

Thermodynamic stability of neutral and anionic PFOAs

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Abstract The thermodynamic stability of the PFOA family of 39 structural isomers was studied using the M06-2X, LC- ω PBE, B97D and B3LYP functionals and with the PM6 method. The PM6 results closely resemble the M06-2X results for neutral PFOAs, but diverge strongly in regard to anions. The four functionals applied behave similarly from a qualitative point of view, but quantitatively speaking, the LC- ω PBE and B97D results are somewhere between the M06-2X and B3LYP stability results. M06-2X ranks highly substituted isomers as more stable than did B3LYP and ranks less branched isomers quite low in relative stability compared to B3LYP. Various similarities with a former PFOSs study applying the M06-2X and B3LYP functionals have been identified. The degree of branching within structural isomers cannot always be precisely determined, and it is not the only aspect that determines thermodynamic stability, as the pattern of substitution also seems to play a significant role.

Keywords PFOA · PFOS · Thermodynamic stability of acids and anions · M06-2X · LC- ω PBE · B97D · B3LYP · PM6

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1 Introduction

Perfluorinated acids (PFAs) have been produced for over six decades for use, among other applications, as protective coatings for different materials, for the semiconductors industry or incorporated as a component of firefighting foams [1, 2]. Perfluorooctane sulfonic acid and perfluorooctane carboxylic acid, the most studied PFAs, as well as their salts, have been linked to various health disorders, including cancer [3–6]. These compounds were declared persistent organic pollutants several years ago, and their production has been under scrutiny in some countries and by international agencies [7, 8]. There is a clear need for a better understanding of their environmental transport and distribution.

The acronym PFOA is used in this work to identify the group of 39 structural isomers of perfluorooctane carboxylic acid (PFOA **n**, **n** = 1–39), while the acronym PFOS identifies the 89 structural isomers of perfluorooctane sulfonic acid (PFOS **n**, **n** = 1–89). The nomenclature system proposed by Rayne et al. [9] is used in this study [see Table S1 of the electronic supplementary material]. This system assigns lower numbers to more branched isomers, while higher **n** values are assigned to less branched ones.

Some authors agree that the predominance of linear isomers of PFAs in human and wildlife blood samples could point to telomerization-based processes as their major source in the environment [10–12]. Similarly, electrochemical fluorination synthesis is the assumed source when the proportion of branched isomers becomes significant. The much greater proportion of linear isomers has also been explained by differences in biological retention [10, 13–15] or in the physico-chemical partition mechanisms associated with both local and global transport [16, 17]. In practice,

the observed synthesis-based profiling of the PFOA family of isomers seems to be kinetically determined rather than driven by thermodynamic stability. This idea has been proposed in previous studies with PFAs to justify their observed relative proportions [18–22].

Whether the linear PFOA isomer (PFOA **39**) is more thermodynamically stable than the branched isomers or not, remains a topic of discussion to this date. However, the well-established experimental fact of the greater thermodynamic stability of branched alkane isomers over linear ones must be seriously considered [23–26]. This pattern has been theoretically observed for alkanes [27] and at some level for PFOSs (after studying the 89 structural isomers in the gas phase, *n*-octanol and water) when using the M06-2X functional [28], but not with B3LYP [18]. Wiberg [29] and Ess et al. [27] indicated that electron correlation determines the stability differences between branched and linear isomers. Thus, for properly describing the thermodynamic stability within a family of structural isomers, the choice of the functional is very important, especially so when there are no experimental data to validate such a study. The B3LYP functional has been known to improperly reproduce heats of formation and bond energies in molecules with more than four carbon atoms [30–36], probably due to its inability to properly describe medium-range dispersion-like forces; thus, it seems unfit for this purpose. However, the functional M06-2X is able to represent medium-range (<5 Å) electron correlation energies which allows a better description of intramolecular non-covalent interactions [37].

