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The fluorine *gauche* effect. Langmuir isotherms report the relative conformational stability of (±)-*erythro*- and (±)-*threo*-9,10-difluorostearic acids†

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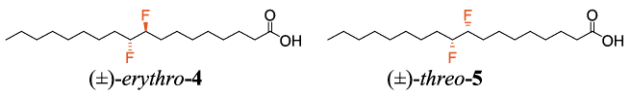
(±)-*Erythro*- and (±)-*threo*- 9,10-difluorostearic acids, which differ only by a stereogenic interconversion of a single C–F bond, have significantly different conformational stabilities.

It is well known that the *gauche* conformer **1a** of 1,2-difluoroethane[1] is lower in energy than the *anti* conformer **1b** (Fig. 1). This contra intuitive observation has been termed the fluorine *gauche effect* and appears to have its origin in optimal C–C σ-bond overlap[2] as well as improved vicinal hyperconjugation possibilities between the electron rich C–H (HOMO) bond and C–F σ*-orbital (LUMO).[3] Both vibrational spectroscopy and *ab initio* calculations[2,4] carried out on 1,2-difluoroethane indicate an energy difference in favour of the *gauche* conformer **1a** of between 0.5–1.0 kcal mol^{-1}.

Fig. 1 Staggered rotamers of 1,2-difluoroethane.

The fluorine *gauche* effect has been shown to influence the relative energies of conformers of both *erythro* (*meso*) and (±)-*threo*-2,3-difluorobutane **2** and **3** (Fig. 2).[5] In particular the two staggered *erythro* conformers **2a** and **2b** were judged to be similar in energy and equally populated in solution, indicating that the increase in energy of bringing two methyl groups *gauche* to each other is compensated by a favourable fluorine *gauche* effect. The *threo* conformer **3a** with the methyl groups *anti* and the fluorines *gauche* emerged as the lowest energy (by ~0.8 kcal mol^{-1}) conformer in that series.

With this background it became pertinent to explore if the fluorine *gauche effect* could influence the conformational stability of longer chain hydrocarbon molecules and in this study we report on the relative conformational stability of (±)-*erythro* and (±)-*threo* 9,10-difluorostearic acids **4** and **5**.



Clearly stearates are important in lipid membranes but extended hydrocarbon chains are also important in the design of materials such as ferroelectric liquid crystalline systems.[6] To this end the study reports the synthesis and Langmuir isotherm analysis of **4** and **5**.

These compounds were synthesized as racemates, however each was prepared in diastereomerically pure form. The synthetic route to the stereoisomers is shown in Scheme 1, and develops a method of Schlosser's which was previously used for the stereocontrolled synthesis of vicinal difluoroalkanes.[7]

† Electronic supplementary information (ESI) available: characterisation of compounds **4**, **5**, **7**–**9**, **11**–**13**. See http://www.rsc.org/suppdata/cc/b2/b202891c/

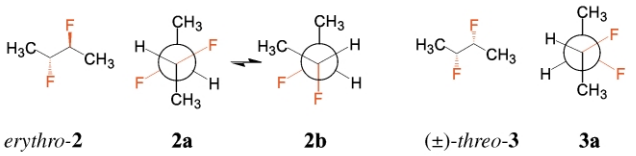
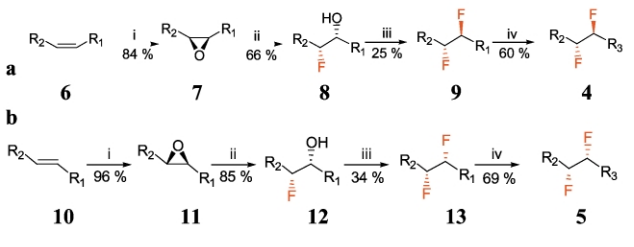


Fig. 2 Staggered rotamers of *erythro* and (±)-*threo* 2,3-difluorobutanes **2** and **3**.

