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Crystal structure and conformational diversity of fluorinated alkyl tosylates

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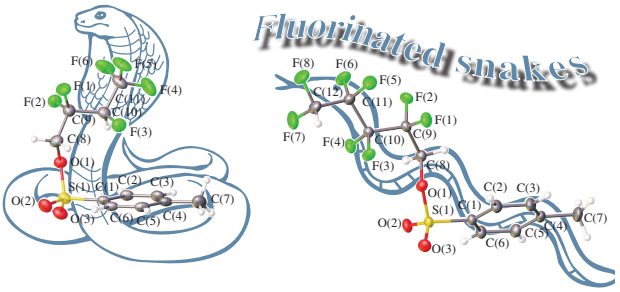
Crystal structures of fluorinated alkyl tosylates $TsOCH_2CF_2CHFCF_3$ and $TsOCH_2(CF_2)_3CHF_2$ have been characterized by X-ray diffraction and quantum chemical calculations. The calculations have revealed the stabilization of head-to-tail conformation for $TsOCH_2CHFCF_2CF_3$ due to intramolecular F···π and C–H···π interactions. Alternatively, for $TsOCH_2(CF_2)_3CHF_2$ these interactions cannot be responsible for the stabilization of head-to-tail conformation, thus the linear conformation is proved to be more stable.



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Compounds containing a fluorinated alkyl moiety demonstrate high biological inertness[1,2] due to their lipophobic nature and surfactant properties. These features are useful for the development of new drugs as well as the agents for drug and oxygen delivery.[3,4] Besides, it is possible to modify existing drugs by addition of fluorinated alkyl moieties.[5] Promising agents for such a modification can be azides bearing fluorinated alkyl moieties, which are synthesized from the corresponding tosylates. In turn, the fluoroalkyl tosylates can be prepared from partially fluorinated alcohols and tosyl chloride.

In this work, using the known synthetic approach,[6] two tosylates $TsOCH_2CF_2CHFCF_3$ **1** and $TsOCH_2(CF_2)_3CHF_2$ **2** have been synthesized (for details, see Online Supplementary Materials). The former compound represents a low-melting crystalline substance, while the latter is a colorless liquid. Nevertheless, we succeeded to grow the crystals appropriate for single crystal X-ray study† to further evaluate, how intra- and intermolecular interactions formed by fluorine atoms in the fluorinated alkyl moieties affect the molecular geometry of the organofluorine compounds. The role of these interactions in the stabilization of different molecular conformations is discussed here using the results of X-ray study and quantum chemical calculations.

According to the X-ray data, molecules of **1** and **2** in the crystals demonstrate a significant difference in a mutual arrangement of the fluorinated alkyl moieties and the substituted phenyl ring. Indeed, the torsion angles C(1)–S(1)–C(9)–C(10) in **1** and **2** are 26.7(2) and 177.56(5)°, respectively. Thus, the molecular conformation of compound **1** can be described as head-to-tail [Figure 1(*a*)], in contrast to compound **2**, where the distance between the substituted phenyl group and the fluorinated alkyl moieties is maximal and the conformation is denoted as linear [Figure 1(*b*)]. A conformer generator tool[10] implemented in the Mercury package Materials Module[11] generated a large number of conformations for both molecules (see Online Supplementary

† Crystals of compounds **1** and **2** were grown from distilled samples by multiple cycles of cooling and heating.

Crystal data for **1**. $C_{11}H_{10}F_6O_3S$, $M = 336.25$, triclinic, space group $P\bar{1}$, 120 K, $a = 7.243(4)$, $b = 9.634(5)$ and $c = 10.799(5)$ Å, $\alpha = 68.820(16)°$, $\beta = 74.498(10)°$, $\gamma = 77.626(12)°$, $Z = 2$, $V = 671.2(6)$ Å^3, $d_{calc} = 1.664$ g cm^{-3}, $F(000) = 340$. Colorless prism-shaped single crystal with dimensions $0.08 \times 0.17 \times 0.23$ mm was selected and intensities of 5004 reflections were measured using a Bruker APEX II CCD diffractometer (ω and ϕ scans, sealed tube, λ[MoKα] = 0.71073 Å, $\mu = 0.319$ mm^{-1}, $2\theta_{max} = 61.09°$). After merging of equivalents and absorption correction, 3967 independent reflections ($R_{int} = 0.0153$) were used for the structure solution and refinement. Final R factors: $R_1 = 0.0574$ [2684 reflections with $I > 2\sigma(I)$], $wR_2 = 0.1606$ (all reflections), GOF = 1.042.

