

Fluorine in Small Molecules: Fluoromethyl Azide and Chalcogenocyanates

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Abstract. Fluoromethylating agents are a highly studied and controversially discussed class of compounds. New fluoromethyl pseudohalides FCH₂N₃, FCH₂SCN, and FCH₂SeCN were prepared for the first time and their physical and spectroscopic properties investigated. Their

synthesis is performed conveniently by fluoromethylation of the respective silver or potassium pseudohalogenides with fluoroiodomethane.

Introduction

The monofluoromethyl halides FCH₂Cl, FCH₂Br, and FCH₂I are extensively investigated materials. However, due to the ozone-depleting effect of some representatives, they are under close observation and are already partially banned under Annex I of Regulation (EC) No 1005/2009.^[1] In addition to their use as coolants, they are mainly used as fluoromethylating agents.^[2] As one of the strategic fluorine-containing building blocks, the fluoromethyl group is used by the pharmaceutical industry in many drugs and drug candidates.^[3] The introduction of this building block unit often leads to dramatic changes in physical and chemical properties. Also the metabolic stability is often drastically increased.^[4] The change in chemical and physical parameters can be observed particularly well with small molecules. For small molecules additional intermolecular interactions are negligible and the effect of the fluoromethyl substituent can be studied without overlapping with other effects. This also would apply for fluoromethyl pseudohalides.

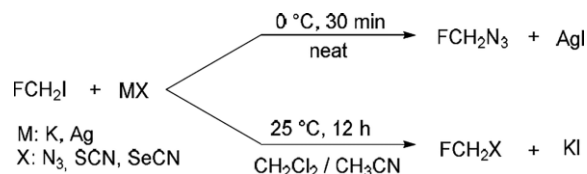
But only a few examples carrying the fluoromethyl group such as the well known fluoroacetonitrile FCH₂CN^[5] and the rather unstable fluoromethyl isocyanate FCH₂NCO^[6] have been isolated and investigated until now. Theoretical investigations for FCH₂R (R = NCO, NCS, N₃ and CNO)^[7] further add to available information. Recently, our initial studies on the system fluoroiodomethane with selected silver salts enabled access to the corresponding fluoromethyl derivatives FCH₂OCIO₃^[8] and FCH₂ONO₂.^[9] In this contribution we

would like to study the reactivity of metal pseudohalides, i.e. azide and chalcogenocyanates, towards fluoroiodomethane.

Results and Discussion

Fluoromethyl Azide

The reaction of freshly prepared dried silver azide with fluoroiodomethane in equimolar mixture resulted in the formation of pure fluoromethyl azide, which was obtained as a highly volatile colorless liquid (Scheme 1)



Scheme 1. Synthesis of fluoromethyl pseudohalides.

Similar to methyl azide, FCH₂N₃ is anticipated to be highly sensitive. The high vapor pressure can be demonstrated by the very fast evaporation on a cooled plate and is also reflected in an estimated boiling point of approx. 22 °C (method of *Siwoloboff*^[10]). With a boiling point of approx. 20 °C,^[11] methyl azide has a slightly lower boiling point than fluoromethyl azide. Final proof of the identity of the compound results from multinuclear NMR spectra ([D₆]DMSO). In the ¹H NMR spectrum, the FCH₂ signal is observed at δ = 5.46 ppm with a coupling constant of ²J(F,H) = 51.5 Hz, the ¹³C{¹H} resonance at δ = 91.6 ppm as a doublet with ¹J_{FC} = 205.4 Hz. Both resonances of fluoromethyl azide are shifted to low field due to the deshielding character of the fluorine substituent compared to CH₃N₃ (¹H NMR: 2.98 ppm. ¹³C NMR: 37.9 ppm).^[12] The ¹⁹F NMR resonance of FCH₂N₃ is detected at -170.1 ppm as a triplet. Since the azide substituent is less electronegative than a nitrate substituent, which with its electronegativity lies between the OCN/NCO cyanates, the resonance of fluoromethyl azide is shifted to lower frequency compared to fluoromethyl nitrate (-155.9 ppm).^[9,13] The ¹⁴N NMR resonances for fluoromethyl azide are observed at -135(N_β), -166(N_γ) and

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–297(N_α) ppm. These are slightly shifted compared to those reported for CH_3N_3 , –129(N_β), –171(N_γ) and –321(N_α) ppm, in C_6F_6 (Table 1).