The thermodynamic stability of the 39 structural PFOA isomers in the gas phase, *n*-octanol and water, taking into account both the neutral and anionic forms, is theoretically studied in this paper. In the absence of experimental data, several methods are applied and the results discussed. A previous thermodynamic stability study on PFOAs focused on the linear (PFOA **39**) and the monomethylated isomers (PFOAs **34–38**) [38]. However, to the best of our knowledge, this is the first in-depth thermodynamic stability study of a complete family of structural isomers of perfluorinated carboxylic acids in the gas phase, *n*-octanol and water. Whenever possible, comparisons are made with the PFOS results previously reported by our group [18, 28].

Accurate standard Gibbs free energies of formation need to be calculated to properly describe and understand the relative thermodynamic stability of these compounds. These data are also required for the calculation of accurate acid dissociation constants in different media and to determine various partition coefficients for PFOAs, work which is currently in preparation. Moreover, accurate physico-chemical properties are required to properly predict the environmental fate of these species, i.e., to better model

their environmental distribution and transport between different media, hence, the relevance of this study.

2 Methodology

Electronic structure calculations were performed with the Gaussian 09 software package [39]. Density functional theory (DFT) calculations were initially performed using the B3LYP functional [40, 41]. Additional functionals such as B97D [34], LC- ω PBE [42] and M06-2X [43], and the semiempirical PM6 [44] method were also applied. The 6-31++ $G(d,p)$ basis set was employed with all the functionals. Additional M06-2X calculations were performed using the 6-311++ $G(3df,3p)$ basis set.

The B97D functional, a semiempirical generalized gradient approximation functional proposed to overcome the difficulties associated with B3LYP, belongs to the group of DFT methods that includes dispersion corrections. This method employs an empirical term of the form C_6/r^6 to account for a correction associated with dispersion. It restricts functional density analysis to short-range electron correlation and uses the C_6/r^6 empirical parameter to describe large- to medium-range interatomic interactions. LC- ω PBE is a corrected functional that optimizes the previous PBE functional [45, 46] to deal with the long-range asymptote of the exchange–correlation potential. M06-2X is a global hybrid meta-exchange–correlation functional with 54 % Hartree–Fock exchange. Its empirical parameterization allows an increased response to dispersion forces and enhances its ability to describe medium-range electron correlation and van der Waals interactions much more effectively than B3LYP [43, 47–49].

Rayne and Forest [38] studied the relative gas-phase enthalpies of several fragments of families of structural isomer involving linear and branched alkanes and some alcohols. They found that the PM6 calculations were consistently in better agreement with experiment than the B3LYP calculations. The experimental data they compiled clearly showed that the more branched an isomer, the lower its relative enthalpy (and as we learn in basic organic chemistry, the greater its thermodynamic stability, i.e., the lower its relative Gibbs free energy of formation value). They also studied the series PFOSs **83–89** and PFOAs **34–39**, which includes the linear and the monomethylated isomers, and found that the M05-2X functional [30, 50] yielded results in agreement with PM6 thermodynamic conclusions for this incomplete families of isomers. The M06 family of functionals succeeded the M05 group of functionals, hence our choice of the M06-2X functional for this and previous related works [28].

As previously performed by our group when studying the 89 isomers of the PFOSs family [18, 28], geometry

optimizations and frequency calculations were performed in the gas phase, water and *n*-octanol for all levels of theory. Solvent effects were accounted for (on geometries and frequencies) by means of the IEF-PCM (with B3LYP only) and SMD continuum solvation methods [51]. UAHF atomic radii were used with PCM calculations to construct the solvent cavity. Stationary points were verified as minima by a harmonic frequency calculation at the same level of theory. Unless otherwise indicated, the M06-2X calculations discussed in this paper make use of the 6-311++G(3df,3p) basis set, and calculations in solution apply the SMD method.