Crystal data for **2**. $C_{12}H_{10}F_8O_3$, $M = 386.26$, triclinic, space group $P\bar{1}$, 120 K, $a = 5.5990(2)$, $b = 10.4514(3)$ and $c = 13.2246(4)$ Å, $\alpha = 75.5700(10)°$, $\beta = 79.9740(10)°$, $\gamma = 83.4210(10)°$, $Z = 2$, $V = 735.95(4)$ Å^3, $d_{calc} = 1.743$ g cm^{-3}, $F(000) = 388$. Colorless prism-shaped single crystal with dimensions $0.12 \times 0.15 \times 0.32$ mm was selected and intensities of 26950 reflections were measured with a Bruker APEX DUO diffractometer (ω and ϕ scans, sealed tube, λ[MoKα] = 0.71073 Å, $\mu = 0.322$ mm^{-1}, $2\theta_{max} = 72.876°$). After merging of equivalents and absorption correction, 6868 independent reflections ($R_{int} = 0.0222$) were used for the structure solution and refinement. The structure was solved by direct method and refined by full-matrix technique against F^2 in anisotropic approximation. Final R factors: $R_1 = 0.0354$ [5734 reflections with $I > 2\sigma(I)$], $wR_2 = 0.1041$ (all reflections), GOF = 1.034.

The structures were solved by direct method and refined by full-matrix technique against F^2 in anisotropic approximation. The positions of hydrogen atoms in methyl and methylene groups were calculated geometrically and refined in rigid body approximation. All calculations were carried out with SHELXT[7] (structures solution) and SHELXL[8] program (structure refinement). Molecular graphics was drawn using OLEX2[9] program.

CCDC 1912690 and 1912691 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

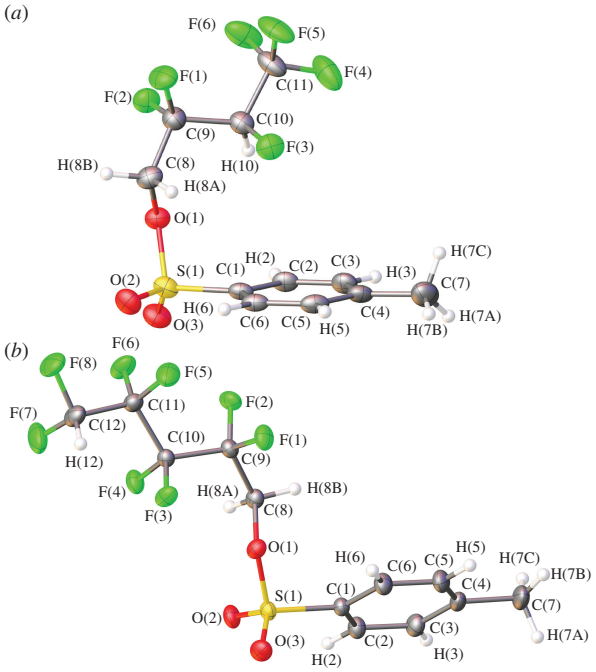

Figure 1 Molecular structures of compounds (*a*) **1** and (*b*) **2**.

Materials, Figure S19) due to flexibility of alkyl chains, and the linear conformation was found for both molecules, while the head-to-tail one was observed only for compound **1**. We assumed that the difference in conformations for molecules of **1** and **2** in the solid state could be explained by the interplay of weak intra- and intermolecular interactions, because both molecules contain similar fragments and the only distinction is the position of partially fluorinated CHF or CHF_2 groups. It is noteworthy that crystal packings of compounds **1** and **2** reveal the absence of strong intermolecular interactions. Indeed, all the F···F distances exceed 2.98 Å, which is close to sum of the corresponding van der Waals radii.[12] Taking into account that molecule of **1** contains a CHF group in the middle of fluorinated alkyl chain while molecule of **2** has a terminal CHF_2 group, as well as our recent data on homologous compounds,[13] we assumed the following. Both fluorine-containing groups participate in weak C–H···O bonds in crystals, distances C···O being equal to 3.173(5) and 3.084(1) Å for compounds **1** and **2**, respectively. The corresponding H···O distances are 2.21 and 2.27 Å, the C–H distances being normalized according to neutron diffraction data to 1.09 Å. It is important that F(3) atom of the CHF group in molecule of **1** is located nearly above the centroid of phenyl ring. Indeed, F(3)···X distance and C(1)XF(3) angle are 3.348(2) Å and 78.96(1)°, where X denotes the centroid of phenyl ring. Therefore, the head-to-tail conformation of **1** can be stabilized by a weak intramolecular F···π interaction. More detailed inspection of the conformational stability and the role of weak interactions was carried out using quantum chemical calculations for molecules of **1** and **2**. All necessary data on the calculated structures can be found in Online Supplementary Materials.

