Structural Characterization of **Dimeric** Perfluoroalkyl Carboxylic Acids (**PFCAs**) Using Experimental and Theoretical Ion Mobility Spectrometry (**IMS**) Analyses

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The authors declare no competing financial interest

Introduction : PFAS problematic

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Article

Per- and Polyfluoroalkyl Substances (PFAS) in PubChem: 7 Million and Growing

Published as part of the Environmental Science & Technology virtual special issue "The Exposome and Human Health".

Emma L. Schymanski,*,§ Jian Zhang, Paul A. Thiessen, Parviel Chirsir, Todor Kondic, and Evan E. Bolton*,§

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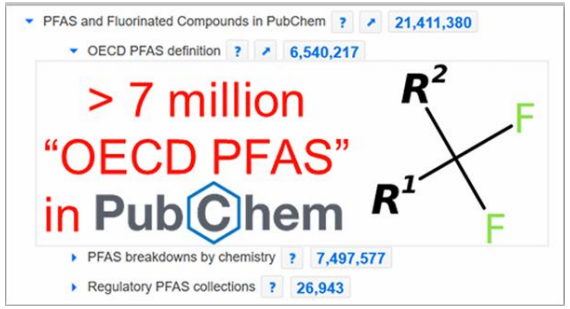


⇒ Need for large-scale suspect and non-targeted screening approaches

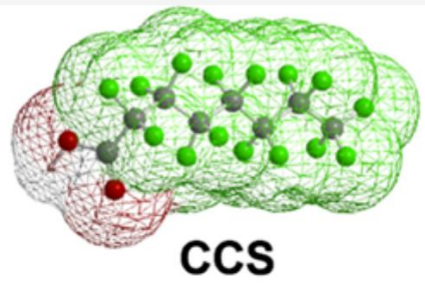
Introduction : PFAS and IMS

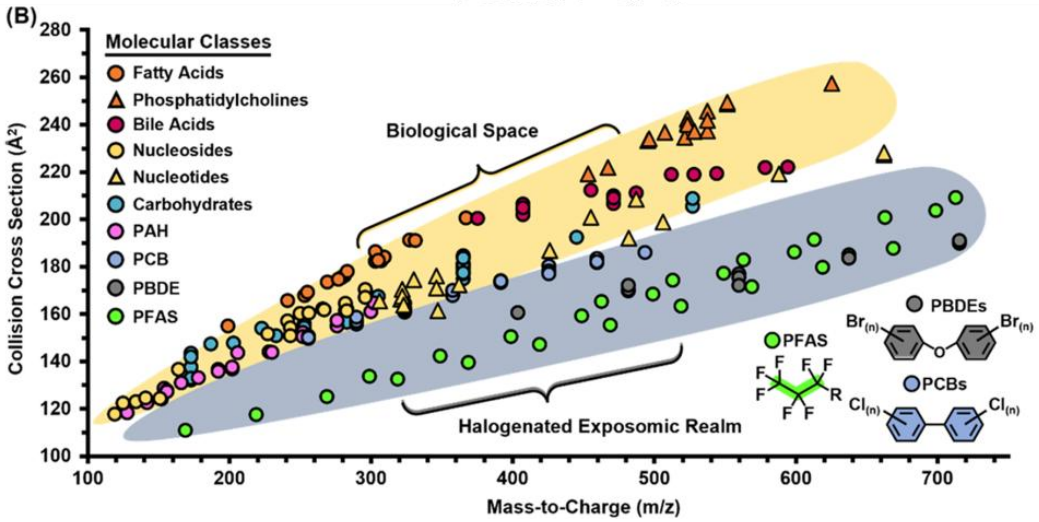
Need for large-scale suspect and non-targeted screening approaches

Foster, M. et al. *Environ. Sci. Technol.* **2022**, *56* (12), 9133–9143. https://doi.org/10.1021/acs.est.2c00201.

Ion mobility spectrometry can be valuable

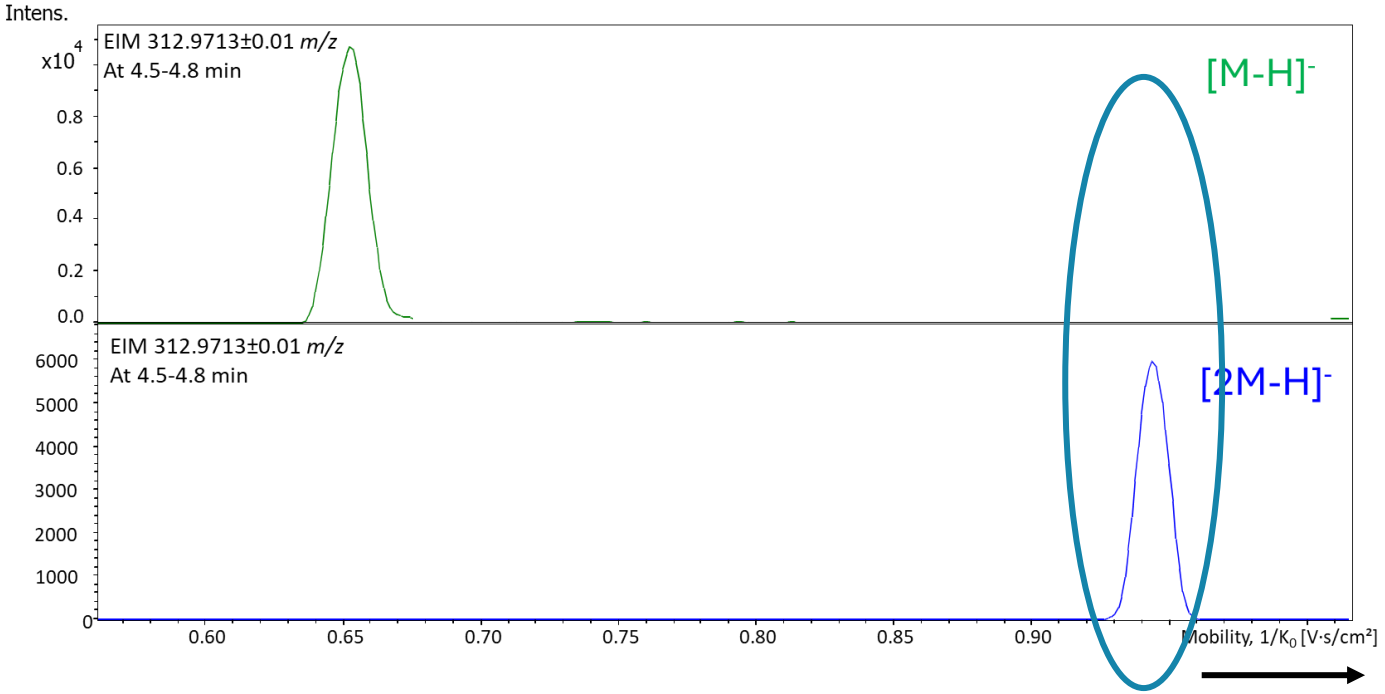
- Additional dimension
- Identification
  - ❖ CCS = Indicative of the apparent size of an ion in a gas
  - ❖ Homologous series: specific CCS-*m/z* trendlines
- Data-prefiltering
  - ❖ PFAS : Specific position in the CCS-*m/z* space