As previously seen (experimentally and theoretically) for the linear PFOS isomer [18, 28], the most stable structure of PFOA **39**, instead of being zigzag (as would be the case for octanoic acid, its non-fluorinated analogue), is helical [52]. This geometry minimizes the electrostatic repulsion between fluorine atoms and is well reproduced with the B3LYP functional, and each of the other methods applied in this study (the LC- ω PBE, M06-2X and B97D functionals, and the PM6 method). Figure S1 shows a compilation of frontal views of the optimized structure of the neutral and anionic PFOA **39** at each of the levels of theory considered in this study, in the gas phase, *n*-octanol and water. The PM6 structures show less helical shape than the others, especially when calculated in water, but they are definitely not zigzag conformations.

The methodology used to obtain the initial geometry to optimize the other 38 isomers was based on making the corresponding chain changes on the optimized gas-phase B3LYP helical structure of PFOA **39**. Because B3LYP was the functional initially used in this study, the optimized B3LYP/6-31++G(*d,p*) gas-phase geometries were used as starting point for the other calculations on each isomer. Since the same procedure is followed for the set of isomers with all the methods applied, we expect the stability comparison to be meaningful. However, we cannot claim to be working with the global minimum geometries of these compounds.

3 Results and discussion

The relative standard Gibbs free energies of formation (relative *G*, in kJ/mol at 298.15 K) for the neutral PFOAs in the gas phase at six levels of theory (using the LC- ω PBE, M06-2X, B3LYP and B97D functionals, and the PM6 method) are shown in Table 1 in the order of stability. Table 2 displays the same information for the anions. Relative *G* values listed following the naming label (i.e., from PFOA **1** to PFOA **39**) in the gas phase, *n*-octanol and water, at the different levels of theory considered, appear in Tables

S2 to S2e for neutral species and in Tables S3 to S3e for anions.

3.1 Method comparison

Various similarities can be observed between the PFOA family and that of the 89 PFOS isomers (previously studied by our group with the B3LYP and M06-2X functionals) [18, 28]. In both cases, the stability ranking of neutral species at any of the levels of theory applied is very little affected by the phase considered (gas phase, *n*-octanol and water). The variability between environments is relatively higher for anions than for neutral species, but the changes are generally within three ranking positions. Differences in *G* values between pairs of environments (gas–octanol, gas–water and octanol–water) for both the neutral and anionic species are also very similar when comparing the results obtained at the different levels of theory considered with the same solvation method (see Tables S4 to S4e, and in particular the mean absolute differences, MAD, reported). Figures S2 (data from Table S2) and S3 (data from Table S3) show the M06-2X results for neutrals and anions, respectively, in the three phases considered, while Figures S4 to S6 display the M06-2X results in each solvent, comparing the relative *G* values of neutrals and anions. Given the similarities observed, comparisons between methods will focus on the results obtained for the neutral PFOAs in the gas phase, unless otherwise indicated.

Various linear correlations were explored (between neutral and anionic species in each environment and between pairs of environments for each type of species); these results are shown in Table S5. Strong correlations (with R^2 values between 0.985 and 0.998) were found when considering neutral PFOAs in any pair of environments, with the exception of the B3LYP-PCM results in gas–octanol ($R^2 = 0.973$) and gas–water ($R^2 = 0.955$). The only strong correlations involving anions were obtained when considering the *G* values in octanol and water with R^2 values of 0.990–0.996 (PM6 values lead to an R^2 value of 0.978). The gas–octanol correlations between anions were usually better (i.e., with a higher R^2 value) than the gas–water correlations. In cases where geometry optimizations could not be performed for a particular species (e.g., some anions decarboxylated when optimized in the gas phase; this was never the case when using the LC- ω PBE functional), these correlations provided a way to estimate relative *G* values. Similar good correlations were also found when studying the 89 PFOS isomers [18, 28].

