

# Theoretical studies on the $pK_a$ values of perfluoroalkyl carboxylic acids: Chain helicity

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## Abstract

Semiempirical, ab initio, and density functional theory (DFT) studies were conducted on a homologous series of straight chain perfluoroalkyl carboxylic acids (PFCAs) ranging in chain length from C<sub>1</sub> (trifluoroacetic acid; TFA) to C<sub>9</sub> (perfluorodecanoic acid). Regardless of perfluoroalkyl chain length and computational method and level employed, no significant change in the electrostatic or steric characteristics of the carboxylate head group was found between C<sub>2</sub> and C<sub>9</sub>. Application of a thermodynamic cycle to calculations at the B3LYP/6-311++G(3df,2p) level provided an accurate prediction of the experimental monomeric pK<sub>a</sub> for TFA. At this – and similar – levels of theory, monomeric pK<sub>a</sub> values of longer straight chain PFCAs are expected to display no significant increase with increasing chain length, having a relatively constant pK<sub>a</sub> value of about 0 that is in excellent agreement with earlier predictions and with recent experimental evidence. Contrary to previous claims, perfluoroalkyl chain helicity does not appear to result in increased monomeric PFCA pK<sub>a</sub> values at chain lengths >5 perfluorocarbons.

## Introduction

Perfluoroalkyl carboxylic acids (PFCAs; Fig. 1) are widespread environmental contaminants that are persistent to natural degradation processes, can undergo long-range transport by both aquatic and atmospheric pathways, and are of toxicological concern (1, 2-4). The  $pK_a$  values of these compounds are of interest given the primary role this property plays in various environmental transport and partitioning processes and biological activities. Waste treatment methods for PFCAs are also likely to display different mechanisms, product profiles, and kinetics from the molecular versus dissociated forms (2). Although the  $pK_a$  of the  $C_1$  PFCA (trifluoroacetic acid [TFA]) is well established at about 0.3 to 0.5 (5, 6), there has been substantial debate in the literature regarding the monomeric acidity constants of longer chain PFCAs such as n-perfluorooctanoic acid (n-PFOA) (7-18).

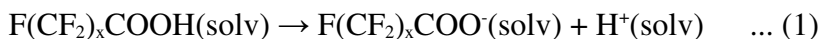
At present, there are three competing estimates for the monomeric  $pK_a$  of n-PFOA in the literature. Goss has argued that based on analogy considerations using other highly fluorinated carboxylic acids, as well as computational data obtained from the COSMOtherm and SPARC software programs, the monomeric  $pK_a$  of n-PFOA should be about 0 (7, 8). Recent experimental evidence by Cheng et al. (16) using electrospray ionization mass spectrometry has boundarized the upper limit of a monomeric n-PFOA  $pK_a$  at  $<1$ , consistent with the prediction of Goss (7). As part of their studies into the air-water partitioning constant of n-PFOA, Kutsuna and Hori proposed a  $pK_a$  of 1.3 from the best fit of their experimental data (13). In contrast, Burns et al. (12) used a potentiometric titration method and recently reported a monomeric n-PFOA  $pK_a$  of  $3.8 \pm 0.1$ . This result has caused controversy (17, 18) not only due to its intrinsically high value (i.e., in the range of non-fluorinated carboxylic acid  $pK_a$  values, and  $>3$  units above that of TFA), but also because Burns et al. (12) indicated that the  $pK_a$  of monomeric n-PFOA was higher than that of its aggregated forms, in contrast to general expectations. Together, this information suggested that previous reports on the  $pK_a$  values of other aggregated PFCAs may accurately represent, or even underestimate, the  $pK_a$  values of the corresponding monomeric forms.

Consequently, the results of Burns et al. (12) caused a re-evaluation of the current and historical composite experimental dataset on PFCA  $pK_a$  values (12,14), suggesting that the computational estimates provided in the literature may be underestimating  $pK_a$  values of longer chain PFCAs, and that – starting at about  $C_4$  – the monomeric  $pK_a$  values of PFCAs may increase with increasing chain length to an upper limit near 3.8 for  $C_7$  and longer homologues.

The rationale put forward by Burns et al. (12) to explain this apparent increase in PFCA monomeric  $pK_a$  by more than 3 units between the short- and long-chain isomers was based on the relative conformations of the perfluoroalkyl chain, and the effects such conformations would have on the acidity of the carboxylate head group. These authors claimed that “[i]t is clear, however, that the rigid perfluoroalkyl helical twist conformation exhibited by long-chain PFCAs mitigates their acidity, causing an increase in  $pK_a$  for the monomeric species, and that a fundamental conformational change, brought about by electronic factors, requires the  $pK_a$  to be different for the short chain PFCAs and their longer chain homologues.” (12) It was also stated in this work that ab initio (Hartree-Fock) and density functional theory (DFT) computational evidence existed to support a significant change in the electronic character of the carboxylate group, but to date, no further details have been provided. In order to help resolve the current controversy in this field, and to shed light on the likely true  $pK_a$  values of monomeric long-chain PFCAs, we have undertaken theoretical studies at the semiempirical, ab initio, and DFT levels on a homologous series of straight chain PFCAs in order to better understand what role, if any, that perfluoroalkyl chain helicity may play in the acidity constants of these important environmental contaminants.