Table 1. Nitrogen chemical shifts $\delta^{14/15}$ ^{d),[14]}

	$\delta^{14/15}\text{N}_\alpha$	$\delta^{14/15}\text{N}_\beta$	$\delta^{14/15}\text{N}_\gamma$
CH_3N_3 ^{a)}	–321.7	–130.2	–171.5
FCH_2N_3 ^{b)}	–297	–135	–166
F_3CN_3 ^{c)}	–286.2	–147.8	–144.7

a) C_6F_6 , b) $[\text{D}_6]\text{DMSO}$. c) Neat. d) For F_2CHN_3 no ^{14}N NMR spectroscopic data are available^[15].

The shielding of the N atoms by the substituent increases from $N_\alpha > N_\gamma > N_\beta$, where N_β and N_γ are in most cases close to each other. In addition, N_α and N_γ are considered most sensitive to inductive and conjugative effects of the substituent. Chemical shifts can usually be explained by the influence of the paramagnetic term:

$$\sigma_p \approx \langle r^{-3} \rangle_{2p} \Sigma Q(\Delta E)^{-1}$$

In the paramagnetic term (σ_p), the radial factor ($\langle r^{-3} \rangle_{2p}$), the asymmetry of the valence electrons (ΣQ) and the excitation energy between the frontier orbitals (ΔE) are included.

This term, which dominates the chemical shift, depends on a virtual excitation of the charge between the HOMO and the LUMO in the magnetic field. A higher energy difference causes a shift to lower frequencies of particularly the N_α but also the N_γ signal. For fluoromethyl azides such as FCH_2N_3 , as well as found for CF_3N_3 , the excitation energy is higher than in CH_3N_3 (Figure 1). However, the experimental finding is contrary for the N_α/N_γ NMR shifts, as also found for $\text{CH}_3/\text{CF}_3\text{-N}_3$.

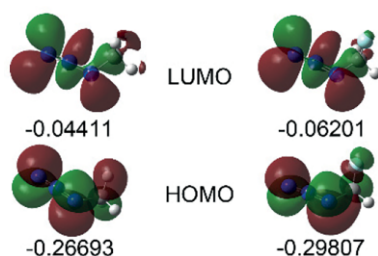


Figure 1. Molecular orbitals (HOMO/LUMO) and their energies in Hartree (below) of methyl azide (left) and fluoromethyl azide (right), calculated at the B3LYP/6-311G+(d,p) level of theory.

The assignments of the vibration modes in the infrared spectrum of the compounds were based on literature data and were supported by quantum mechanical calculations using Gaussian 09 (Table 2).^[15]

Table 2. Selected vibration modes (IR) of CH_3N_3 ^[15a,15b] (gas), CH_3SCN ^[15c] and CH_3SeCN ^[15d] (liquids) and fluoromethyl pseudohalides (liquids).

Vib.	CH_3N_3	FCH_2N_3	Vib.	CH_3SCN	FCH_2SCN	Vib.	CH_3SeCN	FCH_2SeCN
$\nu_{\text{as}}(\text{N}_3)$	2100(s)	2110(s)	$\nu(\text{CN})$	2173(s)	2167(s)	$\nu(\text{CN})$	2153(s)	2162(m)
$\delta(\text{CH}_2)$	1417(w)	1489(w)	$\delta(\text{CH}_2)$	1436(s)	1439(m)	$\delta(\text{CH}_2)$	1421(m)	1434(m)
$\nu(\text{CF})$	–	1034(s)	$\nu(\text{CF})$	–	1003(s)	$\nu(\text{CF})$	–	1011(s)
$\nu(\text{CN})$	910(m)	932(w)	$\nu(\text{CS})$	705(m)	813(w)	$\nu(\text{CSe})$	576(w)	606(s)
$\delta(\text{N}_3)$	–	610(w)	$\nu(\text{SC})$	674(m)	693(s)	$\nu(\text{SeC})$	519(m)	518(m)
$\delta(\text{N}_3)$	666(w)	680(w)	$\delta(\text{SCN})$	460(m)	474(m)	$\delta(\text{SeCN})$	393(w)	408(w)

The vibrations at 2110 and 1269 cm^{-1} correspond to the antisymmetric and symmetric stretching vibrations of the N_3 group. The deformation vibrations of the azide group perpendicular and parallel to the plane appear at 680 and 610 cm^{-1} . Due to the electronegative fluorine substituent compared to methyl azide, a shift to higher wave numbers of the mentioned vibration modes occurs. The molecular ion peak of FCH_2N_3 in the mass spectrum is detected at 75.0228 m/z $[\text{M}]^+$ and that of hydrogen abstraction at 74.0149 m/z $[\text{M}-\text{H}]^+$. Further characteristic fragments are assigned to $[\text{FCH}_2\text{N}_2]^+$ and $[\text{N}_3]^+$ at 61.0284 m/z and 42.0085 m/z , respectively.

