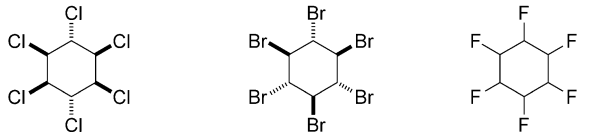
Benzene Hexafluoride

DOI: 10.1002/anie.201205577

The Synthesis of η-1,2,3,4,5,6-Hexafluorocyclohexane (Benzene Hexafluoride) from Benzene**

*Alastair J. Durie, Alexandra M. Z. Slawin, Tomas Lebl, and David O'Hagan**

In 1825 Michael Faraday reported the preparation and isolation of hexachlorocyclohexane (HCCH), also known as benzene hexachloride, after a photochemical reaction of chlorine gas with benzene.[1] The reaction generates up to five stereoisomers of hexachlorocyclohexane, a combination that was subsequently marketed in the 1940s as Lindane, and became an important insecticide.[2] The active constituent is stereoisomer **1** (γ-HCCH), and Lindane has been used as an insecticide for over 50 years, until it was widely banned due to its persistence in the environment.[3] A decade after Faraday's chlorine experiment, Eilhard Mitscherlich working in Berlin in 1835, reported the isolation of hexabromocyclohexane **2** (HBCH)[4] after combining bromine and benzene to give a white solid. It was subsequently shown that the reaction generates two major stereoisomers the predominant one being the β-isomer **2**.[5] The analogous hexaiodocyclohexane is an unknown compound. There is only one report in the literature, from 1969,[6] suggesting an identification of an analagous hexafluorocyclohexane (HFCH) **3**. The reaction involved direct fluorination of benzene with CoF_3/KF/F_2. A range of fluorinated products resulted and a minor component (ca. 2%) of the product mixture was isolated as a solid (m.p. 123-124°C). The authors proposed the all-*trans* (β-HFCH) structure of **3** based on analytical data and empirical logic, although the structure and stereochemistry was never established. Their account stated: "*When set aside, fraction 6 gave a crystalline solid (VII), which was filtered off. … Analysis of (VII) indicated that it had an empirical formula corresponding to $C_6H_6F_6$. The mass spectrum of (VII) gave a parent ion of 192 and a cracking pattern which indicated the presence of CHF groups only. The ^1H and ^{19}F NMR spectra also indicated that only CHF groups were present. The compound was resistant to oxidation and could not be dehydrofluorinated under a variety of conditions. These facts suggest that compound (VII) is a 1,2,3,4,5,6-hexafluorocyclohexane very probably with the trans structure.*"[6]



1 **2** **3**

The only other commentary in the literature on HFCH is a theory study[7] which calculated the relative energies of the thirteen possible chair conformers from the nine possible configurational isomers of **3**. The relative energies are reproduced in the histogram in Figure 1. The different isomers have different energies. The all-*syn* isomer **3b** is calculated to be of highest energy, and isomer **3c** of lowest energy, not the *trans* structure (all equatorial **3d**, Figure 1) which might be intuitively predicted.[6]

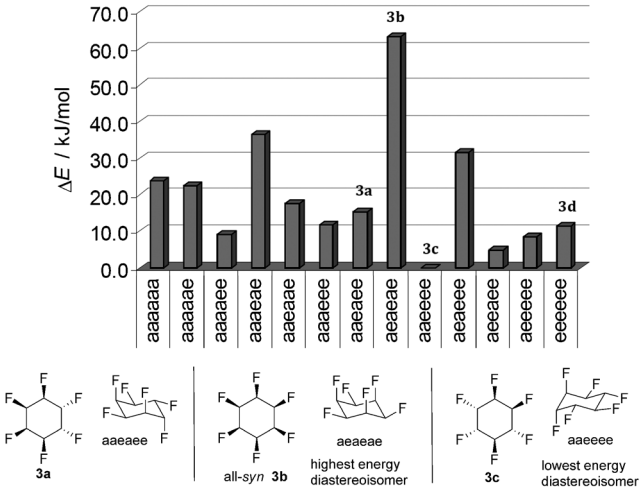


Figure 1. Calculated relative energies of the thirteen possible stereoisomers of the chair forms of the nine configurational isomers of HFCH. The highest-energy structure is all-*syn* **3b** and the lowest-energy structure is isomer **3c**.[7]