## Methods

The theoretical monomeric  $pK_a$  for PFCAs was calculated using the following approach (6). In aqueous solution, PFCAs dissociate according to the following reaction:



The  $pK_a$  value of  $F(CF_2)_xCOOH(aq)$  is defined as the  $-\log K$  of equation (1) (i.e., the  $K_a$ ), and can be related to the total Gibbs free energy ( $\Delta G^\circ(t)$ ) of reaction (1) via equation (2):

$$pK_a = \Delta G^\circ(t) / 2.303RT \quad \dots (2)$$

$\Delta G^\circ(t)$  can be obtained via a thermodynamic cycle comprised of equations (3) through (5),

$$\Delta G^\circ(t) = \Delta G^\circ(g) + \delta\Delta G^\circ(soln) \quad \dots (3)$$

$$\Delta G^\circ(g) = G^\circ(g, F(CF_2)_xCOO^-) + G^\circ(g, H^+) - G^\circ(g, F(CF_2)_xCOOH) \quad \dots (4)$$

$$\delta\Delta G^\circ(soln) = \Delta G^\circ(soln, F(CF_2)_xCOO^-) + \Delta G^\circ(soln, H^+) - \Delta G^\circ(soln, F(CF_2)_xCOOH) \quad \dots (5)$$

where  $\Delta G^\circ(g)$  is the gas phase Gibbs free energy change of reaction (1) and  $\delta\Delta G^\circ(soln)$  is the sum of the solvation energies for each species, where  $G^\circ(g, H^+)$  is  $-6.28$  kcal/mol and  $\Delta G^\circ(soln, H^+)$  is  $-264.61$  kcal/mol, and a value of  $1.89$  kcal/mol has been added to calculated gas phase energies to convert from standard state of  $1$  atm to  $1$  mol/L (19).

AM1 (20), PM3 (21), and PM6 (22) semiempirical calculations and Hartree-Fock ab initio and B3LYP hybrid functional (23, 24) DFT calculations using the 6-31G(d,p), 6-31++G(d,p), 6-311++G(d,p), and B3LYP/6-311++G(3df,2p) basis sets were conducted using Gaussian 09 (25) on the Western Canada Research Grid (WestGrid; project #100185 [K. Forest]). All calculations used the same gas phase starting geometries obtained with the PM6 semiempirical method (22) as employed in MOPAC 2009 (<http://www.openmopac.net/>; v. 9.099). Aqueous phase calculations in Gaussian 09 employed the polarizable continuum model (PCM) (26) for both geometry optimizations and frequency calculations. All optimized structures were confirmed as true minima by vibrational analysis at the same level.

## Results and Discussion

Geometry optimizations and frequency calculations were conducted at the AM1, PM3, PM6, HF/6-31G(d,p), HF/6-31++G(d,p), HF/6-311++G(d,p), B3LYP/6-31G(d,p), B3LYP/6-31++G(d,p), and B3LYP/6-311++G(d,p) levels of theory in both the gas and aqueous phases for the molecular acid and dissociated anion forms of the following PFCA isomers: C<sub>1</sub>, trifluoroacetic acid (TFA); C<sub>2</sub>, n-perfluoropropanoic acid (n-PFPrA); C<sub>3</sub>, n-perfluorobutanoic acid (n-PFBA); C<sub>4</sub>, n-perfluoropentanoic acid (n-PFPeA); C<sub>5</sub>, n-perfluorohexanoic acid (n-PFHxA); C<sub>6</sub>, n-perfluoroheptanoic acid (n-PFHpA); C<sub>7</sub>, n-perfluorooctanoic acid (n-PFOA); C<sub>8</sub>, n-perfluorononanoic acid (n-PFNA); and C<sub>9</sub>, n-perfluorodecanoic acid (n-PFDeA). At all levels of theory, the perfluoroalkyl chain begins to adopt a twisted (helical) geometry at  $\geq C_2$  to minimize repulsive interactions between adjacent -CF<sub>2</sub>- moieties as the chain sequentially lengthens for both the acid and anionic forms (see Fig. 2 for a sequential illustration of such behavior at the PCM-B3LYP/6-311++G(d,p) level in water). This helical nature of perfluoroalkane chains is well known from studies on the analogous perfluoroalkyl sulfonic acids (27, 28) and the parent perfluorinated n-alkanes (29). Both the HF and DFT methods with all examined basis sets, as well as the PM3 method, yielded approximately equivalent twist angles for the acid and anionic