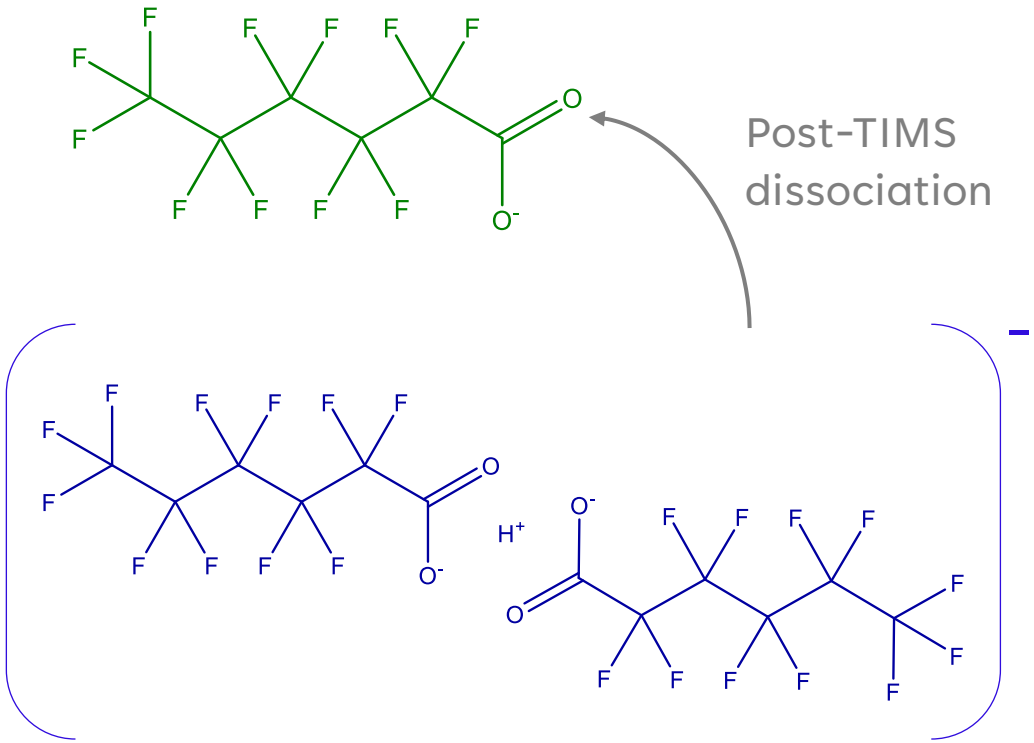


PFCA dimer formation in IMS

PFHxA in LC-TIMS-TOF:



$1/K_0$ (∝CCS)



PFCA dimer formation in IMS

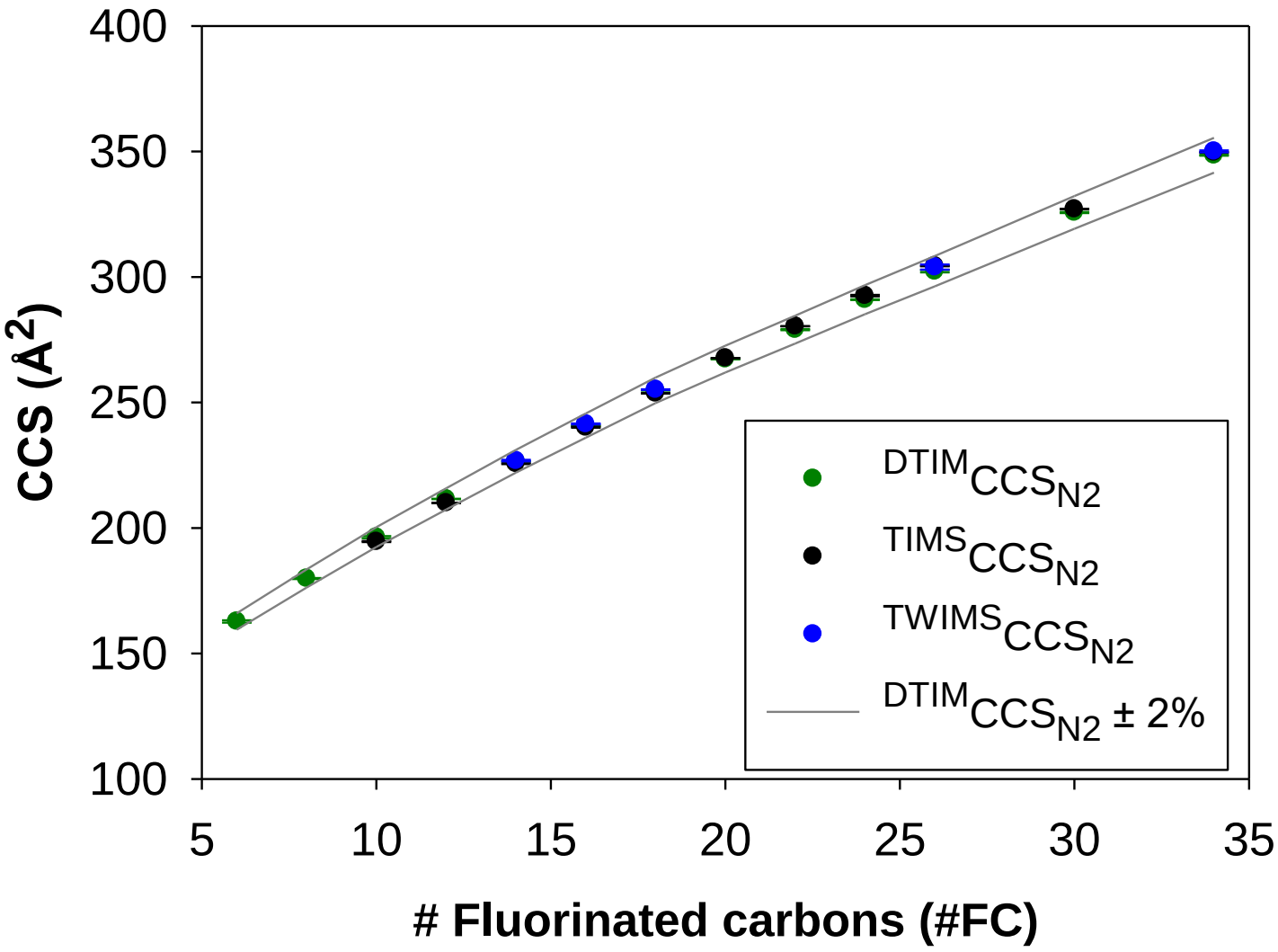
Comparison with other IMS setups

→ Gas-phase conformation of these dimers?

$^{DTIMS}CCS_{N2}$ values of PFCA $[2M-H]^-$ ions obtained with Agilent 6560.