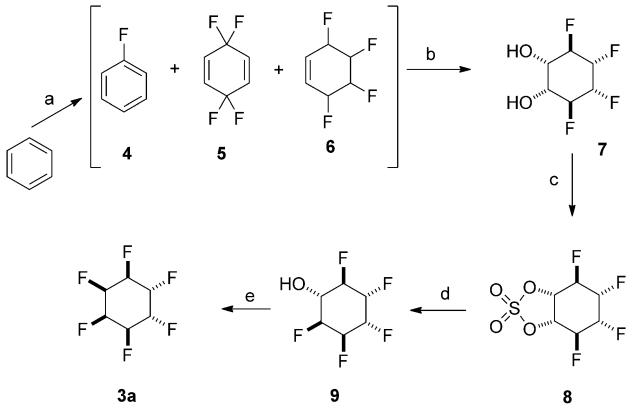
Here we report the first unambiguous synthesis of a HFCH **3** stereoisomer. The route begins from benzene. AgF_2 has previously been reported[8] as a reagent for the conversion of benzene to fluorobenzene **4** (Scheme 1). The major product is fluorobenzene (ca. 45%), although there are also a number of side-products with higher levels of fluorination including tetrafluorocyclohexenes **5** and **6** and unreacted benzene. Although these compounds were not isolated in the original report, their structure and stereochemistry was deduced by NMR analysis. In our hands this conversion was reproducible but the isolation of **5** or **6** proved

[*] A. J. Durie, Prof. A. M. Z. Slawin, Dr. T. Lebl, Prof. D. O'Hagan
EaStChem School of Chemistry, University of St. Andrews
North Haugh, St. Andrews, Fife KY16 9ST (UK)
E-mail: do1@st-andrews.ac.uk
Homepage: http://chemistry.st-and.ac.uk/staff/doh/group

[**] D.O'H. thanks the EPSRC and the ERC for an Advanced Investigator Grant to support this research. We thank the EPSRC for a research grant and for financial support through a DTG Studentship (A.J.D.).

Supporting information for this article (full experimental procedures and characterization data for all compounds, ^{19}F NMR spectrum of **3a**, and crystallographic data for **3a**, **8**, and **9**) is available on the WWW under http://dx.doi.org/10.1002/anie.201205577.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Reagents and conditions: a) AgF_2, CH_2Cl_2, RT; b) $KMnO_4$, $MgSO_4$, EtOAc, EtOH, H_2O, 0 °C→RT; c) SO_2Cl_2, Et_3N, EtOAc, 2.3% from 3 steps; d) $Et_3N{\cdot}3HF$, 120 °C, 86%; e) Deoxofluor, THF, 55%.

difficult due to a complex mixture of related organofluorines and product volatility. Therefore, the product mixture was oxidized directly with permanganate, to generate vicinal diol **7**, a reaction we have used to advantage in the preparation of acyclic vicinal fluorinated alkanes.[9] By using a modification of a Sharpless protocol,[10,11] diol **7** was converted to the corresponding cyclic sulfate **8**. Although this compound was isolated in a low overall yield from benzene, it was the first tractable compound of the route and it could be secured by chromatography. The structure and relative stereochemistry of **8** was confirmed at this stage by X-ray structure analysis of a suitable crystal (Figure 2). Hydrogen fluoride treatment of **8** then gave the pentafluoroalcohol **9** in an efficient conversion. This alcohol was also a crystalline solid and X-ray analysis (Figure 2) confirmed the relative stereochemistry and that an inversion of configuration has occurred during the substitution reaction. Finally a high-temperature dehydroxyfluorination reaction of **9**, by using Deoxofluor,[12] generated HFCH **3a**.

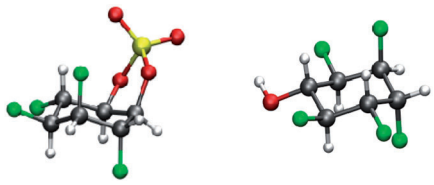


Figure 2. X-ray structures which confirm structure and relative stereochemistry of intermediates **8** and **9**.[20]

HFCH **3a** is a white solid (m.p. 99–100 °C), and a suitable crystal was subjected to X-ray crystallography. The structure is shown in Figure 3, confirming the sterochemistry and consistent with an inversion of configuration during the final fluorination reaction. The structure reveals two 1,3-diaxial C–F bonds. Although formally a *meso* compound, the chair conformation of **3a** is chiral and the X-ray structure is composed of alternating enantiomers within the unit cell. The enantiomers interconvert with ring inversion. The shortest CF···HC contact within the unit cell is 2.44 Å, suggesting a weak CF···HC hydrogen bond.[13] ^{19}F NMR analysis at