forms, whereas the AM1 and PM6 methods gave lower twist angles compared to these other methods for both acid and anion forms (Fig. 3). In addition, both the AM1 and PM6 methods predict much reduced helicity for the anionic form compared to its acid equivalent. Zhang and Lerner (27) reported twist angles between 15 to 20° for the analogous gas phase perfluorooctanesulfonate anion at the B3LYP/3-21G\* level with C-C bond lengths ranging between 1.51-1.53 Å. Jang et al. (29) calculated an average twist angle of 16° for gas phase perfluorohexane at the B3LYP/6-31G\* level. Our PCM-B3LYP/6-311++G(d,p) data in water is in excellent agreement with these prior reports, with mid-helix twist angles ranging between about 16 to 18.5° and adjacent perfluorocarbon bond lengths of 1.56-1.57 Å (close to the typical C-C single bond length of 1.54 Å) (Table 1).

Quantitative structure-property relationships (QSPRs) for estimating the  $pK_a$  values of organic oxyacids often employ (in addition to other solute/solvent descriptors) the calculated charges on the oxygen ( $q_O$ ) and hydrogen ( $q_H$ ) atoms in the acid (and the charge difference between these atoms), as well as the estimated O-H bond length ( $r(O-H)$ ) (see, e.g., ref. (30-34) and references therein). Depending on the QSPR, these calculations may be conducted in the gas or aqueous phases, or both. At all levels of theory we investigated, we do not find significant changes in  $q_O$ ,  $q_H$ , or  $r(O-H)$  as a function of linear PFCA perfluoroalkyl chain length in either the gas or aqueous phase (Fig. 4). While in some cases there is a significant change in a descriptor on moving from TFA, where a  $CF_3$  moiety is adjacent to the carboxyl group, to n-PFPrA, where a  $CF_2$  moiety is inserted into this  $\alpha$ -position ( $r(O-H)$  and  $q_H$  both generally increase between TFA and n-PFPrA), there are – more importantly – no significant calculated changes in  $q_O$ ,  $q_H$ , or  $r(O-H)$  between n-PFPrA and n-PFDeA. As a result, there appears to be no substantial perfluoroalkyl chain helicity induced changes in the electrostatic or steric characteristics of the carboxylate head group on PFCAs as the perfluoroalkyl chain lengthens beyond  $C_2$  in either the gas or aqueous phases. Consequently, QSPRs based on these molecular properties would not be expected to predict any changes in  $pK_a$  for linear PFCAs with two or more perfluorocarbons, and we

find no evidence for a helicity-based argument regarding perfluoroalkyl chain length changes in either the steric or electronic nature of the PFCA head group.

Using the thermodynamic cycle described above at the B3LYP/6-311++G(3df,2p) level of theory yields an estimated absolute  $pK_a$  value of -0.1 for TFA. There is excellent agreement between the experimental  $pK_a$  range of 0.3 to 0.5 for TFA and the B3LYP/6-311++G(3df,2p) estimate of -0.1, suggesting that  $pK_a$  predictions for n-PFOA at this level of theory may have a reasonable degree of absolute accuracy. If one accepts that, for calculations without the addition of explicit solvent molecules, the slope of the computationally derived  $pK_a$  scale is about 0.5 (35-38), this gives B3LYP/6-311++G(3df,2p) estimated absolute  $pK_a$  values of 0.0 for TFA and about -0.8 for n-PFOA. At the less computationally expensive B3LYP/6-311++G(d,p) level, there is a  $\Delta pK_a$  of -0.3 between TFA and n-PFOA. As shown in Table 2, the B3LYP/6-311++G(d,p) level calculations predict no substantial changes in straight chain monomeric  $pK_a$  between the C<sub>2</sub> and C<sub>9</sub> PFCA isomers, consistent with the  $q_O$ ,  $q_H$ , and  $r(O-H)$  data at all levels of semiempirical, Hartree-Fock, and DFT theory examined herein for both gas and aqueous phases, and with previously published COSMOtherm, SPARC, and PM6 results (7, 14). The monomeric  $pK_a$  estimate for n-PFOA (between 0.0 and 0.2 depending on whether the  $pK_a$  of TFA is taken to be 0.3 or 0.5) at the B3LYP/6-311++G(d,p) level is in excellent agreement with the prediction of 0 made by Goss (7, 8) and the experimental data of Cheng et al. (16) which boundarized the upper limit for a monomeric n-PFOA  $pK_a$  at <1.