Because it would be overwhelming to discuss the data gathered in extreme detail, we have organized the 39 isomers into three groups of 13 members each. Group A contains the 13 most stable isomers, group B is made up of the 13 isomers with intermediate stability, and group C

Table 1 Stability order of the 39 neutral PFOA isomers calculated at the M06-2X, PM6, LC- ω PBE, B97D, B3LYP and levels of theory in the gas phase

| Stability order | M06-2X/ 6-311++G(3df,3p) | | M06-2X/ 6-31++G(d,p) | | PM6 | | LC- ω PBE/ 6-31++G(d,p) | | B97D/ 6-31++G(d,p) | | B3LYP/ 6-31++G(d,p) | |
|-----------------|-----------------------------|-------------|-------------------------|-------------|-----------|-------------|-----------------------------------|--------------|-----------------------|-------------|------------------------|-------------|
| 1 | 24 | <i>0.0</i> | 24 | <i>0.0</i> | 5 | <i>0.0</i> | 24 | <i>0.0</i> | 24 | <i>0.0</i> | 24 | <i>0.0</i> |
| 2 | 5 | <i>0.4</i> | 5 | <i>3.1</i> | 24 | <i>12.3</i> | 13 | <i>12.4</i> | 13 | <i>14.5</i> | 13 | <i>15.9</i> |
| 3 | 13 | <i>4.8</i> | 13 | <i>4.5</i> | 13 | <i>13.3</i> | 16 | <i>15.7</i> | 16 | <i>15.9</i> | 34 | <i>17.0</i> |
| 4 | 16 | <i>4.9</i> | 16 | <i>6.2</i> | 3 | <i>17.6</i> | 33 | <i>18.3</i> | 33 | <i>16.9</i> | 33 | <i>18.3</i> |
| 5 | 3 | <i>7.1</i> | 3 | <i>8.6</i> | 16 | <i>20.0</i> | 3 | <i>22.8</i> | 6 | <i>18.3</i> | 6 | <i>19.3</i> |
| 6 | 33 | <i>15.0</i> | 33 | <i>16.3</i> | 12 | <i>28.4</i> | 6 | <i>26.9</i> | 3 | <i>20.2</i> | 16 | <i>19.5</i> |
| 7 | 12 | <i>22.3</i> | 6 | <i>20.6</i> | 33 | <i>31.0</i> | 34 | <i>28.5</i> | 27 | <i>22.6</i> | 27 | <i>20.6</i> |
| 8 | 6 | <i>23.0</i> | 12 | <i>22.7</i> | 2 | <i>32.7</i> | 27 | <i>28.5</i> | 34 | <i>25.8</i> | 20 | <i>22.3</i> |
| 9 | 2 | <i>28.6</i> | 2 | <i>26.9</i> | 6 | <i>34.1</i> | 5 | <i>31.4</i> | 21 | <i>27.5</i> | 21 | <i>23.0</i> |
| 10 | 28 | <i>28.8</i> | 28 | <i>28.9</i> | 14 | <i>35.7</i> | 21 | <i>34.2</i> | 20 | <i>27.5</i> | 3 | <i>28.3</i> |
| 11 | 27 | <i>32.8</i> | 27 | <i>32.1</i> | 28 | <i>36.0</i> | 12 | <i>34.6</i> | 5 | <i>31.0</i> | 39 | <i>29.5</i> |
| 12 | 1 | <i>35.8</i> | 1 | <i>32.8</i> | 27 | <i>42.5</i> | 28 | <i>35.9</i> | 28 | <i>31.0</i> | 8 | <i>32.4</i> |
| 13 | 4 | <i>38.2</i> | 4 | <i>37.5</i> | 4 | <i>45.6</i> | 20 | <i>36.1</i> | 12 | <i>31.7</i> | 38 | <i>32.6</i> |
| 14 | 14 | <i>38.5</i> | 31 | <i>38.0</i> | 18 | <i>48.4</i> | 8 | <i>40.1</i> | 26 | <i>35.9</i> | 26 | <i>33.0</i> |
| 15 | 31 | <i>38.7</i> | 14 | <i>40.6</i> | 1 | <i>49.8</i> | 26 | <i>40.3</i> | 8 | <i>36.2</i> | 28 | <i>35.5</i> |
| 16 | 18 | <i>40.2</i> | 26 | <i>41.8</i> | 31 | <i>50.6</i> | 2 | <i>41.9</i> | 2 | <i>38.5</i> | 12 | <i>37.3</i> |
