

Theoretical studies on the pK_a values of perfluoroalkyl carboxylic acids: Non-helical conformation acidity constants for n-perfluorooctanoic acid (n-PFOA)

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Abstract

A molecular mechanics force field method (MMFF94) systematic rotor conformational search was conducted on the well known environmental contaminant n-perfluorooctanoic acid (n-PFOA). The MMFF94 conformational search yielded 2915 separate low- through high-energy conformers of n-PFOA. Ranking of these structures gave the 94 lowest MMFF94 energy conformations that were subjected to subsequent density functional theory (DFT) computational investigations at the B3LYP/6-311++G(d,p) level of theory. Application of a thermodynamic cycle approach, coupled with aqueous and gas phase DFT calculations on the molecular and anionic forms for each of the 94 lowest energy n-PFOA conformers, gave estimated acidity constants (pK_a values) for a final converged set of twelve n-PFOA conformers, including the global minimum helical perfluoroalkyl chain geometry and eleven non-helical higher energy conformations. Collectively, the twelve lowest energy conformers appear to encompass 85% of the total conformational space for n-PFOA, indicating no higher energy conformations likely remain that could appreciably influence the observed composite aqueous pK_a of this compound. The estimated pK_a values of all eleven non-helical n-PFOA conformers were within 0.2 pK_a units of the helical conformer pK_a . The findings support previous predictions and recent experimental evidence for an aqueous phase n-PFOA monomeric pK_a of about zero.

Keywords: n-perfluorooctanoic acid; pK_a ; acidity constant; environmental fate; conformational search

Introduction

The acidity constants (pK_a values) of environmental contaminants play a major role in their environmental fate and distribution, the mechanisms and products of natural and anthropogenic degradation processes, and toxicological endpoints in humans and wildlife. As a result, there has been much recent interest and debate in the pK_a value for n-perfluorooctanoic acid (n-PFOA) ^[1-6], a well known perfluoroalkyl carboxylic acid (PFCA) that is widely distributed in environmental systems and associated biota ^[7-9]. In order to develop and optimize treatment methods ^[7, 10, 11], better model transport pathways and fate ^[12-20], and generally improve our understanding about the biological behavior of PFCAs ^[21-24], the monomeric aqueous pK_a values of these compounds – particularly n-PFOA – need to be better constrained.

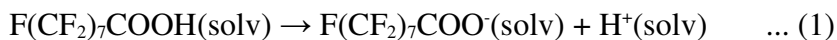
Early studies by Moroi et al. demonstrated a change in the apparent pK_a values of straight chain PFCAs as a function of chain length, whereby the acidity constants increased (i.e., decreasing pK_a) between the C_1 and C_3/C_4 isomers (from about a pK_a of 0.6 to 0.4), but then decreased sharply between C_4 and C_{11} (from about a pK_a of 0.4 to 3.2) ^[25]. However, these authors were careful to note that their measured PFCA acidity constants were not for the monomeric acid species, but for some undefined oligomeric species. As such, this work was not, at the time, directly applicable to better understanding the monomeric pK_a values of longer chain PFCAs in environmental and biological systems. A recent study by Burns et al. ^[3] reported two significant findings that forced a potential reinterpretation of our historical understanding regarding monomeric PFCA pK_a values. The first finding was that the monomeric pK_a of n-PFOA was 3.8 ± 0.1 ; and the second finding was that the monomeric pK_a values of long-chain PFCAs were not lower than their aggregated counterparts (as was expected), but were instead higher.

Consequently, using this information from Burns et al. ^[3], the aggregated long-chain PFCA pK_a data of Moroi et al. ^[25] could be assumed to possibly under-represent the corresponding monomeric pK_a values for these compounds, resulting in a combined dataset whereby the monomeric PFCA pK_a values decreased slightly between C₁ and C₃, after which they increased substantially to values near 4 for the longer chain analogs. If this trend was real, most major pK_a estimation software programs (e.g., COSMOtherm ^[1, 2], SPARC ^[1, 2, 6, 26, 27], PM6 ^[6], etc.) were underestimating the monomeric pK_a values of long-chain PFCAs by up to several pK_a units, representing a potentially large fundamental error in our understanding of the molecular controls on acidity for these compounds.