With strong agreement between the B3LYP/6-311++G(d,p) estimated and experimental monomeric  $\Delta pK_a$  values of both TFA and n-PFOA, we also conducted calculations at this level of theory for the monomethyl branched n-PFOA isomers that are also known to be present in environmental samples. Where the monomethyl branching occurs at the  $\beta$  (i.e., 2-) or further positions from the carboxylate group, no substantial deviations from the  $pK_a$  of the straight chain analog are expected. In contrast, the 1-CF<sub>3</sub>-PFOA is predicted to have a  $pK_a$  of -0.5 to -0.3 (about 0.3 to 0.7 units lower than n-PFOA). We



also note the excellent agreement between the estimated  $pK_a$  values of all PFCAs (including the branched isomers) at the B3LYP/6-311++G(d,p) level compared to our previous semiempirical PM6 estimates that used the  $pK_a$  prediction module in MOPAC 2007 (14). In this prior work, the PM6  $pK_a$  prediction module gave estimated values of about -0.2 for the straight chain PFCAs (compared to values ranging between 0.0 to 0.3 at the B3LYP/6-311++G(d,p) level), a value of -1.7 for 1-CF<sub>3</sub>-PFOA (modestly lower than the B3LYP/6-311++G(d,p) estimate of -0.5 to -0.3), and predicted no significant deviation from the n-PFOA  $pK_a$  for the 3-, 4-, and 5-CF<sub>3</sub>-PFOA isomers (also in agreement with the B3LYP/6-311++G(d,p) data). The only modest deviation between our prior PM6 estimates and the current B3LYP/6-311++G(d,p) studies is for 2-CF<sub>3</sub>-PFOA, where the PM6 method predicted a  $pK_a$  of -1.3 and the B3LYP/6-311++G(d,p) data predicts a value of 0.0 to 0.2. Overall, however, there is strong agreement between these two methods for both linear and branched PFCA isomers. Furthermore, in contrast to a previous claim (12), the five monomethyl branched PFOA isomers also exhibit chain helicity (Fig. 5), with the -CF<sub>3</sub> moiety effectively taking the place of a fluorine atom along the helical perfluoroalkyl chain.

The findings presented here support the prediction of Goss (7), prior COSMOtherm, SPARC, and semiempirical PM6 estimates (7, 14), and the experimental data of Cheng et al. (16) for a relatively chain length independent monomeric  $pK_a$  of about 0 for straight chain PFCAs with  $\geq 2$  perfluorocarbons. The results also do not support the hypothesis put forward by Burns et al. (12) for a perfluoroalkyl chain helicity-based rationalization of their proposed monomeric  $pK_a$  for n-PFOA of  $3.8 \pm 0.1$ . If this proposed monomeric n-PFOA  $pK_a$  of 3.8 by Burns et al. (12) is real, despite it contrasting sharply with the experimental value of  $< 1$  reported by Cheng et al. (16), it must be rationalized based on theoretical grounds other than helicity of the perfluoroalkyl chain. In the current work, we have shown using various computational methods and levels of theory, that for a homologous series of short- through long-chain linear PFCAs exhibiting helical perfluoroalkyl chains, there is no significant change in the electrostatic or steric structure of the carboxyl head group, nor do thermodynamic cycle approaches

predict any substantial  $pK_a$  variation among the compounds. Rather, it appears that either the n-PFOA concentration dependent  $pK_a$  data determined by Burns et al. (12) cannot be reliably back-extrapolated to infinite dilution (i.e., that the apparent  $pK_a$  of n-PFOA decreases significantly between infinite dilution and 1 mM, reversing any perceived inverse  $pK_a$  versus concentration trend at concentrations >1 mM), or that other structural arguments must be raised to support the anomalously high monomeric  $pK_a$  value.

Further support for the lack of change in the structural or electronic characteristics of the carboxylate head group comes indirectly from the recently published octanol-water distribution constants (log D values) for the straight chain n-PFBA through n-PFDeA by Jing et al. (39), and our subsequent thermodynamic analysis of their data (40). In brief, the significant linearity of the relationship between the log D values and number of perfluorocarbons over this chain length range strongly implies there is no corresponding fundamental change in the characteristics of the carboxylate head group, since such changes (particularly those that would need to occur to give rise to a >3  $pK_a$  unit increase for the acid forms) would likely also manifest themselves in substantial non-linearities in the log D versus chain length relationship.