$^{TWIMS}CCS_{N2}$ values of PFCA $[2M-H]^-$ ions obtained with Synapt G2 HDMS

$^{TIMS}CCS_{N2}$: $1/K_0$ range = 0.4-2.0, with TIMSTOF Pro2



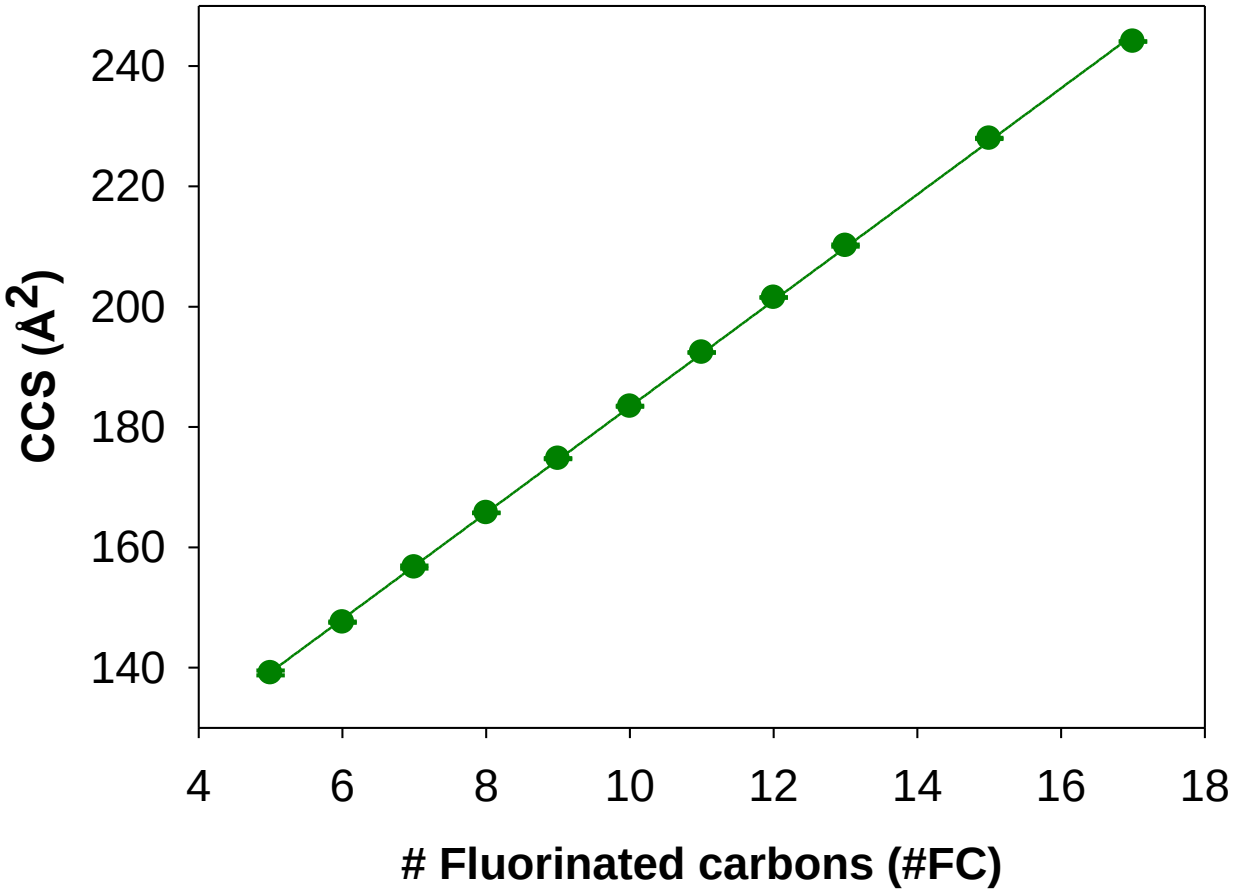
Structural Insights into PFCA ions

Initial hypotheses based on experimental CCS trends :

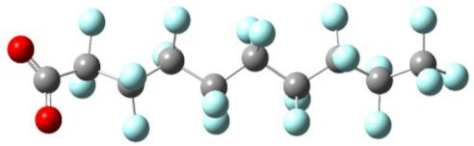
Haler, J. R. N.; et al.. *J. Am. Soc. Mass Spectrom.* **2022**, *33* (2), 273–283. https://doi.org/10.1021/jasms.1c00266 J.Am.

$$\Omega = A \cdot \mathrm{DP}^{pow}$$

Monomeric ions



Monomers :
Linear CCS trend
➡ Cylindrical shape :



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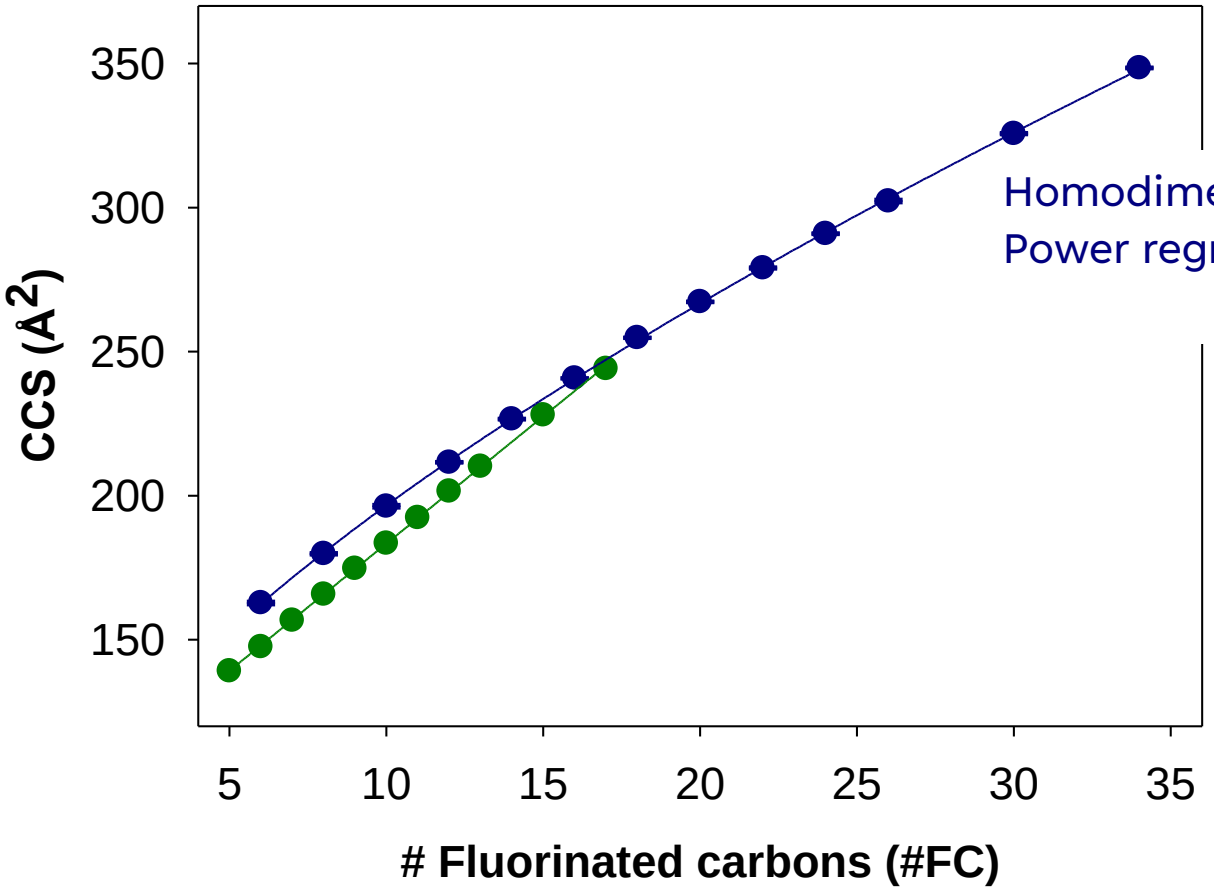
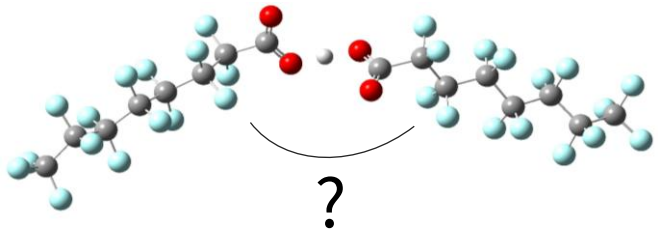