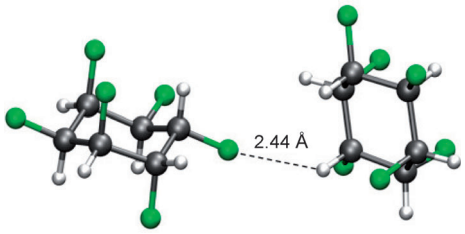


Figure 3. X-ray structure of HFCH **3a** showing an enantiomer dimer within the unit cell. The shortest CF···HC contact in the solid state is shown.[20]

ambient temperature revealed two relatively sharp signals and one almost imperceptible broad, base-line signal (Figure 4A). A more informative spectrum was revealed at −70 °C (CD_2Cl_2) where the ring interconversion is slowed

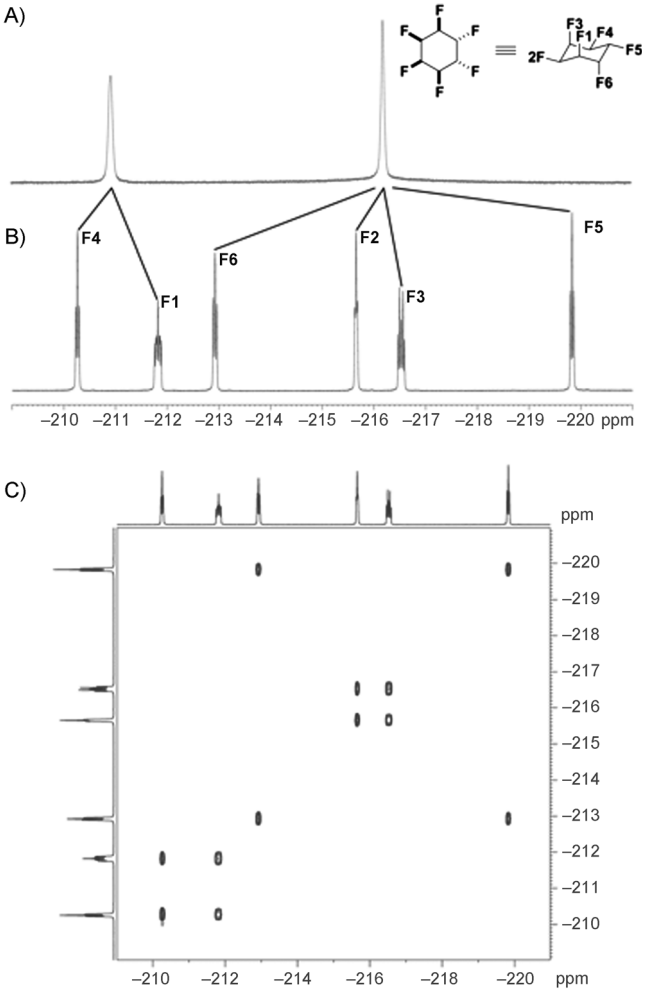


Figure 4. $^{19}F\{^1H\}$ NMR spectrum of **3a** at A) room temperature and B) −70 °C in CD_2Cl_2. At room temperature there are two peaks and a broad featureless peak, the latter arising due to the relatively large chemical shift difference between F^5 and F^6. Six unique peaks resolve on cooling to −70 °C. C) 2D-^{19}F-EXSY correlation spectroscopy (mixing time 100 ms) at −70 °C with three sets of correlating peaks indicating the axial/equatorial interconversions with ring inversion. A 2D-^{19}F-EXSY with overlaid ^{19}F-COSY spectrum (see Figure S1 in the Supporting Information) illustrates additional correlations between the individual fluorines in the chair conformation.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