Within this context, however, it must be recognized that longer chain PFCAs display concentration dependent  $pK_a$  values, with a significant increase (potentially up to 4 units) in moving from the monomeric species to oligomeric and micellar based structures. In relatively unpolluted waters, the lower monomeric  $pK_a$  values near 0 should be used for modeling purposes, whereas in highly polluted natural waters and waste waters – where concentrations can exceed values where molecular associations may be expected (2) – higher  $pK_a$  values may need to be used in order to more accurately simulate actual in situ acid-base behavior of these important environmental contaminants. At present, the concentration dependent apparent  $pK_a$  values of longer chain PFCAs remains poorly defined at environmentally relevant concentrations, and further work in this area of study is strongly warranted.

## **Acknowledgments**

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## Figure Captions

**Figure 1.** Structures of the perfluoroalkyl carboxylic acids under consideration.

**Figure 2.** Axial perfluoroalkyl chain views of the optimized aqueous phase geometries for the acid and anion forms of the straight chain  $C_1$  (TFA) through  $C_9$  (n-PFDeA) PFCAs at the PCM-B3LYP/6-311++G(d,p) level in water.

**Figure 3.** Axial perfluoroalkyl chain views of the optimized aqueous phase geometries using the polarizable continuum model for the acid form of n-PFOA using the AM1, PM3, and PM6 semiempirical methods and the ab initio HF and density functional theory B3LYP methods with the respective 6-31G(d,p), 6-31++G(d,p), and 6-311++G(d,p) basis sets.

**Figure 4.** Calculated gas (g) and aqueous (aq) phase partial charges on the oxygen ( $q_O$ ) and hydrogen ( $q_H$ ) atoms of the carboxyl O-H moiety and carboxyl O-H bond lengths ( $r(O-H)$ ) as functions of perfluoroalkyl chain length at the various levels of theory under investigation.

**Figure 5.** Axial perfluoroalkyl chain views of the optimized aqueous phase geometries for the acid forms of the five monomethyl branched PFOA isomers at the PCM-B3LYP/6-311++G(d,p) level in water.

**Table 1.** Calculated bond lengths between adjacent perfluorocarbons and the associated FCCF twist angles for the C<sub>2</sub> through C<sub>9</sub> straight chain PFCAs at the PCM-B3LYP/6-311++G(d,p) level in water.

		C <sub>1</sub> -C <sub>2</sub>	C <sub>2</sub> -C <sub>3</sub>	C <sub>3</sub> -C <sub>4</sub>	C <sub>4</sub> -C <sub>5</sub>	C <sub>5</sub> -C <sub>6</sub>	C <sub>6</sub> -C <sub>7</sub>	C <sub>7</sub> -C <sub>8</sub>	C <sub>8</sub> -C <sub>9</sub>
n-PFPrA	length (Å)	1.56							
	twist angle (°)	7.1							
n-PFBA	length (Å)	1.56	1.56						
	twist angle (°)	9.0	4.1						
n-PFPeA	length (Å)	1.57	1.57	1.57					
	twist angle (°)	14.5	16.1	6.2					
n-PFHxA	length (Å)	1.57	1.57	1.57	1.57				
	twist angle (°)	14.3	18.0	16.0	6.1				
n-PFHpA	length (Å)	1.57	1.57	1.57	1.57	1.57			
	twist angle (°)	15.0	17.7	17.4	15.6	7.6			
n-PFOA	length (Å)	1.57	1.57	1.57	1.57	1.57	1.57		
	twist angle (°)	14.5	18.4	17.7	18.0	17.3	7.9		
n-PFNA	length (Å)	1.57	1.57	1.57	1.57	1.57	1.57	1.57	
	twist angle (°)	16.7	17.5	17.2	17.5	17.1	15.1	6.7	
n-PFDeA	length (Å)	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57
	twist angle (°)	14.0	17.7	17.5	17.8	18.0	17.6	16.6	7.6

**Table 2.** Calculated  $\Delta pK_a$  values (relative to TFA and using the thermodynamic cycle as described in the text), gas (g) and aqueous (aq) phase carboxyl O-H bond lengths ( $r(\text{O-H})$ ), and gas and aqueous phase partial atomic charges on the oxygen ( $q_{\text{O}}$ ) and hydrogen ( $q_{\text{H}}$ ) atoms of the carboxyl O-H moiety for the  $\text{C}_1$  through  $\text{C}_9$  straight chain PFCAs and the monomethyl branched PFOA isomers at the B3LYP/6-311++G(d,p) and PCM-B3LYP/6-311++G(d,p) levels of theory, respectively.