| 17 | 26 | <i>42.9</i> | 18 | <i>42.2</i> | 17 | <i>50.8</i> | 38 | <i>44.6</i> | 38 | <i>38.6</i> | 30 | <i>39.4</i> |
| 18 | 8 | <i>43.9</i> | 8 | <i>42.8</i> | 34 | <i>52.9</i> | 1 | <i>44.9</i> | 14 | <i>39.0</i> | 25 | <i>39.7</i> |
| 19 | 30 | <i>44.9</i> | 34 | <i>43.2</i> | 26 | <i>53.2</i> | 30 | <i>45.1</i> | 30 | <i>40.4</i> | 35 | <i>39.9</i> |
| 20 | 7 | <i>45.0</i> | 30 | <i>43.7</i> | 8 | <i>54.6</i> | 25 | <i>45.2</i> | 39 | <i>40.5</i> | 36 | <i>43.3</i> |
| 21 | 34 | <i>45.8</i> | 7 | <i>44.5</i> | 25 | <i>56.9</i> | 14 | <i>45.2</i> | 7 | <i>41.1</i> | 37 | <i>43.9</i> |
| 22 | 25 | <i>47.1</i> | 20 | <i>44.8</i> | 20 | <i>57.9</i> | 39 | <i>45.6</i> | 31 | <i>41.3</i> | 31 | <i>44.2</i> |
| 23 | 20 | <i>47.2</i> | 25 | <i>46.0</i> | 38 | <i>58.0</i> | 31 | <i>47.2</i> | 25 | <i>42.2</i> | 2 | <i>44.3</i> |
| 24 | 21 | <i>48.8</i> | 21 | <i>46.6</i> | 21 | <i>58.3</i> | 4 | <i>49.0</i> | 4 | <i>42.4</i> | 7 | <i>45.5</i> |
| 25 | 17 | <i>51.4</i> | 38 | <i>50.0</i> | 19 | <i>58.9</i> | 7 | <i>50.3</i> | 35 | <i>44.0</i> | 5 | <i>45.5</i> |
| 26 | 38 | <i>52.0</i> | 17 | <i>52.3</i> | 30 | <i>59.1</i> | 35 | <i>51.9</i> | 1 | <i>46.5</i> | 14 | <i>46.7</i> |
| 27 | 19 | <i>54.8</i> | 19 | <i>52.8</i> | 15 | <i>61.6</i> | 36 | <i>54.6</i> | 37 | <i>49.2</i> | 4 | <i>46.9</i> |
| 28 | 10 | <i>55.4</i> | 10 | <i>54.2</i> | 35 | <i>62.9</i> | 19 | <i>55.0</i> | 19 | <i>49.3</i> | 1 | <i>47.0</i> |
| 29 | 9 | <i>59.6</i> | 35 | <i>56.7</i> | 39 | <i>68.5</i> | 37 | <i>56.0</i> | 36 | <i>49.6</i> | 19 | <i>48.3</i> |
| 30 | 35 | <i>60.1</i> | 9 | <i>57.7</i> | 7 | <i>68.7</i> | 18 | <i>62.2</i> | 18 | <i>55.2</i> | 9 | <i>56.2</i> |
| 31 | 36 | <i>60.6</i> | 36 | <i>58.6</i> | 37 | <i>69.3</i> | 9 | <i>62.8</i> | 9 | <i>55.8</i> | 22 | <i>60.2</i> |
| 32 | 37 | <i>62.2</i> | 39 | <i>59.5</i> | 10 | <i>69.7</i> | 15 | <i>64.2</i> | 22 | <i>61.1</i> | 18 | <i>64.6</i> |
| 33 | 39 | <i>62.5</i> | 37 | <i>59.6</i> | 36 | <i>69.8</i> | 10 | <i>68.6</i> | 10 | <i>62.6</i> | 23 | <i>66.9</i> |
| 34 | 15 | <i>67.6</i> | 15 | <i>67.0</i> | 32 | <i>77.1</i> | 17 | <i>71.8</i> | 17 | <i>65.6</i> | 10 | <i>67.6</i> |
| 35 | 32 | <i>72.2</i> | 32 | <i>71.4</i> | 9 | <i>77.9</i> | 22 | <i>74.5</i> | 32 | <i>70.6</i> | 32 | <i>69.9</i> |
| 36 | 29 | <i>77.6</i> | 29 | <i>75.4</i> | 22 | <i>79.2</i> | 32 | <i>78.1</i> | 15 | <i>72.1</i> | 15 | <i>73.1</i> |
| 37 | 22 | <i>78.8</i> | 22 | <i>76.6</i> | 11 | <i>84.2</i> | 23 | <i>79.7</i> | 23 | <i>73.3</i> | 17 | <i>74.9</i> |
| 38 | 23 | <i>82.9</i> | 23 | <i>79.6</i> | 29 | <i>84.3</i> | 29 | <i>86.2</i> | 29 | <i>76.1</i> | 29 | <i>76.3</i> |
| 39 | 11 | <i>95.8</i> | 11 | <i>94.5</i> | 23 | <i>86.3</i> | 11 | <i>102.2</i> | 11 | <i>94.4</i> | 11 | <i>92.9</i> |