In their work, Burns et al. ^[3] rationalized the apparent monomeric pK_a of 3.8 for n-PFOA as resulting from the chain length dependent helical conformations of the perfluoroalkyl group, and that such helicity increases the pK_a of the carboxylic acid head group by more than 3 units compared to trifluoroacetic acid (TFA). TFA has only one perfluorocarbon, and no potential to adopt a helical perfluoroalkyl chain structure, unlike its longer chain analogs. We have previously provided strong theoretical evidence that discounts this theory, showing that chain helicity is not expected to alter the structural or electronic characteristics of the carboxylate group, and that helical PFCAs are not expected to have monomeric pK_a values higher than TFA ^[28]. To complete our theoretical studies regarding the monomeric pK_a values of PFCAs, and complement our recent work involving perfluoroalkyl chain helicity based influences on the acidity constants of carboxylic acids, we report here the findings from a conformational investigation into the pK_a values of non-helical n-PFOA conformers.

Materials and Methods

The theoretical monomeric pK_a for the various conformers of n-PFOA was calculated using the following approach ^[29]. In aqueous solution, n-PFOA dissociates according to the following reaction:



The pK_a value of $F(CF_2)_7COOH(aq)$ 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),

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

$$\Delta G^\circ(g) = G^\circ(g, F(CF_2)_7COO^-) + G^\circ(g, H^+) - G^\circ(g, F(CF_2)_7COOH) \quad \dots (4)$$

$$\delta\Delta G^\circ(soln) = \Delta G^\circ(soln, F(CF_2)_7COO^-) + \Delta G^\circ(soln, H^+) - \Delta G^\circ(soln, F(CF_2)_7COOH) \quad \dots (5)$$

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 states of 1 atm to 1 mol/L ^[30].

B3LYP hybrid functional^[31,32] DFT calculations with the 6-311++G(d,p) basis set were conducted using Gaussian 09^[33] on the Western Canada Research Grid (WestGrid; project #100185 [K. Forest]). All calculations used starting geometries obtained with the PM6 semiempirical method^[34] as employed in MOPAC 2009 (<http://www.openmopac.net/>; v. 9.099). Aqueous phase calculations in Gaussian 09 employed the polarizable continuum model (PCM)^[35] 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

A MMFF94 molecular mechanics force field method systematic rotor search yielded 2915 separate low- through high-energy conformers of n-PFOA. Ranking of these structures gave the 94 lowest energy conformations that were subjected to DFT investigations at the B3LYP/6-311++G(d,p) level of theory. For these 94 individual starting structures, geometry optimizations and frequency calculations and associated vibrational analyses were performed at the B3LYP/6-311++G(d,p) level for each of the acid and anionic forms in the gas and aqueous phases, giving a total of 376 calculations. The lowest energy n-PFOA conformation was found to be the helical geometry (Figure 1(1); $G_{\text{acid(solv)}}=-1954.052767$ H, $G_{\text{acid(g)}}=-1954.042809$ H, $G_{\text{anion(solv)}}=-1953.628494$ H; $G_{\text{anion(g)}}=-1953.544499$ H) with an absolute pK_a estimate of about zero we previously reported in our examination of PFCA chain helicity effects on pK_a values for the C_1 through C_9 straight chain isomers and the monomethyl branched n-PFOA congeners^[28], and consistent with a wide range of previous work showing the global helical minima of perfluoroalkyl moieties^[36-56]. The gas and aqueous phase acid calculations resulted in a convergence of the other 93 starting MMFF94 conformer geometries to a final set of 11 additional

B3LYP/6-311++G(d,p) optimized aqueous phase geometries (Figure 1(2-12)). This observed convergence of minima with increasing level of theory is consistent with previous semiempirical and ab initio studies on C₅ through C₇ perfluoroalkanes.^[51]

These 11 non-helical acid geometries range in energy from 2.7 to 6.8 kcal mol⁻¹ less thermodynamically stable than the helical conformer **1** (Figure 2(a)) in the aqueous phase, and from 2.3 to 6.3 kcal mol⁻¹ higher energy than the helical global minimum in the gas phase (Figure 2(b)).

Carboxylic acid proton removals from these 24 total (12 aqueous and 12 gas phase) optimized acid forms and re-optimization to the corresponding anionic structures in the respective aqueous and gas phases resulted in the following pairs of acid conformers converging on equivalent anionic geometries for both phases: **2/3**, **5/7**, **6/9**, and **11/12**. Thus, 12 starting acid conformer geometries in each phase converged to a final set of 8 anionic geometries in each phase (Figure 2(c) and (d)). The non-helical anionic conformers range from 2.8 to 6.6 kcal mol⁻¹ and 1.9 to 4.9 kcal mol⁻¹ higher energy than the corresponding helical conformer in the aqueous and gas phases, respectively.

At 25°C, the global minimum helical conformer will make up the largest single contribution to the overall distribution of n-PFOA conformers in aqueous solution (Figure 3). However, although the most stable helical conformation will be at least three times more abundant than any other individual conformer, the helical conformer will comprise only about one-third of the total abundance of the 12 conformers under study. Whereas additional mid-energy conformers exist that will modestly contribute to the total abundance of non-helical n-PFOA conformers in solution, a projection of our relationship between the 12 lowest energy conformers and the cumulative abundance ratio using a single-exponential fit with x- and y-axis offsets ($r=0.9992$) suggests a maximum cumulative abundance ratio of about 3.4 if all possible n-PFOA conformations are considered. Thus, our range of 12 conformers

encompasses about 85% of the total potential cumulative conformational abundance space for n-PFOA. This indicates that even if mid- to high-energy conformers not included in the present work have unusually high individual pK_a values of up to 4 to 5, these high energy conformations would only increase the solution composite pK_a to 0.07 if the average pK_a of the dominant conformations was 0.00. Consequently, high energy/high pK_a conformations not considered herein will not play a significant role in determining the composite monomeric pK_a for n-PFOA.

Applying the thermodynamic cycle described above to the B3LYP/6-311++G(d,p) data for each of the 12 major aqueous phase conformations of n-PFOA yields the conformer-specific relative pK_a (ΔpK_a ; compared to the global minimum helical conformer) estimates given in Table 1. The individual conformer ΔpK_a values, assuming a slope of 0.5 in the pK_a scale for such calculations without explicit solvent molecules^[57-60], range from -0.2 to +0.2, and average to 0.0 based on abundance distribution weighting of their respective K_a values. Thus, while the non-helical conformations of n-PFOA will result in differences among the various conformer-specific pK_a values, these pK_a variations are small ($\leq \pm 0.2$ deviation from the estimated pK_a of about zero for the dominant helical conformation) and the composite monomeric pK_a of n-PFOA weighted across all potential conformations of the perfluoroalkyl chain is not estimated to deviate significantly from the pK_a of the most dominant helical conformation.

We also sought to investigate any potential intramolecular $F \cdots H$ bonding that could reduce the acidity of the carboxylate group via energetic stabilization of the molecular form. From the PCM-B3LYP/6-311++G(d,p) calculations in water on the 12 different major undissociated molecular conformers of n-PFOA, the minimum $F \cdots H$ distance between the carboxylic acid hydrogen atom and any fluorine on the perfluoroalkyl chain ranged between 3.46 to 3.65 Å, much longer than the typical upper limit of < 2.5 to 3.0 Å required for a significant $F \cdots H$ hydrogen bond^[61, 62]. Consequently, there appear to be no

potentially important contributions from intramolecular $-C-F \cdots H-O-$ hydrogen bonds in any major n-PFOA aqueous phase molecular conformation that could stabilize the undissociated form, and thereby substantially lower the dissociation constant of the carboxylate moiety. These results are similar to gas phase work on the n:2 fluorotelomer alcohols, where Krusic et al. ^[63] found that the experimental and B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) computational studies both consistently indicated an absence of significant intramolecular $-C-F \cdots H-O-$ bonding in these analogous compounds. In an attempt to rationalize the anomalously high monomeric pK_a of 3.8 for n-PFOA proposed by Burns et al. ^[3], their associated claims of a higher pK_a for the monomeric versus aggregated forms of longer chain PFCAs, and the resulting implications for the monomeric pK_a values of other long chain PFCAs, we hypothesized that some form of intramolecular $-C-F \cdots H-O-$ bonding may be present in long chain PFCAs that could reduce the acidity of the carboxylate group ^[6]. This effect would only likely be present where five/six-membered (and higher) intramolecular rings could form between the undissociated carboxylic acid function and fluorines at least several perfluorocarbons away on the chain, thereby potentially explaining how the results of Burns et al. ^[3] implied that monomeric pK_a values of PFCAs purportedly increased substantially starting at chain lengths where intramolecular ring formation could be possible. However, the theoretical studies herein attest to the absence of any energetically plausible intramolecular $F \cdots H$ bonding in PFCAs.

In concert with our previous study ^[28] on the lack of possibly significant chain length and helicity influences, the collective results appear to map the chemical space of possible structural rationalizations for the monomeric pK_a values of PFCAs. All results support the previous prediction ^[1,2] and experimental ^[64] evidence that the monomeric pK_a values of all PFCAs (both short- and long-chain, linear and branched) are <1 , and most likely near or less than zero. There is a collective absence of any theoretical, predictive, or experimental support for the proposed experimental ^[3] monomeric pK_a of 3.8

for n-PFOA. If the monomeric pK_a of n-PFOA is indeed near 4, this finding would likely represent one of the largest monomeric pK_a anomalies known for carbon oxyacids that directly contradicts a growing quantity of theoretical and experimental work suggesting the true monomeric pK_a value is more likely near or below zero. Unless additional rigorous experimental evidence can be adduced to support the claim of this high monomeric pK_a value, it appears that all future environmental modeling work, toxicological studies, and waste treatment investigations should assume a relatively uniform monomeric pK_a value near zero for all possible PFCAs.

Acknowledgements

The Western Canada Research Grid (WestGrid) provided computational support under project #100185 at Okanagan College (K. Forest).

Figure Captions

Figure 1. Optimized geometries of the 12 lowest energy conformers of n-PFOA calculated at the PCM-B3LYP/6-311++G(d,p) level in water.

Figure 2. Relative aqueous and gas phase free energies of the 12 lowest energy conformers for the acid form of n-PFOA and the corresponding 8 lowest energy conformers for the anionic form calculated at the B3LYP/6-311++G(d,p) level.

Figure 3. Individual and cumulative abundance ratios for the 12 lowest energy conformers of n-PFOA calculated at the B3LYP/6-311++G(d,p).

Table 1. Relative pK_a values (ΔpK_a) for the 11 lowest energy non-helical n-PFOA local minima conformers calculated at the B3LYP/6-311++G(d,p) level compared to the global minimum helical conformation.

Conformer no.	ΔpK_a
1 (helical)	0.0
2	+0.2
3	0.0
4	-0.2
5	+0.1
6	0.0
7	0.0
8	0.0
9	-0.2
10	-0.1
11	+0.2
12	-0.1
distribution wgt avg	0.0

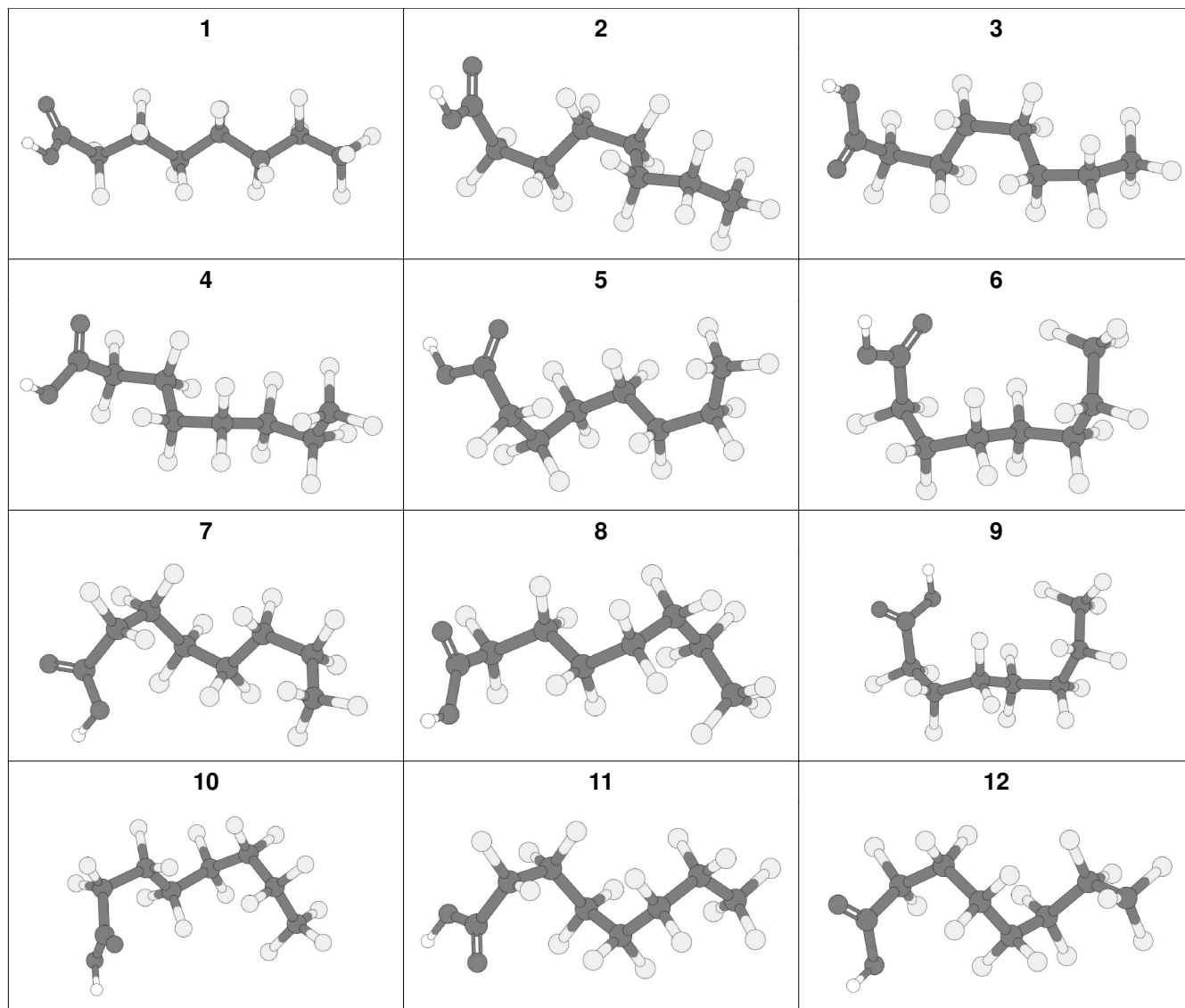


Fig. 1.