Homodimers :
Power regression model
➡ V-shape? :



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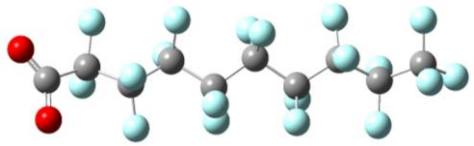
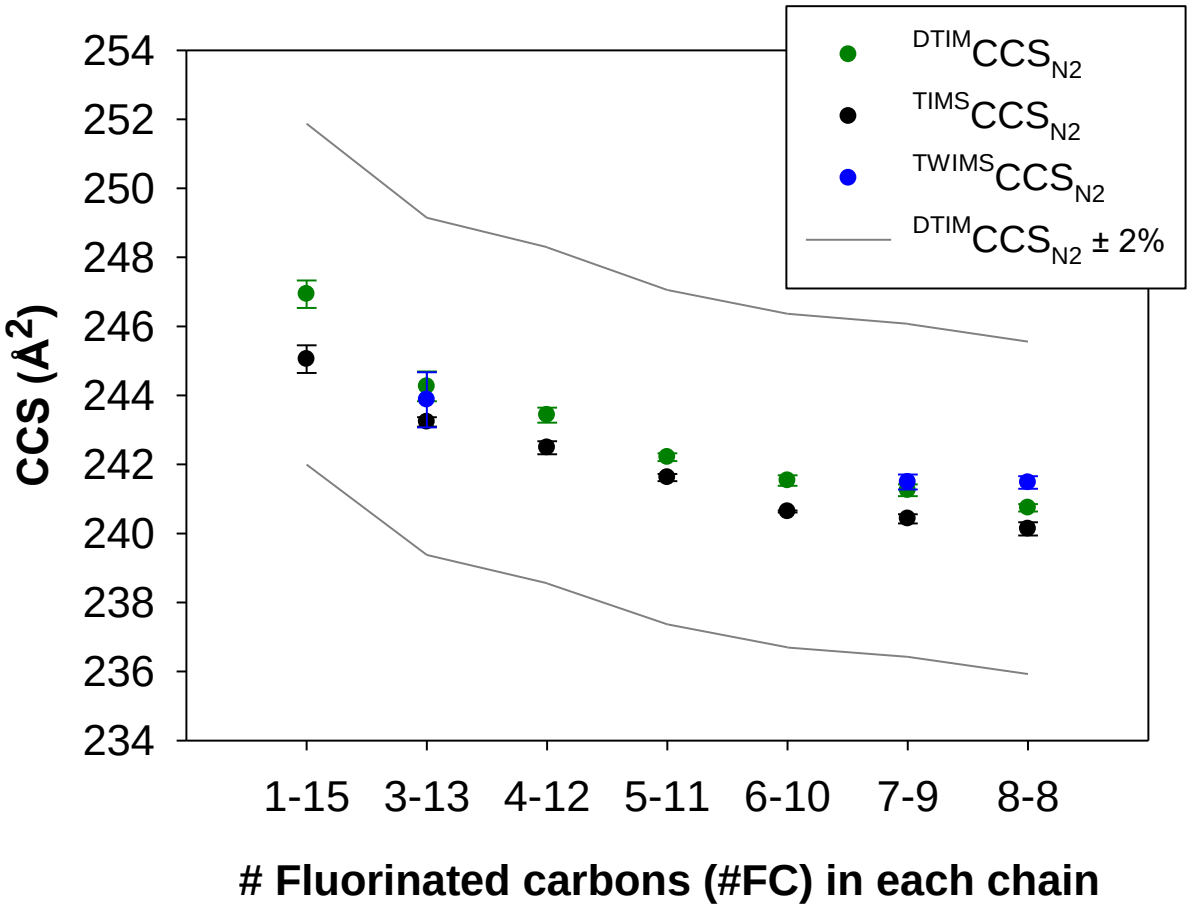
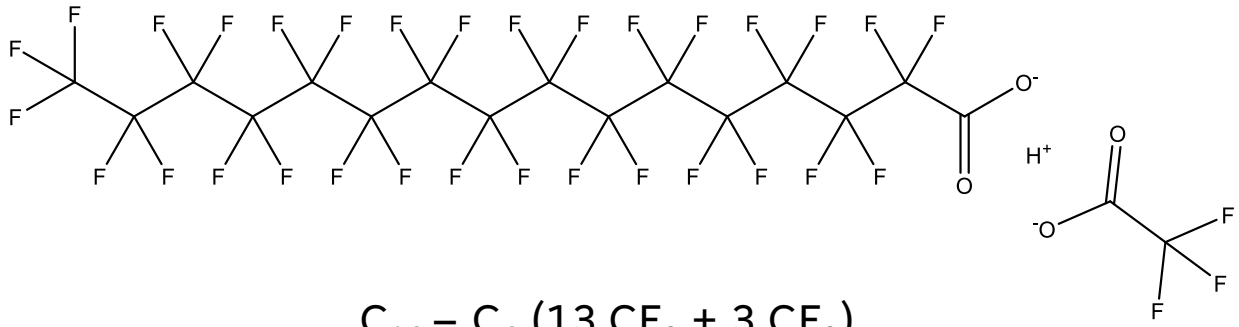


Structural Insights into PFCA ions

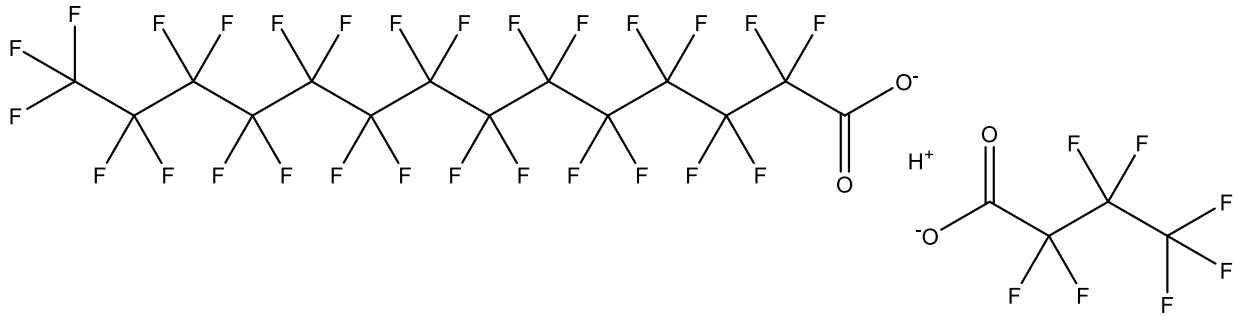
Initial hypotheses based on experimental CCS trends : asymmetrical isobaric dimers



