 °C consistent with rapid ring inversion on the NMR timescale, however as the temperature is lowered to −75 °C, ring interconversion slows sufficiently to resolve the axial and equatorial -CF3 groups.[18] This is illustrated in Figure 2b. The overall barrier to ring interconversion for 13 of ΔG ≈ 10.3 kcal mol−1, as measured by Eyring plot analysis (see Figure S1-1) of the VT-NMR data, gave a value a little lower than that for cyclohexane itself (≈ 11 kcal mol−1), which was unexpected however there is complexity.[19] The asymmetric nature of the coalescence of the axial and equatorial CF3 peaks[18] in the 19F{1H}-NMR with temperature, as shown in Figure 2b, is a notable feature of the variable temperature experiment, and suggests the presence of an additional minor (higher energy) conformer population in solution, which most probably arises from interconverting "twist boats". A com-
The structure of 14 indicates that the cyclohexane ring adopts a shallow chair conformation due to a significant splay between the axial -CF₃ groups from the anticipated steric crowding. The diffraction data indicate that the triaxial -CF₃ groups have six splay angles (CF₃,6-C...C(CF₃)) ranging between 107.9° and 113.2°, and with an average value of 110.8°. This deviates significantly from the ideal angle of 90° in cyclohexane and is wider than that observed in the X-ray structure of hexamethycyclohexane 7 (110.8° versus 105.5°) consistent with the greater steric impact of -CF₃ over -CH₂. It is also wider than the average for these angles in 17 (108.9°) where an axial -CH₂F group replaces an axial -CF₃.

A computed electrostatic potential map of 14 (B3LYP/6-31G*) reveals a large diffuse electronegative area associated with the -CF₃ groups on one face of the ring, with a much more concentrated electropositive area (blue) on the opposite face associated with the hydrogens (Figure 3c). In another hydrogenation reaction of benzene 16, an adduct between 17, the major product of the hydrogenation reaction and lactam 18 co-eluted during chromatography. This adduct was amenable to X-ray crystallography and the resultant structure shown in Figure 4, demonstrated that the amide carbonyl is coordinated to the electropositive region on the hydrogen face of this cyclohexane in the solid state. Lactam 18 was recently shown to derive from reaction of (CAAC)Rh catalyst 10a with molecular oxygen. [23]

In order to explore the Janus face aspect of cyclohexane 14 further, 1H-NMR spectra were recorded in different solvents to compare relative chemical shift changes of the H₆ax and H₆eq signals. Comparative spectral data are shown in Figure 5. There is a very clear upfield shift associated with each set of hydrogens in toluene, relative to DCM, a shift which is significantly larger for the axial hydrogens (H₆ax Δδ = 1.25 ppm & H₆eq Δδ = 0.6 ppm). This is consistent with the aromatic ring of toluene associating with the electropositive hydrogen face of cyclohexane 14 and inducing a larger anisotropic influence on the axial relative to the equatorial exocyclic dehydrofluorinations, followed by hydrogenation to the “hydrogen” face, and directed away from the remaining -CF₃ groups. The desired all-cis isomer 14 (13% yield) is a white and rather amorphous material (mp 47–51 °C) but was sufficiently micro-crystalline to obtain an X-ray structure, illustrations of which are shown Figure 3b, with and without (for clarity) fluorines.

Figure 3. a) Aryl hydrogenation of 16 gave cyclohexanes 14 (13% yield) and 17 (40% yield). b) Hexane, H2 (60 bar), silica gel (7 equiv), cat 10a (20%), 50 °C, 14 days. c) X-ray structure of all-cis-1,2,3,4,5,6-hexakis-(trifluoromethyl)cyclohexane 14 (left) and without the fluorines (right) for clarity. [24] c) Electrostatic potential map of 14 illustrates a focused positive charge density (blue) on the hydrogen face.

Figure 4. An X-ray structure [25] of a co-complex of 17 with catalyst derived lactam 18.

Having achieved a synthesis of 13 by direct hydrogenation, attention focussed on a preparation of all-cis hexakis-(trifluoromethyl)cyclohexane 14 by direct hydrogenation. The required benzene 16 was prepared by an exhaustive copper catalysed trifluoromethylation of hexaiodobenzene as previously described. [20] Substrate 16 was then exposed to direct hydrogenation with catalyst 10a (Figure 3a). In this case the conversion was poor although some improvement was achieved with an increase in catalyst loading (20%), as well as increasing the reaction pressure (60 bar) and temperature (50 °C). The production of 14 was slow and did not progress significantly after several days under these conditions. The reaction was monitored over an extended time period and in the event a sample of 14 was isolated in low yield, after 14 days. Purification required careful chromatography eluting initially with pentane, and then progressively introducing diethyl ether and then dichloromethane as the eluent. The major product (≈ 40% yield) from this reaction, eluting in the diethyl ether fractions is 17 with five -CF₃ groups and rather unexpectedly, one fluoromethyl (-CFH₂) moiety, but with an overall all-cis stereochemistry. The structure of 17 was confirmed by X-ray structure analysis [26] which shows that the fluoromethyl group is orientated axial among the sterically more congested axial -CF₃ groups (See SI). Cyclohexane 17 presumably arises after two successive
hydrogens. Conversely there is a very strong downfield shift, particularly for the -H ax protons when the NMR is recorded in acetone, consistent with hydrogen bonding contacts between the carbonyl oxygen of solvent molecules and the electro-positive hydrogens. This interaction of 14 with acetone has a model in amide coordination in the co-crystal of 17 with lactam 18 (Figure 4).