PFOA labels shown in bold, relative G values (in kJ/mol at 298.15 K) shown in italics

contains the 13 least stable isomers. Analysis of the results for the 39 neutral and anionic isomers using Tables 1 and 2 is relatively incomplete when focused only upon comparison of the least branched isomers (PFOAs 34–39). Little information can be obtained about the relative stability of the entire family of 39 isomers if all of them are not

considered. The relative stability distribution of PFOAs 34–39 among groups {A, B, C}, where A, B and C denote the number of isomers in each group, depends on the method applied. The M06-2X distribution of these six isomers is {0, 1, 5} with the largest basis set (with the smaller basis set, the distribution is very similar {0, 2, 4}). PM6 is the

Table 2 Stability order of the 39 anionic PFOA isomers calculated at the M06-2X, PM6, LC- ω PBE, B97D, B3LYP levels of theory in the gas phase

| Stability order | M06-2X/ 6-311++G(3df,3p) | | M06-2X/ 6-31++G(d,p) | | PM6 | LC- ω PBE/ 6-31++G(d,p) | | B97D/ 6-31++G(d,p) | B3LYP/ 6-31++G(d,p) | | | |
|-----------------|-----------------------------|-------------------------|-------------------------|-------------------------|-----------|-----------------------------------|-----------|-------------------------|------------------------|-------------------------|-----------|-------------------------|
| 1 | 5 | <i>0.0^a</i> | 24 | <i>0.0^a</i> | 5 | <i>0.0^a</i> | 24 | <i>0.0^a</i> | 24 | <i>0.0^a</i> | 24 | <i>0.0^a</i> |
| 2 | 24 | <i>0.0^a</i> | 3 | <i>1.7</i> | 13 | <i>25.0^a</i> | 13 | <i>11.9^a</i> | 13 | <i>15.3^a</i> | 21 | <i>19.2</i> |
| 3 | 3 | <i>0.0</i> | 5 | <i>3.0^a</i> | 24 | <i>29.6^a</i> | 3 | <i>13.8</i> | 3 | <i>18.7</i> | 20 | <i>19.9</i> |
| 4 | 13 | <i>5.9^a</i> | 13 | <i>6.6^a</i> | 3 | <i>40.4</i> | 16 | <i>18.1</i> | 16 | <i>18.9</i> | 3 | <i>20.8</i> |