sufficiently such that all of the six fluorine atoms of **3a** are resolved (Figure 4B). The individual signals were assigned by ^{19}F NMR 2D-EXSY correlation spectroscopy.[14,15] This analysis reveals that the two 1,3-diaxial C–F bonds show a large through-space coupling ($^4J_{HF} = 30.6$ Hz) confirming their close proximity in space. The F···F distance in the X-ray structure is 2.8 Å which is at the van der Waal's contact distance. Through-space F···F couplings of this magnitude are rarely observed except in rigid molecular systems,[16] although they have been observed recently in the structurally related all-*syn* 1,2,3,4-tetrafluorinated cyclohexane[15] and a difluorinated hexose.[17] Rate constants were determined by complete lineshape analysis of the ^{19}F NMR spectra recorded across the temperature range 200–242 K. Fitting the experimental data to the Eyring equation[18] allowed the activation parameters for cyclohexane ring interconversion to be determined as $\Delta G^{\ddagger}_{298} = 11.5$ kcal mol^{-1}, $\Delta H^{\ddagger} = 10.6$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -2.9$ kcal mol^{-1} (see Supporting Information). The enthalpy difference is very similar to cyclohexane itself ($\Delta H^{\ddagger} = 10.8$ kcal mol^{-1}).[19] It might be expected that eclipsing C–F interactions would raise this barrier during ring interconversion transition states of **3a** relative to cyclohexane, however the ground-state energy of **3a** is also raised, presumably by a similar magnitude, such that the relative differences are similar.

In conclusion, HFCH **3a**, was prepared as a single stereoisomer from benzene by a five-step route. Benzene was also used by Faraday and Mitscherlich for their respective syntheses of the hexachloro and hexabromo analogues in the early 19th century. Coe et al.[6] suggested in 1969 that a HFCH **3** may have formed after direct fluorination of benzene with CoF_3 although this was never confirmed, thus the synthesis of **3a** is the first unambiguous preparation of a HFCH **3** stereoisomer.

Received: July 13, 2012
Published online: September 11, 2012

Keywords: benzene hexafluoride · conformational analysis · hexafluorocyclohexane · organofluorine chemistry

[1] M. Faraday, *Ann. Chem. Phys.* **1825**, 274–291.
[2] K. L. Willett, E. M. Ulrich, R. A. Hines, *Environ. Sci. Technol.* **1998**, *32*, 2197–2207.
[3] K. Walker, D. A. Vallero, R. G. Lewis, *Environ. Sci. Technol.* **1999**, *33*, 4373–4378.
[4] E. Mitscherlich, *Ann. Phys.* **1835**, *111*, 370–374.
[5] F. E. Matthews, *J. Chem. Soc.* **1892**, *61*, 103–114.
[6] P. L. Coe, R. G. Plevey, J. C. Tatlow, *J. Chem. Soc. C* **1969**, 1060–1063.
[7] Z. Zdravkovski, *Bull. Chem. Technol. Maced.* **2004**, *23*, 131–137.
[8] Z. Zweig, R. G. Fischer, J. E. Lancaster, *J. Org. Chem.* **1980**, *45*, 3597–3603.
[9] D. O'Hagan, *J. Org. Chem.* **2012**, *77*, 3689–3699; L. Hunter, P. Kirsch, A. M. Z. Slawin, D. O'Hagan, *Angew. Chem.* **2009**, *121*, 5565–5568; *Angew. Chem. Int. Ed.* **2009**, *48*, 5457–5460.
[10] Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.
[11] M. Alonso, A. Riera, *Tetrahedron: Asymmetry* **2005**, *16*, 3908–3912.
[12] Y. Chang, A. Tewari, A.-I. Adi, C. Bae, *Tetrahedron* **2008**, *64*, 9837–9842.
[13] R. Fröhlich, T. C. Rosen, O. G. J. Meyer, K. Rissanen, G. Haufe, *J. Mol. Struct.* **2006**, *787*, 50–62; J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89–98; J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12613–12622.
[14] S. Bresciani, T. Lebl, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2010**, *46*, 5434–5437; C. L. Perrin, T. J. Dwyer, *Chem. Rev.* **1990**, *90*, 935–967.
[15] A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan, *Chem. Commun.* **2011**, *47*, 8265–8267.
[16] C. F. Matta, N. Castillo, R. J. Boyd, *J. Phys. Chem. A* **2005**, *109*, 3669–3681.
[17] G. T. Giuffredi, L. E. Jennings, B. Bernet, V. Gouverneur, *J. Fluorine Chem.* **2011**, *132*, 772–778.
[18] H. Eyring, *J. Chem. Phys.* **1935**, *3*, 107–115.
[19] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.
[20] CCDC 899837 (**3c**), 899838 (**8**), and 899839 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim