

pK_a prediction of n-PFCA

COSMO*therm* vs. experiment

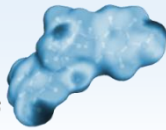
Summary

- PFOA (perfluorooctanoic acid): COSMO*therm* pK_a prediction turned out to be in agreement with recent experiments, while originally trusted experimental values deviate.
- COSMO*therm* predictions were argued to be wrong as they deviate more than 2 units from experimental data, see S. Rayne and K. Forest¹.
Meanwhile newer experiments lead the same authors to predict values close to COSMO*therm* by themselves² and raised the question how QSAR based methods could predict the earlier (misleading) experimental values.
- This demonstrates the value of robust, fundamental prediction methods like COSMO*therm*.

1) [S. Rayne, K. Forest, ADME/Tox WEB in silico predictions of longer chain perfluoroalkyl carboxylic acid pKa values are more accurate than other computational methods Nature Precedings : hdl:10101/npre.2009.2936.1 : Posted 9 Mar 2009](https://doi.org/10.1038/npre.2009.2936.1)

2) [S. Rayne, K. Forest, Theoretical studies on the pKa values of perfluoroalkyl carboxylic acids Nature Precedings : doi:10.1038/npre.2010.3829.2](https://doi.org/10.1038/npre.2010.3829.2)

1. Introduction
2. Experimental data
3. COSMO*therm* theory and data
4. Discussion



Introduction

Straight chain perfluoroalky carboxylic acids (PFCAs)

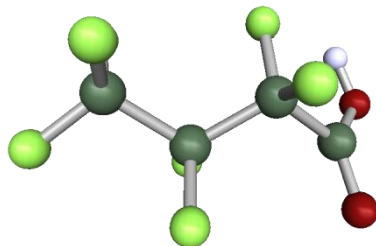
Use

- PFCAs are generally precursors of perfluorinated polymers
- Several thousands tons of perfluorinated compounds are produced every year

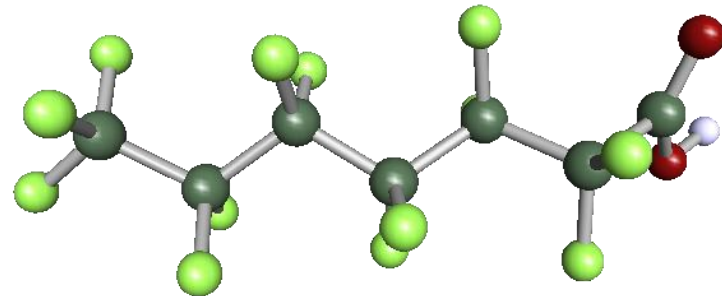
Environmental problems

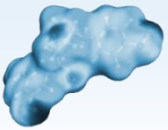
- Some PFCAs are already found in soil and water around the world
- PFCAs are toxic, persistent to natural degradation processes and potentially bio-accumulative

Perfluorobutanoic acid



Perfluoroheptanoic acid



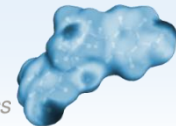


Introduction

Relevance of the pK_a

Properties and pK_a

- The environmentally found concentrations are low enough to suggest, that aggregation found at higher concentrations is not relevant.
- The molecular pK_a and many other properties like distribution coefficients differ significantly between aggregated and non aggregated forms.
- The pK_a is thus highly relevant for the prediction of properties like solubility and bio-accumulation



General aspects

- Due to aggregation effects at low concentrations the pK_a of longer chain PFCAs cannot be measured easily
- The values for trifluoroacetic acid is known to be around 0.3 to 0.5 (1, 2)

Homologous series of carboxylic acids

Compound	pK_a
acetic acid	4.8
propionic acid	4.9
butyric acid	4.8
pentanoic acid	4.8
octanoic acid	4.9

Experimental data for long chain PFCAs

Compound	pK_a	Literature	Comment
Perfluorooctanoic acid	3.8	3	2008, Potentiometric measurement
Perfluorooctanoic acid	1.3	4	2008, Inert-gas stripping measurement
PFCAs	<1	5	2009, Electro-spray ionization mass spectroscopy