$C_{16} - C_2$ (15 CF_2 + 1CF_2)



$C_{14} - C_4$ (13 CF_2 + 3 CF_2)



Decreasing asymmetry

Structural Insights into PFCA ions

Aim of the work : Provide probable structures for PFCA dimeric ions

→ Generate multiple conformers/structures

→ Calculate their CCS values

→ Low energy + theoretical CCS value close to experimental = probable conformer

Structural Insights into PFCA ions

Aim of the work : Provide probable structures for PFCA dimeric ions

→ **Generate multiple conformers/structures**

Usually via **Molecular Dynamics** using parametrized force fields

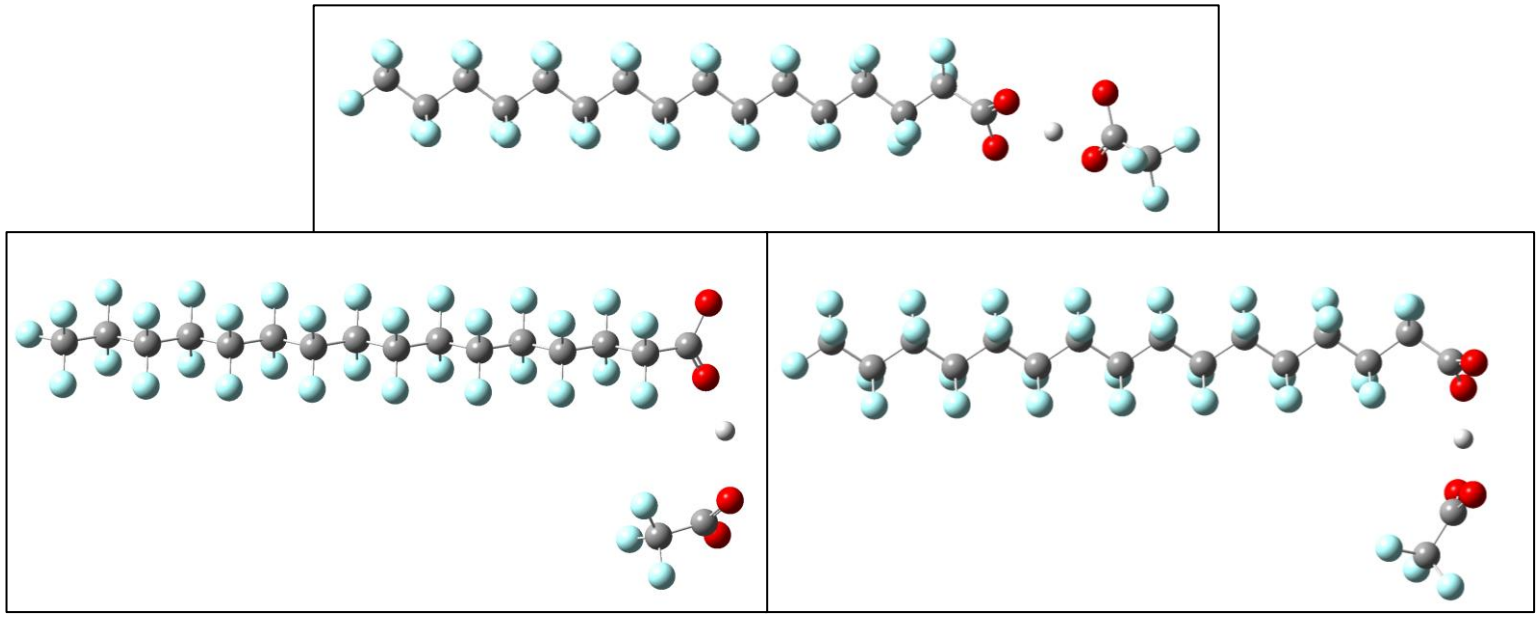
→ Adequate for PFAS and noncovalent binding?
→ **Alternative** workflow for conformer generation, using **ab initio calculations** (Gaussian 16).

Nielson, F. F.; et al. *Anal. Chem.* **2021**, *93* (8), 3830–3838. https://doi.org/10.1021/acs.analchem.0c04341

Structural Insights into PFCA ions

→ **Alternative** workflow for conformer generation, using **ab initio calculations**.

15 initial geometries
(i.e.,different orientation of H^+ versus CO_2 groups)



Structural Insights into PFCA ions

→ **Alternative** workflow for conformer generation, using **ab initio calculations**.

15 initial geometries
(i.e.,different orientation of H^+ versus CO_2 groups)

PM6 + DFT M06-2X

15 optimized geometries

Additional conformer generation

5 lowest-energy geometries

Scan of the two dihedrals next to first F-C-C-F a CO_2 group

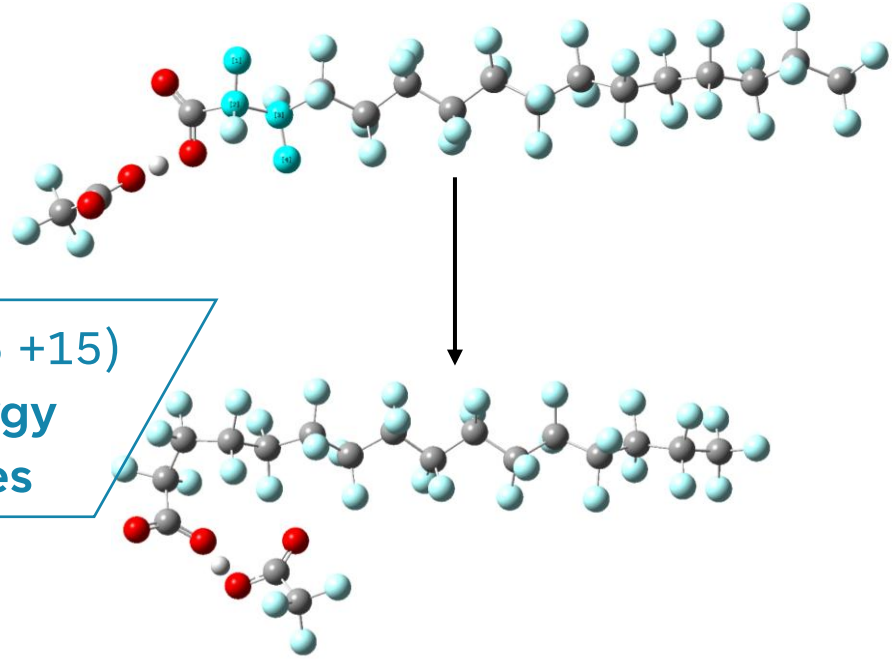
5 * 72 conformers

5 * 3 conformers

DFT M06-2X

15 additional conformers

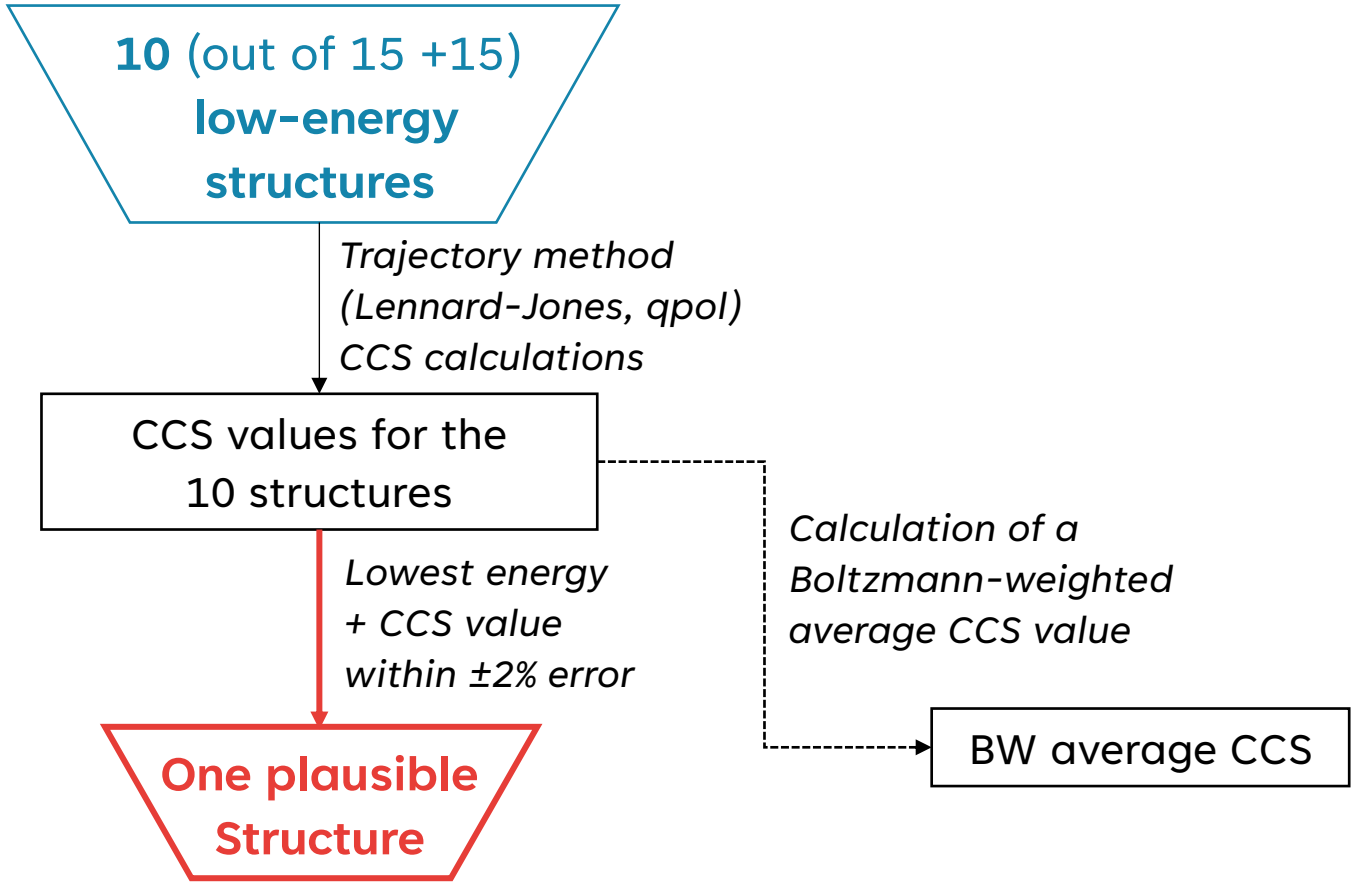
10 (out of 15 +15) **low-energy structures**



Structural Insights into PFCA ions

→ **Alternative** workflow for conformer generation, using **ab initio calculations**.

→ Calculate their CCS values



Structural Insights into PFCA ions

BW average CCS values : used for the monomeric ions to assess the theoretical workflow.

Geometry optimization and energy ranking:

- Functionals used for geometry optimization : **M06-2X** more adequate than CAM-B3LYP or WB97XD

- Basis sets used : 6-31+G(d,p) or 6-311++G(d,p) : similar results but **6-311++G(d,p)** preferred for dimers

CCS calculation (IMOS software):

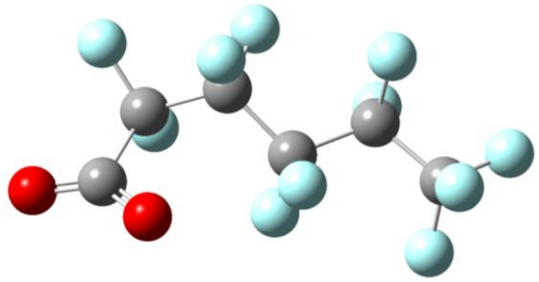
- Inclusion of **ion-quadrupole** potential for nitrogen in TMLJ necessary

- Charge description : Mulliken, Natural Bond Order (NBO), or Merz–Kollman (MK) = similar results. **Mulliken** preferred.

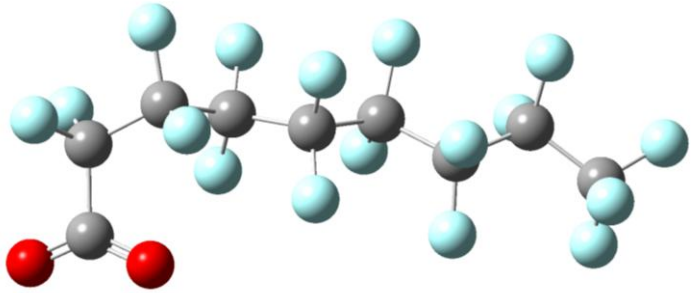
"Prediction performance" :
55% within 2%
73% within 3%
100% within 5%

Structural Insights into PFCA ions

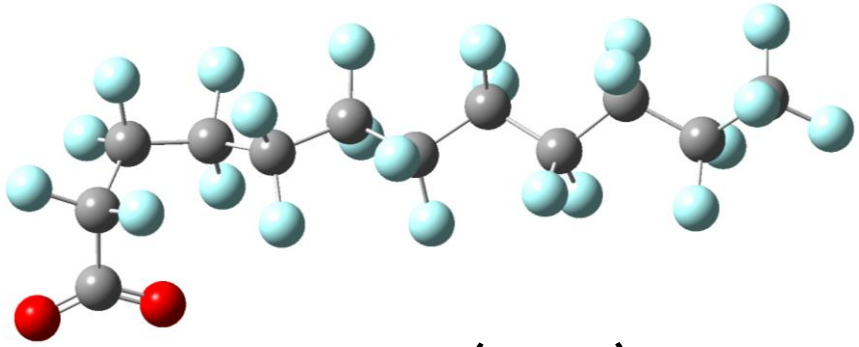
Probable conformers for Monomeric ions:
(6-311++G(d,p), Mulliken)



PFHxA (5 FC)



PFNA (8 FC)



PFTeDA (13 FC)