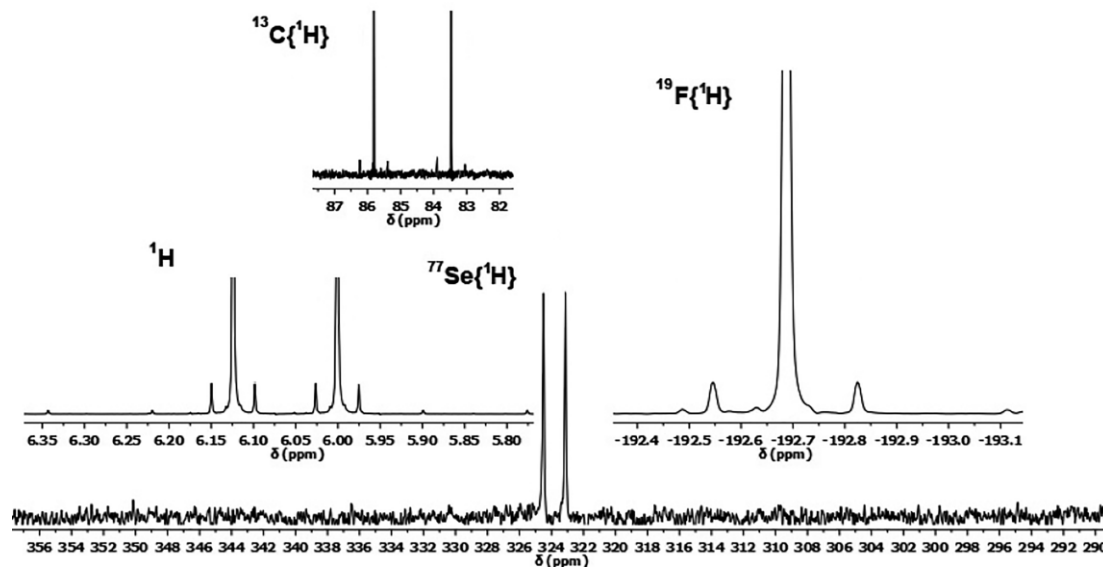
Fluoromethyl Thiocyanate

Fluoromethyl thiocyanate was obtained from the reaction of KSCN with fluoroiodomethane in a solvent mixture of acetonitrile and dichloromethane (Scheme 1). In contrast to fluoromethyl azide, fluoromethyl thiocyanate is a slightly yellowish, air-stable liquid with an estimated melting point of –28 °C and a boiling point of 155 °C (DTA). Compared to the methyl analogue CH_3SCN , the melting and boiling points are increased.^[16] Since the pseudohalogens are close to iodine in terms of electronegativity (Table 3),^[17] the NMR chemical shifts and coupling constants are very similar to fluoroiodomethane and towards each other.^[18] Thus, similar to FCH_2I ($\delta = 5.63$ ppm, $^2J_{\text{H,F}} = 49.5$ Hz), the ^1H NMR resonance of FCH_2SCN is observed at $\delta = 5.90$ ppm with a coupling constant $^2J_{\text{H,F}} = 49.4$ Hz. The ^{13}C NMR resonance is observed as a doublet at $\delta = 87.4$ ppm with $^1J_{\text{C,F}} = 227.6$ Hz. Another good proof of the electronegativity concept is very obvious in ^{19}F NMR spectroscopy. Here, the resonance of FCH_2SCN is detected at –189.2 ppm (CD_3CN) in close proximity to that of fluoroiodomethane at –190.3 ppm (CD_3CN).

In the IR spectrum of FCH_2SCN an opposite trend is observed regarding the SCN stretching vibration at 2167 cm^{-1} : a shift to lower wave numbers compared to the methyl analogue. The influence of the more electropositive and heavier pseudohalide SCN can be illustrated by the $\nu(\text{CF})$ stretching vibration and its shift towards lower wave numbers compared to fluoromethyl azide. The fluorine substituent, on the other hand, causes a shift to higher wave numbers of the C–SCN and S–CN stretching vibrations at 705 and 674 cm^{-1} compared to methyl thiocyanate. In the mass spectrum, the molecular ion peak is detected at 90.9888 m/z $[\text{M}]^+$, the $[\text{M}-\text{H}]^+$ ion at 98.9810 m/z , and at 57.9781 m/z the $[\text{SCN}]^+$ fragment.