A titration of 14 with chloride ion (Cl⁻) was explored, titrating tetrabutylammonium chloride (TBACl) into a solution of 14 in DCM and monitoring by 1H-NMR. The titration progression is illustrated in the 1H-NMR profiles in Figure 6. A very large chemical shift change, again particularly for the axial hydrogens (ΔH ax = 2.4 ppm) is observed up to the addition of approximately two equivalents of Cl⁻/C0, and then the chemical shifts of both the H ax and H eq hydrogens remain much more stable. An association constant for chloride ion was evaluated at K ≈ 10⁵ (Figure SI-17). A similar 1H-NMR titration analysis for fluoride indicated a lower affinity (K = 10³) and this reduced further for the softer iodide. When the tetrabutylammonium fluoride (TBAF) titration of 14 was monitored by 19F-NMR, it could be observed that decomposition occurred after 2 equivalents of TBAF was added (see Figs SI-13 & SI-14), consistent with fluoride ion acting as a base to promote exocyclic dehydrohalogenations. Endocyclic dehydrohalogenation decomposition was previously observed when hexafluorocyclohexane 8 was titrated with fluoride.[13]

In an effort to explore the barrier to cyclohexane ring inversion for 14, VT-NMR experiments were conducted between +80°C to −80°C, however there were no significant changes in chemical shifts in the 1H-NMR or 19F[NH]-NMR spectra over this temperature range and no polarisation transfer could be detected between the 1H- or 19F-NMR nuclei in exchange correlation (EXSY) NMR experiments, even at the higher temperatures. This indicated that the barrier to ring inversion for 14 is high and that the rate is slow on the NMR timescale. To complement these findings, DFT calculations were performed at the B3LYP-D3 level, and this located transition states (TSs) that are likely to be involved in connecting the minima. The lowest of these TSs is a boat structure involved in connecting two enantiomeric twist boat (TB) minima, with a ΔG° relative to the twist-boat intermediate of 5.9 kcal mol⁻¹ at RT. Chair and twist-boat minima are indicated to interconvert via a half-chair or envelope-like structure with a large computed barrier of ΔG° = 27.1 kcal mol⁻¹ at room temperature as illustrated in Figure 7 (and Figure SI-23). At the highest theory level explored, including a continuum model for the solvent (DCM), the TB conformer of 14 is computed to be significantly higher in energy than the chair (C) conformer, with a value of ΔG° = 10.2 kcal mol⁻¹ at room temperature. The complete pathway for chair inversion was not traced due to complexity involved in deconvoluting several additional intermediates and transition states which arise due to the interlocking -CF₃ groups. It is clear, however,
that much higher barriers for this process are required than the hexamethyl- or hexafluoro-cyclohexanes 7 and 8 respectively, and thus 14 emerges as the most sterically demanding example of an all-cis hexakis substituted cyclohexane prepared to date.

In summary we have prepared all-cis substituted cyclohexanes with four 13 and six 14 trifluoromethyl (-CF₃) groups on one hemisphere of the ring. The ground state conformation in each case is a chair although for all-cis 1,2,4,5-tetakis(trifluoromethyl)cyclohexane 13 DFT computation indicated that the chair and twist boat conformers are close in energy and that the twist boat should be relevant in solution, consistent with the observed VT-NMR profiling. All-cis 1,2,3,4,5,6-hexakis(trifluoromethyl)cyclohexane 14 has the highest barrier ($\Delta G^+ = 27.1$ kcal mol⁻¹) to ring inversion of the small family of all-cis hexakis substituted cyclohexanes (1–8, 14) prepared so far. The stereochemical arrangement of the -CF₃ groups in 14 leads to a large diffuse electronegative fluorine face and a much more concentrated electropositive fluorine face on one hemisphere of the ring. The ground state conformation in each case is a chair although for all-cis cyclohexane following from the preparation and demonstrated properties of 8.

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Conflict of interest

The authors declare no conflict of interest.

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