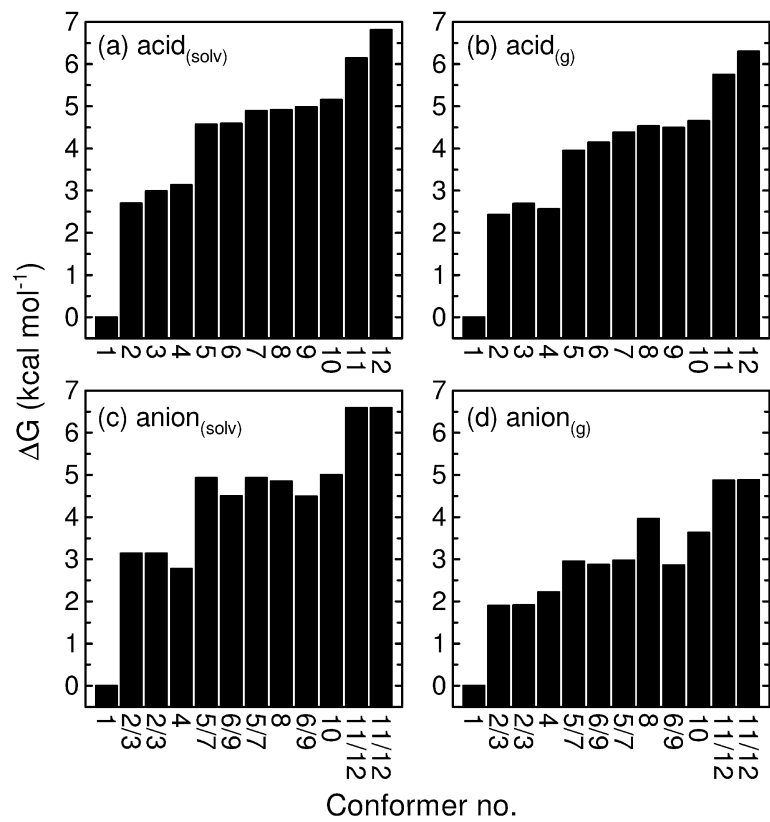


Fig. 2.

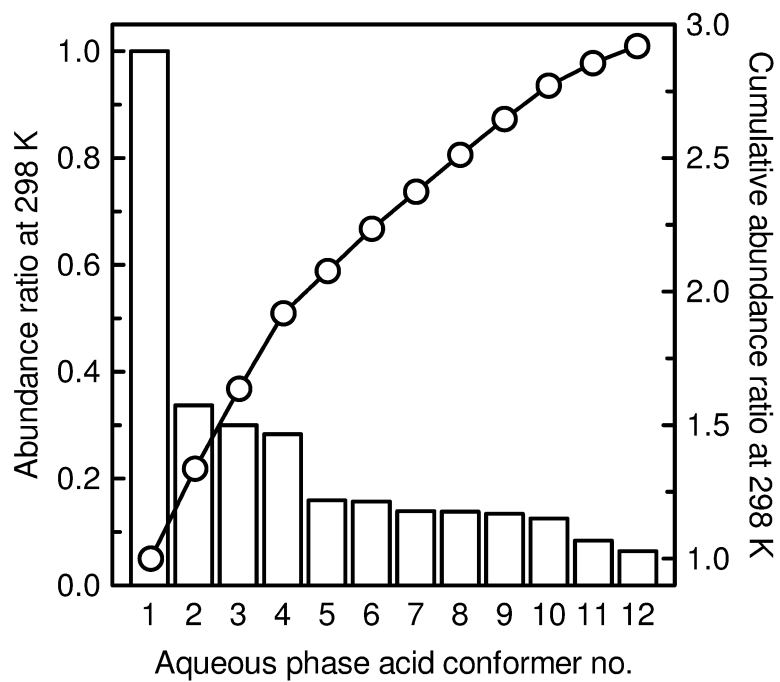


Fig. 3.

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