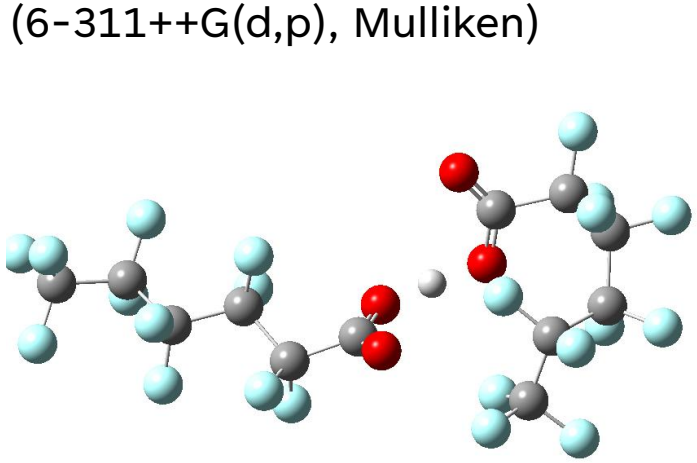
Lorpaiboon, W.; et al. *J. Phys. Chem. A* **2023**, *127* (38), 7943–7953
https://doi.org/10.1021/acs.jpca.3c04750

Schilberg, R. N.; et al. *Chem. Phys. Lett.* **2021**, *778*, 138789
https://doi.org/10.1016/j.cplett.2021.138789

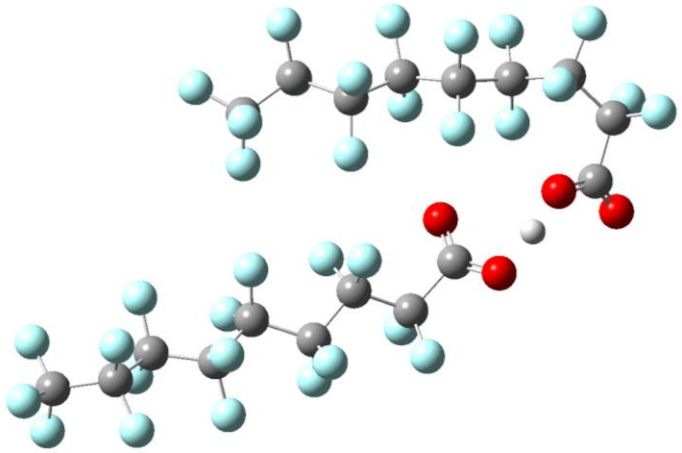
Structural Insights into PFCA ions

Probable conformers for symmetrical dimeric ions:

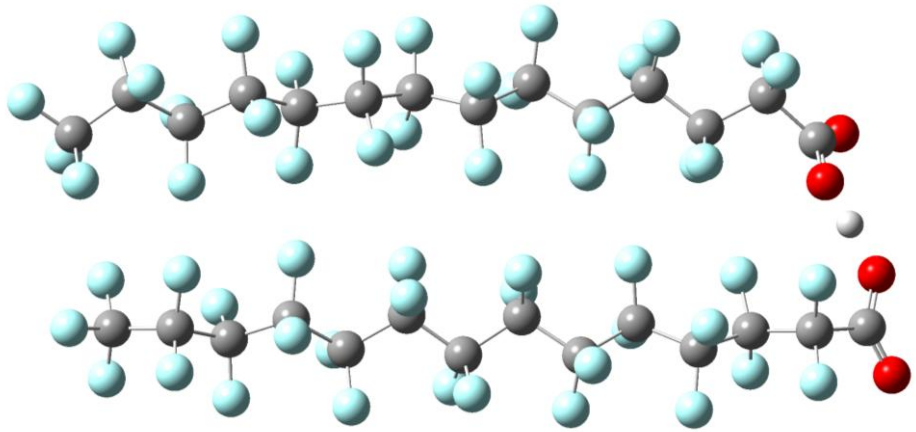
(6-311++G(d,p), Mulliken)



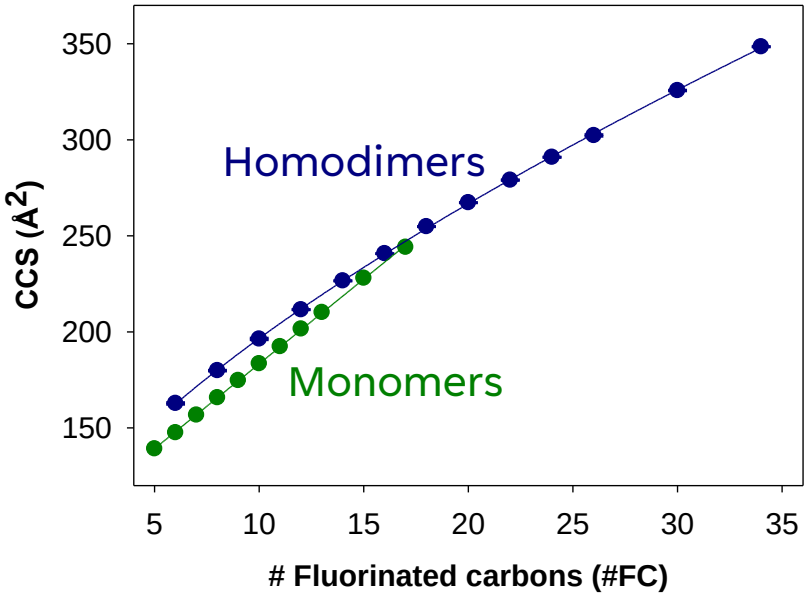
C_6-C_6 (FC = 5-5)



C_9-C_9 (FC = 8-8)



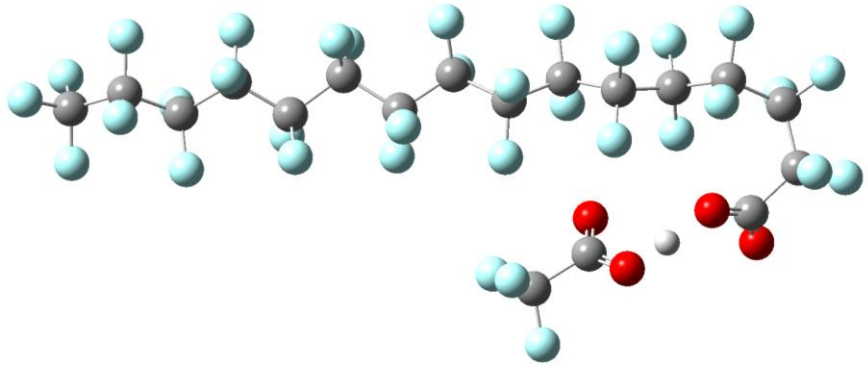
C_{14}-C_{14} (FC = 13-13)



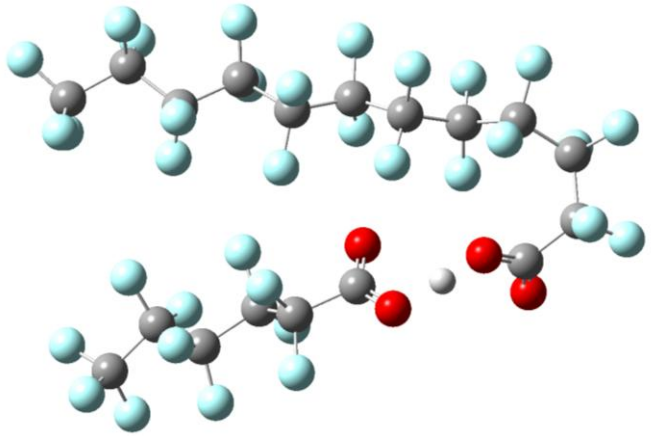
Structural Insights into PFCA ions

Probable conformers for asymmetrical dimeric ions:

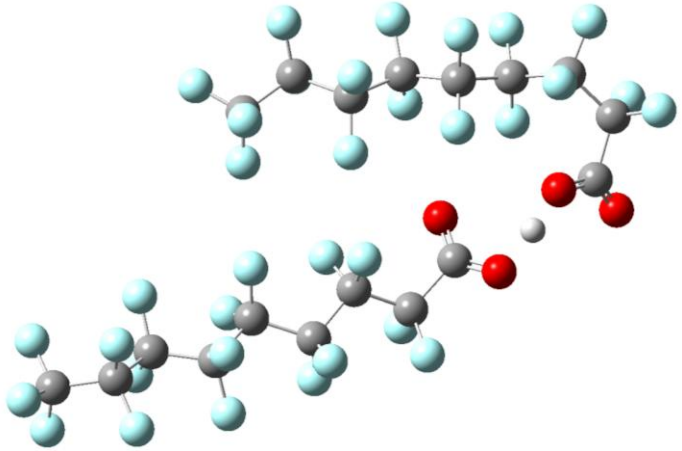
(6-311++G(d,p), Mulliken)



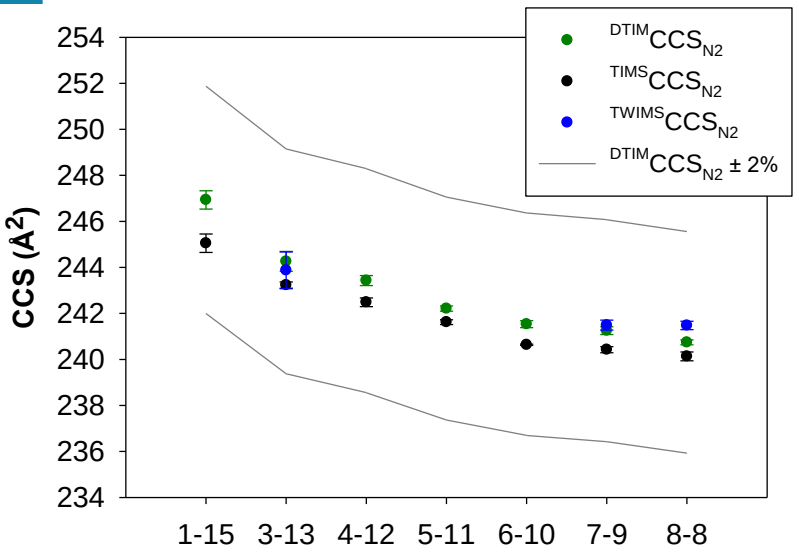
C_2-C_{16} (FC = 1-15)



C_6-C_{12} (FC = 5-11)

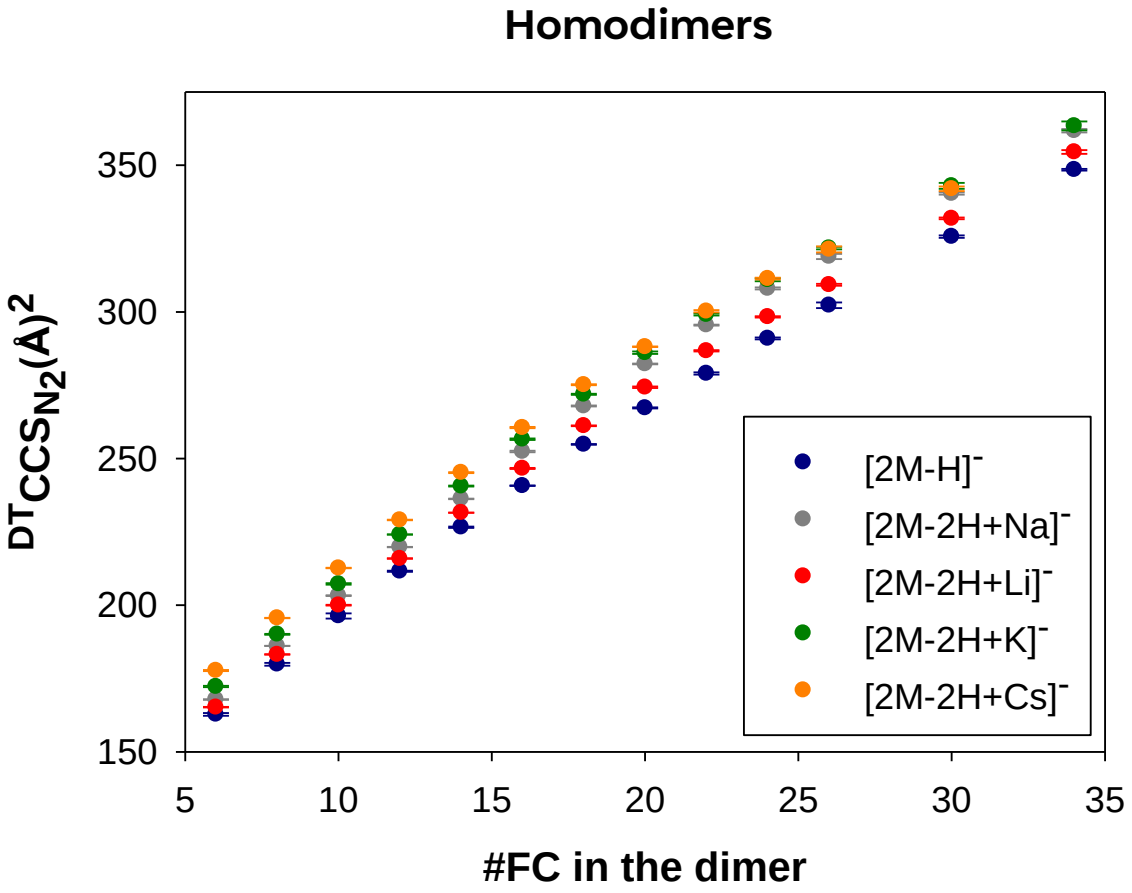


C_9-C_9 (FC = 8-8)



Effect of other singly charged cations?

Direct injection of PFCA solutions containing Li^+, Na^+, K^+, or Cs^+.



Potential challenges for conformer generation and CCS calculation:

- Non-optimized LJ parameters for Li, Na, K, or Cs?
- Mulliken charge description still relevant?

Conclusions

- PFCA dimeric ions identified using three different IMS setups : DTIM, TIMS and TWIMS

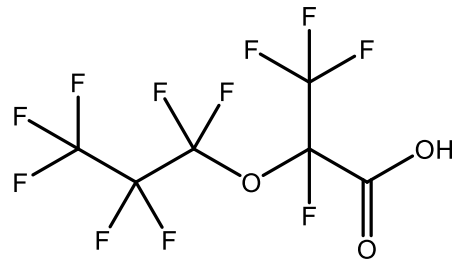
  ⟶ CCS values within ± 2%

- Workflow for conformer generation and CCS calculations :

  ⟶ Plausible structures for the dimers : **fluorinated chains** likely in **close proximity**, especially for the dimers with the longer fluorinated chains.

- Similar behavior with other cations (Li^+, Na^+, K^+, or Cs^+)?

- Similar behavior with other carboxylated PFAS (e.g. with ether bond)?



HFPO-DA (Gen-X)

Thank you !

More information:

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