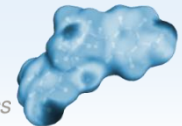
1) Henne, A. L.; Fox, C. J. Ionization constants of fluorinated acids. *J. AM. Chem. Soc.* **1951**, 73, 2323-2325

2) Namazian, M.; Zakery, M.; Noorbala, M. R.; Coote, M. L. Accurate calculation of the pK_a of trifluoroacetic acid using high level ab initio calculations. *Chem. Phys. Lett.* **2008**, 451, 163-168

3) Burns, D. C.; Ellis, D. A.; Li, H.; McMurdo, C. J.; Webster, E. Experimental pK_a determination for perfluorooctanoic acid (PFOA) and the potential impact of pK_a concentration dependence on laboratory-measured partitioning phenomena and environmental modeling. *Environ. Sci. Technol.* **2008**, 42, 9283-9288

4) Kutsuna, S.; Hori, H. Experimental determination of Henry's law constant of perfluorooctanoic acid (PFOA) at 298 K by means of an inert-gas stripping method with helical plate. *Atmos. Environ.* **2008**, 42, 8883-8892

5) Cheng, J.; Psillakis, E.; Hoffmann, M. R.; Colussi, A. J. Acid dissociation versus molecular association of perfluoroalkyl oxoacids: Environmental implications. *J. Phys Chem A* **2009**, 113, 8152-8156



Linear Free Energy Relationship (LFER)

- The pK_a of a compound can be expressed as linear free energy relationship in solution.
- It is thus necessary to calculate the free energy of the ionic and neutral form in solution.
- COSMO-RS can account for the energy difference between gas phase and solution.
- c_0 and c_1 are fitting parameters. Each solvent has to be fitted separately.

$$pK_A = c_0 + c_1 (\Delta G_{neutral}^j - \Delta G_{ion}^j)$$

General aspects

- Only the lowest energy conformer has been used
- The COSMO calculation were done with TURBOMOLE in the BP-TZVP density functional level
- Water has been applied as solvent
- COSMOtherm C21_0110 has been used.

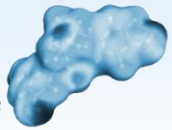
pK_a predictions with COSMOtherm

Compound	pK _a	ΔpK _a to TFA
Trifluoroacetic acid TFA	1.04	
Perfluoropropionic acid	0.90	-0.13
Perfluorobutanoic acid	0.90	-0.14
Perfluoropentanoic acid	0.84	-0.19
Perfluorohexanoic acid	0.85	-0.19
Perfluoroheptanoic acid	0.85	-0.19
Perfluorooctanoic acid	0.83	-0.21
Perfluorononanoic acid	0.82	-0.22

COSMOtherm literature

- In 2008 Goss¹ has used COSMOtherm and was the first to predict the pK_a values for PFCAs. His COSMOtherm predictions gave values around 0.7.
- He found no evidence for an increasing pK_a for longer chain PFCAs

1) [Goss, K. The pKa values of PFOA and other highly fluorinated carboxylic acids. Environ. Sci. Technol. 2008, 42, 456-458](#)



Discussion

COSMO*therm* vs. experiment

Expected tendencies

- The pK_a of all perfluorinated carboxylic acids is expected to be well below the corresponding non fluorinated carboxylic acids. The “electron pulling” effect of fluorine polarizes the acid group.
- In contrast to non fluorinated acids, a decrease in the pK_a is expected when going from TFA (Trifluoroacetic acid) over Perfluoropropionic acid to longer chain PCFAs. The effect should be very small for perfluorobutanoic acid and longer chains, as the “electron pulling” effect is very short ranged.
- Aggregation tendencies increase with chain length

Experiment vs. prediction

- Apart from Burns et. al, all recent experimental findings are consistent with the general expectations.
- COSMO*therm* predictions are consistent with most measurements and expectations.
- COSMO*therm* was able to predict the pK_a of PCFAs correctly before reliable measurements were available.