The synthesis began by epoxidation of either methyl *Z*-9,10-octadecenoate (methyl oleate) **6** or methyl *E*-9,10-octadecenoate (methyl elaidate) **10** with *m*-chloroperoxybenzoic acid[8] (*m*CPBA) to generate *cis*- and *trans*-epoxides **7** and **11** respectively. The epoxides **7** and **11** were then treated with HF·pyridine[9] to afford (±)-*erythro* and (±)-*threo* fluoroalcohols **8** and **12** as a 1 : 1 mixture of regioisomers (only one regioisomer shown in Scheme 1). These products were recrystallised in hexane prior to treatment with diethylaminosulfur trifluoride (DAST).[7] This generated methyl (±)-*erythro* and (±)-*threo* 9,10-difluorostearate **9** and **13** respectively. The DAST reaction of both **9** and **13** gave a considerable amount (~50%) of the corresponding elimination products, however these were conveniently removed by ozonolysis[10] followed by chromatography. Finally hydrolysis of esters **9** and **13** with aqueous NaOH–MeOH solution[11] followed by acidic work up gave the desired stearic acids (±)-**4** and (±)-**5**. The products and intermediates were fully characterised (See ESI†).

It was a concern at the outset that there may be some stereochemical crossover between the two synthetic routes particularly after the DAST reactions on fluoroalcohols **8** and **12**. However this proved to be unfounded. The ^{19}F-NMR signals for each of the resultant diastereoisomers of methyl 9,10-difluorosterates (**9** and **13**) are resolved and after a series of ad-mix control NMR-experiments it was clear that each of the products was uncontaminated with the other stereoisomer. It was surprising to note ~20 °C difference in melting points between the two stearic acids (67–69 °C for (±)-*erythro*-**4** and 86–88 °C for (±)-*threo*-**5**) providing an immediate indication of the relative conformational mobilities of the two stereoisomers.

The extended *zig-zag* conformation **4a** of (±)-*erythro* **4** has the vicinal fluorines *anti* to each other and the system does not



R_1 = -{CH_2}$_7CO_2Me$; R_2 = -{CH_2}$_7CH_3$; R_3 = -{CH_2}$_7CO_2H$

Scheme 1 (i) *m*CPBA (1.3 equiv.), CH_2Cl_2, rt, 21 h. ii) HF·pyridine (1.5 equiv.), CH_2Cl_2, rt, 15 min (a) / 4 h (b) iii) DAST (1.6 equiv.), CH_2Cl_2, −78 °C to rt, 5 h (a) / 1 h (b) iv) NaOH–MeOH, reflux, 18 h.

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benefit from the fluorine *gauche effect*. On the other hand, the extended *zig-zag* conformation **5a** of (±)-*threo* **5** has the vicinal fluorine atoms *gauche* to each other (Fig. 3). As a consequence it was anticipated that the *threo* stereoisomer **5** would be the conformationally more stable system of the two.

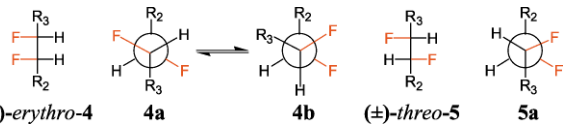

Fig. 3 Staggered rotamers of (±)-*erythro* and (±)-*threo* 9,10-difluorostearic acids **4** and **5**.

Indeed a competition was anticipated between the *anti-zig-zag* conformer of **4a** and the *gauche–gauche* conformer **4b**. If the fluorine atoms achieve a *gauche* relationship this will necessarily result in chain disorder as the carbon chains (R_1 and R_2) must adopt a *gauche* relationship. It was not clear whether the *gauche effect* would be sufficient to over-ride the classical anti *zig-zag* preference in these stearic acids. In order to test this each of the difluorostearic acids **4** and **5** was deposited from a solution in chloroform (conc. approx. 0.5 g l^{-1}) onto the surface of ultrapure water (pH 5.8 ± 0.2, temperature 20 ± 2 °C) in a Langmuir trough (Molecular Photonics LB700) and surface pressures (mN m^{-1}) *versus* area per molecule (nm^2 molecule^{-1}) measured. The compression rate was about 1×10^{-2} nm^2 molecule^{-1} s^{-1}. Surface pressure *versus* area analysis of selectively fluorinated stearic acids has already been used as a sensitive method to assess their conformational mobility on a water subphase.[11,12] The resultant Langmuir isotherms of (±)-*erythro* **4** and (±)-*threo* **5** are shown in Fig. 4. The shape of