Comparison of the energies calculated for head-to-tail and linear conformations of isolated molecule of **1** has revealed that the former is 8.1 kJ mol^{-1} more stable than the latter. The head-to-tail conformation of an isolated molecule of **1** is similar to that in crystal. However, the mutual arrangements of F(3) atom and phenyl ring differ considerably. Both F(3) and H(10) atoms in the CHF group participate in F···π and C–H···π interactions with phenyl ring, which has been confirmed by an analysis of electron density distribution in terms of Bader's quantum theory 'Atoms in molecules' (QTAIM).[14] To reveal the role of intermolecular weak C–H···O bonds in the stabilization, the most straightforward way

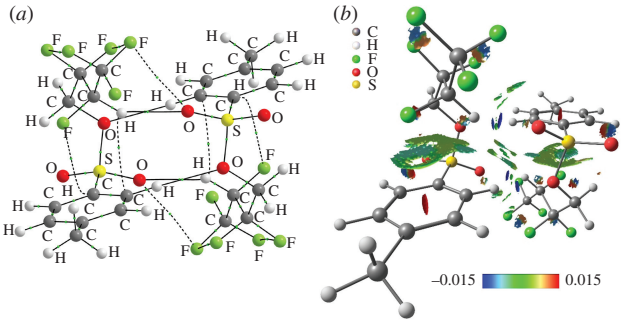

Figure 2 Dimer of **1**: (*a*) molecular graph and (*b*) RDG isosurface with contour value of 0.4 a.u. colored according to sign of $\lambda_2\rho$ function.[8]

is to calculate the molecular associates that partially mimic a crystal environment. Therefore, the calculation of H-bonded dimer, generated by the (1–*x*,1–*y*,1–*z*) symmetry operation, where the hydrogen atom in the CHF group participated in C–H···O bond with the oxygen atom of adjacent SO_2 group, was carried out. Optimized geometry for this dimer is close to the experimental one, however, the F(3)···X distance is 3.001 Å, that is 0.35 Å less than in crystal. An intramolecular F···π interaction and intermolecular C–H···O bonds were visualized using molecular graphs and NCI method[15,16] (Figure 2). The latter approximation utilized reduced density gradient (RDG) function that allowed one to underline the regions where an electron density was perturbed due to formation of weak interactions. The RDG isosurfaces were colored according to the values of the electron density multiplied by its second eigenvalue $\lambda_2\rho(r)$ to reveal the regions that correspond to attraction and repulsion from the negative and positive values of $\lambda_2\rho(r)$, respectively.

QTAIM analysis revealed the presence of weak H···C and F···C interactions in the optimized dimer of **1**. However, NCI results clearly demonstrate the occurrence of interaction between the CHF group and π-system of phenyl ring rather than two separate H···C and F···C interactions.

The geometry of the optimized head-to-tail conformation for compound **2** is significantly different from that for compound **1**. In fact, the former conformation can be described as 'L-shaped' one (Figure S12). In this case, the F(1) atom bonded to the C(9) one participates in the F···π interaction. However, the energy of the head-to-tail conformation for compound **2** is lower than that of the linear one by 0.68 kJ mol^{-1}. Small differences in the energy of head-to-tail and linear conformations of compound **2** together with the absence of steric hindrance are the rational for possible ready transformation of them to one another in solution or upon crystallization.

The obtained X-ray data and the results of quantum chemical calculations allowed us to conclude that the conformations of molecules of **1** and **2** were governed by position of the CHF moiety in the fluorinated alkyl chain. Due to electron-withdrawing effect of fluorine atom, the hydrogen atom of CHF group can demonstrate an acidic character. For compound **1**, this group is in the δ-position relative to the S atom, so the formation of intramolecular C–H···π interaction is crucial for the stabilization of the head-to-tail conformation. The CHF_2 moiety in compound **2** is far from phenyl ring, therefore only F···π interaction can occur, but it is not sufficient to stabilize head-to-tail conformation. On the contrary, the terminal CHF_2 group in the crystal packing of compound **2** participates in weak C–H···O bonds with SO_2 group, thus affording an additional stabilization of the linear conformation.

In summary, our study has revealed that the intermolecular interactions with participation of fluorine atom lead to stabilization of head-to-tail conformation, which can be promising for the areas of molecular design, transport and recognition.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.034.

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