Table 3. Group electronegativities (χ_p) of selected pseudohalides, halogenides and functional groups (R) by decreasing EN.^[18]

R	χ_p	R	χ_p	R	χ_p	R	χ_p
F	4.00	CF ₃	3.16	N ₃	2.95	SCN	2.64
ClO ₄	3.40	OCN	3.07	NCS	2.78	SeCN	2.60
SO ₃ F	3.30	OH	3.03	CN	2.76	FCH ₂	2.56
Cl	3.16	NCO	2.98	I	2.66	CH ₃	2.40

**Figure 2.** ¹H, ¹³C, ¹⁹F and ⁷⁷Se NMR spectra of fluoromethyl selenocyanate in CD₃CN (25 °C).

Fluoromethyl Selenocyanate

With similar conditions as above, the reaction of selenocyanate with fluoriodomethane results in the formation of fluoromethyl selenocyanate (Scheme 1). Compared to fluoromethyl thiocyanate with a more aromatic odor, the selenocyanate FCH₂SeCN has an unpleasant, disgusting odor (a drop was sufficient to refuse entry into a lab for several weeks). Due to its low volatility and a boiling point of +185 °C (DTA), the smell of the yellowish compound, which solidifies at approximately –32 °C, stays for a long time. Due to the almost identical electronegativities of thiocyanate and selenocyanate, the NMR chemical shifts differ more from those of the azide. Thus, in the ¹H NMR spectrum the FCH₂ group is observed at $\delta = 6.20$ ppm with a coupling constant of 49.3 Hz. The coupling to selenium ²J_{Se,H}, as determined from ⁷⁷Se satellites is 20.5 Hz. Similar, selenium satellites with a coupling constant of 84.9 Hz ¹J_{Se,C} are observed in the ¹³C NMR spectrum, in which the FCH₂ resonance occurs at $\delta = 84.6$ ppm. The 105.0 Hz ²J_{Se,F} coupling constant, as determined from the Se satellites in the ¹⁹F NMR spectrum, correspond to the coupling of the doublet at $\delta = 323$ ppm in ⁷⁷Se NMR spectroscopy (Figure 2). The ¹⁴N NMR resonance of the selenocyanate unit is detected at –90 ppm, slightly low-field shifted to that of the thiocyanate, which was observed at –103 ppm.

Isotope effects in nuclear shielding can well be determined for all three compounds. The ¹Δ¹⁹F(¹³/¹²C) absolute values increase steadily from fluoromethyl selenocyanate to fluo-

romethyl thiocyanate to fluoromethyl azide (Table 4) and correspond to the isotope effects of other fluoromethanes (CH₂F₂, –112 ppb; CHF₃, –127 ppb; CFCl₃, –194 ppb).^[19]

Table 4. Isotope effects in nuclear shielding in ppb.

	FCH ₂ N ₃	FCH ₂ SCN	FCH ₂ SeCN
¹ Δ ¹⁹ F(¹³ / ¹² C)	–187.0	–122.2	–112.6

In the IR spectrum of fluoromethyl selenocyanate the vibration modes are shifted in comparison to methyl selenocyanate to higher wave numbers. The SeC≡N stretching vibration is detected at 2162 cm^{–1}, the C–SeCN stretching vibration at 606 cm^{–1} and the Se–CN stretching vibration at 518 cm^{–1}. The CF stretching vibration compared to fluoromethyl azide is shifted to lower wave numbers, but due to the comparable electronegativities of SCN and SeCN in the same range as fluoromethyl thiocyanate. The low volatility of fluoromethyl selenocyanate can also be observed in mass spectra due to the low relative intensity of the molecule peak at 138.9330 *m/z* [M]⁺ and the peak at 105.9188 *m/z* assigned for the fragment [SeCN]⁺.

Attempts to fluoromethylate cyanate and tellurocyanate anions remained unsuccessful. Regarding the reaction of FCH₂I with KOCN, the starting materials were recovered without any sign of conversion. Interestingly, the corresponding methylation of cyanate with methyl iodide as well did not result in the formation of methyl cyanate. Based on literature,

methyl cyanate can only be isolated starting from complicated precursor compounds by thermal decomposition.^[6,20] In the case of tellurocyanate TeCN^- , which was generated according to a literature procedure,^[21] the formation of HF was observed, even if using dried solvents and working under inert atmosphere.

While this manuscript was in its final stage for submission, another report of the synthesis of fluoromethyl azide appeared in the recent press.^[22]

Conclusions

The fluoromethyl-substituted pseudohalides, FCH_2N_3 , FCH_2SCN , and FCH_2SeCN were synthesized conveniently from their silver and potassium salts with fluoroiodomethane. The compounds were investigated using spectroscopic methods and compared with their methyl derivatives. For fluoromethyl thiocyanate, fluoromethyl selenocyanate and fluoromethyl azide, the physical properties are changed towards higher boiling and melting points compared to their methyl analogues.

Supporting Information (see footnote on the first page of this article): General experimental details; NMR and Vibrational spectroscopy details.

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Keywords: Fluoromethyl pseudohalides; Fluoroiodomethane; Fluoromethylation; Isotope effects; NMR spectroscopy

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