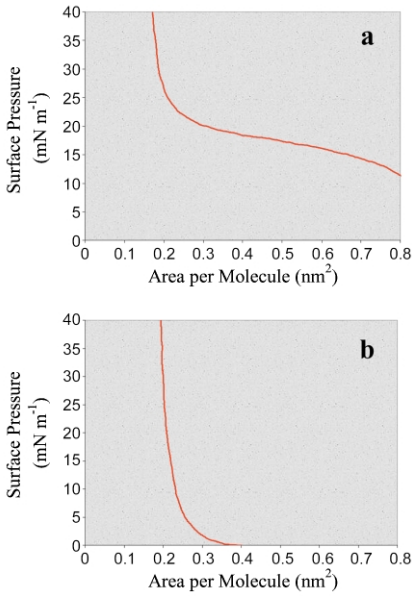

Fig. 4 Langmuir isotherms of (±)-*erythro*-**4** (**a**) and (±)-*threo*-**5** (**b**) on a water subphase showing condensed pressure *versus* area curves at 20 °C.

the Langmuir isotherm for the *erythro* isomer **4** (Fig. 4a) is extremely expanded indicating a significant level of conformational disorder prior to attainment of a condensed monolayer with a limiting area per molecule (*i.e.* extrapolated to zero surface pressure) of *ca.* 0.20 ± 0.1 nm^2 molecule^{-1}.[13] However, the isotherm for the *threo* isomer **5** (Fig. 4b) is similar to that for stearic acid (data not shown) with a limiting surface area per molecule also of *ca.* 0.20 ± 0.1 nm^2 molecule^{-1}. Clearly in **5** the presence of the fluorine atoms does not significantly perturb the isotherm relative to the hydrocarbon model. Surprisingly the different behaviour of **4** and **5** arises as a consequence of a single stereochemical inversion of one C–F bond. In **4** the fluorine *gauche effect* is competing with the classical *anti-zig-zag* preference of the R groups leading to considerable conformational disorder. It is well known from rotational energy profiles of butane that the *anti* conformer is ~0.6 kcal mol^{-1} more stable than the *gauche* conformer in solution.[14] However in this case the fluorine *gauche* effect contributes upto 0.9 kcal mol^{-1} stabilisation to conformer **4b** and thus the opposing effects result in conformers **4a** and **4b** becoming closer in energy and thus more equally populated. The increased chain disorder in **4** accounts for the lower melting point and the expanded isotherm shown in Fig 4a.

In conclusion the study illustrates that the fluorine *gauche effect* is of a significant magnitude that it can influence the conformational stability of extended hydrocarbon chains, a property which could be used to design mobility into hydrocarbon chains *e.g.* in membrane models and liquid crystalline materials.

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Notes and references

1 N. C. Craig, A. Chen, K. H. Suh, S. Klee, G. C. Mellau, B. P. Winnewiser and M. Winnewiser, *J. Am. Chem. Soc.*, 1997, **119**, 4789.
2 K. B. Wiberg, *Acc. Chem. Res.*, 1996, **29**, 229.
3 P. R. Rablen, R. W. Hoffmann, D. A. Hrovat and W. T. Borden, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1719.
4 J. R. Durig, J. Liu, T. S. Little and V. F. Kalasinsky, *J. Phys. Chem.*, 1992, **96**, 8224; M. Muir and J. Baker, *Mol. Phys.*, 1996, **89**, 211.
5 G. Angelini, E. Gavuzzo, A. L. Segre and M. Speranz, *J. Phys. Chem.*, 1990, **94**, 8762.
6 (*a*) W. N. Thurmes, M. D. Wand, R. T. Vohra and D. M. Walba, *Ferroelectrics*, 1991, **121**, 213; (*b*) M. D. Wand, W. N. Thurmes, R. T. Vohra, K. More and D. M. Walba, *Ferroelectrics*, 1991, **121**, 219.
7 T. Hamatani, S. Matsubara, H. Matsuda and M. Schlosser, *Tetrahedron*, 1988, **44**, 2875.
8 Y. Nagai and H. Uno, *Chem. Pharm. Bull.*, 1979, **27**, 2056.
9 P. H. Buist, K. A. Alexopoulos, B. Behrouzian, B. Dawson and B. Black, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2617.
10 J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, 1993, **58**, 3675.
11 D. O'Hagan, I. Kumadaki, M. Petty, H. Takaya and C. Pearson, *J. Fluorine Chem.*, 1998, **90**, 133.
12 L. Dasaradhi, D. O'Hagan, M. C. Petty and C. Pearson, *J. Chem. Soc., Perkin Trans. 2*, 1995, 221.
13 M. C. Petty, *Langmuir-Blodgett Films*, Cambridge University Press, Cambridge, 1996.
14 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994.