	$\Delta pK_a$	$r(\text{O-H})$ (Å)		$q_{\text{O}}$		$q_{\text{H}}$	
		g	aq	g	aq	g	aq
TFA	0.0	0.9700	0.9723	-0.1669	-0.1851	0.2991	0.3382
n-PFPrA	-0.1	0.9704	0.9726	-0.1385	-0.1469	0.3095	0.3452
n-PFBA	-0.2	0.9705	0.9727	-0.1247	-0.1476	0.3027	0.3470
n-PFPeA	-0.3	0.9705	0.9728	-0.1210	-0.1382	0.3020	0.3404
n-PFHxA	-0.2	0.9705	0.9728	-0.1181	-0.1357	0.3009	0.3394
n-PFHpA	-0.3	0.9705	0.9728	-0.1154	-0.1323	0.2998	0.3381
n-PFOA	-0.3	0.9705	0.9728	-0.1142	-0.1313	0.2993	0.3379
n-PFNA	-0.2	0.9704	0.9729	-0.1137	-0.1299	0.2992	0.3375
n-PFDeA	-0.3	0.9706	0.9728	-0.1129	-0.1284	0.2990	0.3369
1-CF <sub>3</sub> -PFOA	-0.8	0.9706	0.9730	-0.0494	-0.0718	0.2915	0.3315
2-CF <sub>3</sub> -PFOA	-0.3	0.9704	0.9727	-0.1054	-0.1208	0.3027	0.3410
3-CF <sub>3</sub> -PFOA	-0.3	0.9704	0.9727	-0.1368	-0.1448	0.3089	0.3448
4-CF <sub>3</sub> -PFOA	-0.4	0.9705	0.9728	-0.1149	-0.1319	0.2994	0.3380
5-CF <sub>3</sub> -PFOA	-0.3	0.9705	0.9728	-0.1157	-0.1309	0.2998	0.3377

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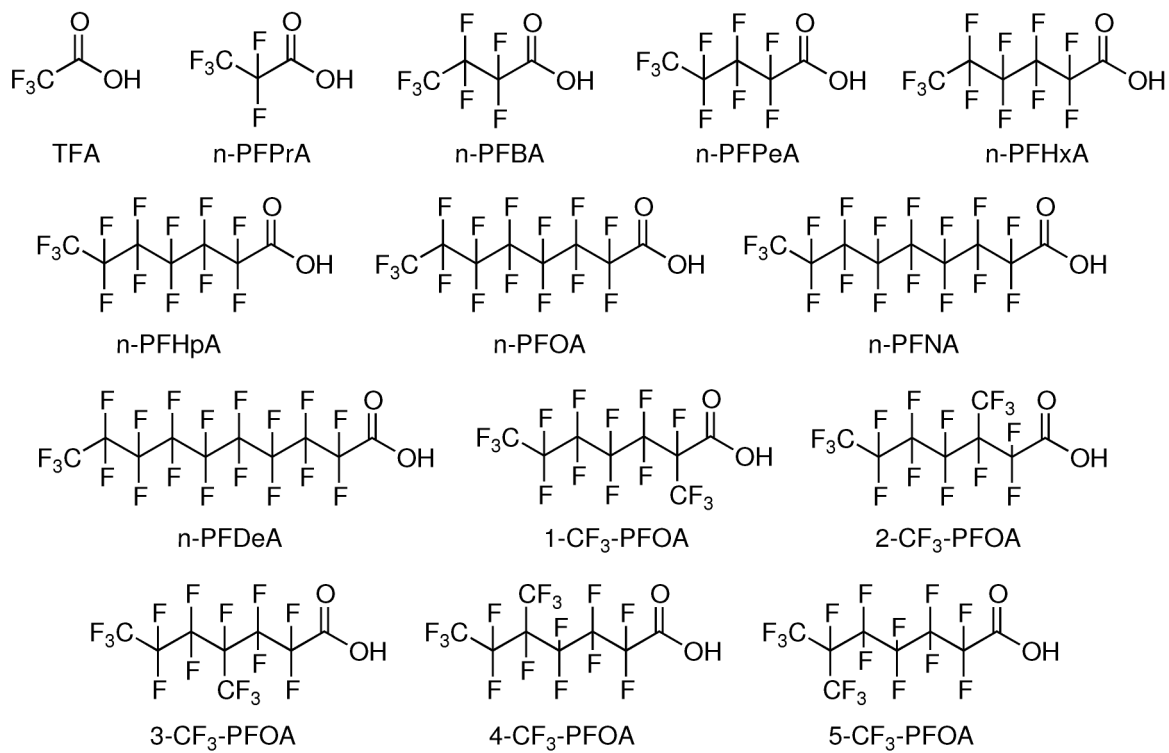
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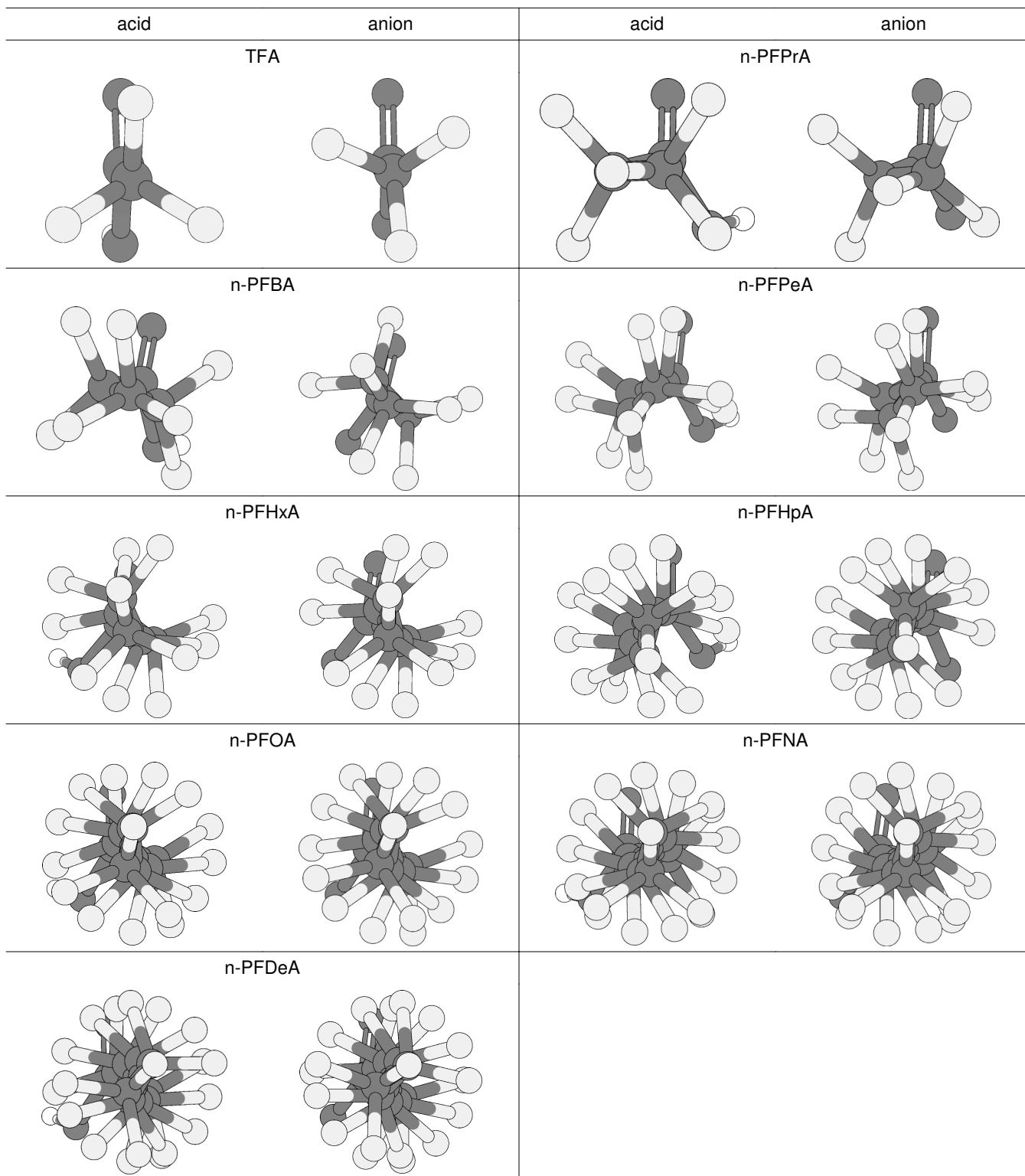
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**Fig. 1.**



**Fig. 2.**



**Fig. 3.**

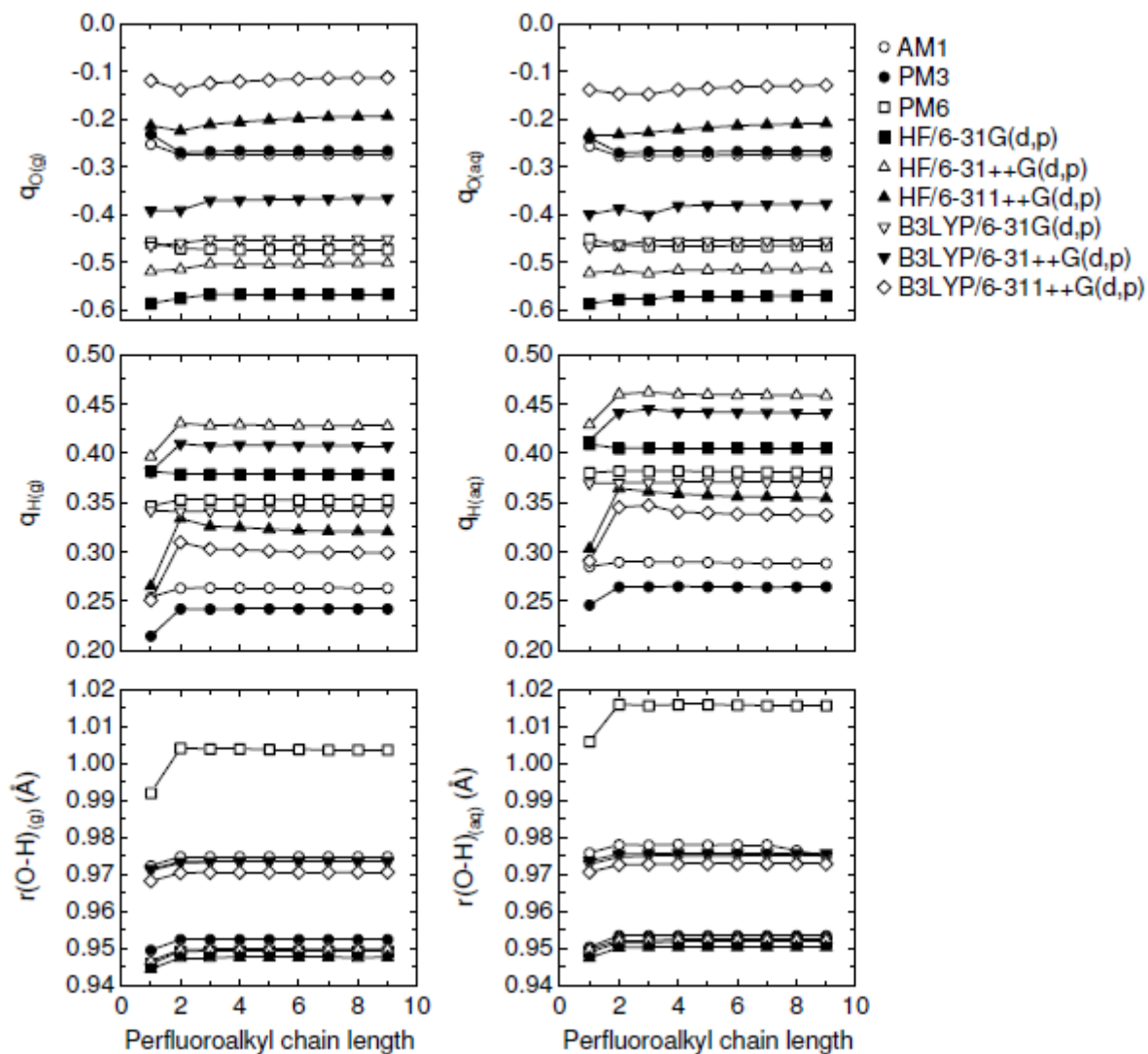
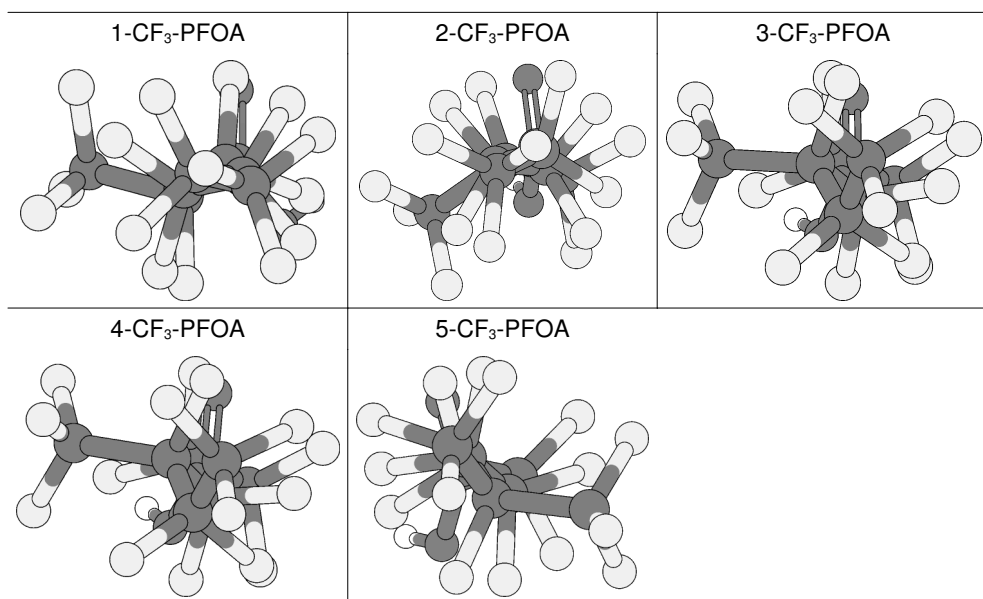


Fig. 4.



**Fig. 5**