| 5 | 16 | <i>11.7</i> | 16 | <i>13.4</i> | 12 | <i>43.4^a</i> | 6 | <i>27.3^a</i> | 6 | <i>19.8^a</i> | 13 | <i>21.0^a</i> |
| 6 | 12 | <i>22.4^a</i> | 6 | <i>22.0^a</i> | 2 | <i>45.2^a</i> | 27 | <i>30.2</i> | 21 | <i>26.8</i> | 6 | <i>21.1^a</i> |
| 7 | 6 | <i>23.7^a</i> | 12 | <i>22.7^a</i> | 6 | <i>47.1^a</i> | 5 | <i>30.4^a</i> | 27 | <i>28.6</i> | 16 | <i>21.2</i> |
| 8 | 14 | <i>26.8</i> | 14 | <i>26.2</i> | 16 | <i>47.4</i> | 21 | <i>31.2</i> | 20 | <i>28.8</i> | 34 | <i>21.3</i> |
| 9 | 1 | <i>31.4^a</i> | 1 | <i>28.8^a</i> | 4 | <i>65.4</i> | 34 | <i>33.0</i> | 34 | <i>32.4</i> | 27 | <i>22.8</i> |
| 10 | 4 | <i>32.7</i> | 4 | <i>31.9</i> | 1 | <i>65.6^a</i> | 20 | <i>33.1</i> | 12 | <i>35.2^a</i> | 8 | <i>29.6</i> |
| 11 | 2 | <i>33.9^a</i> | 2 | <i>34.4^a</i> | 14 | <i>66.7</i> | 33 | <i>33.1</i> | 8 | <i>35.5</i> | 33 | <i>33.8</i> |
| 12 | 33 | <i>34.5</i> | 33 | <i>36.5</i> | 28 | <i>75.8</i> | 8 | <i>37.3</i> | 5 | <i>37.2^a</i> | 26 | <i>35.0</i> |
| 13 | 27 | <i>40.7</i> | 27 | <i>39.3</i> | 27 | <i>81.0</i> | 12 | <i>37.8^a</i> | 33 | <i>37.7</i> | 4 | <i>38.0</i> |
| 14 | 8 | <i>42.7</i> | 28 | <i>41.9</i> | 17 | <i>82.2</i> | 14 | <i>37.9</i> | 4 | <i>39.5</i> | 12 | <i>39.2^a</i> |
| 15 | 28 | <i>43.1</i> | 8 | <i>42.3</i> | 33 | <i>85.3</i> | 4 | <i>39.1</i> | 14 | <i>40.1</i> | 7 | <i>41.1</i> |
| 16 | 7 | <i>45.8</i> | 20 | <i>44.8</i> | 9 | <i>88.1</i> | 1 | <i>41.2^a</i> | 7 | <i>41.5</i> | 25 | <i>42.2</i> |
| 17 | 20 | <i>46.9</i> | 21 | <i>45.2</i> | 26 | <i>88.3</i> | 26 | <i>42.1</i> | 26 | <i>41.7</i> | 28 | <i>42.8</i> |
| 18 | 26 | <i>48.7</i> | 7 | <i>45.4</i> | 18 | <i>89.2</i> | 28 | <i>43.7</i> | 28 | <i>44.6</i> | 14 | <i>43.7</i> |
| 19 | 21 | <i>48.7</i> | 26 | <i>47.4</i> | 8 | <i>89.4</i> | 7 | <i>46.0</i> | 19 | <i>49.2</i> | 1 | <i>44.9^a</i> |
| 20 | 34 | <i>49.2</i> | 34 | <i>49.0</i> | 25 | <i>90.2</i> | 25 | <i>48.2</i> | 25 | <i>49.6</i> | 19 | <i>45.0</i> |
| 21 | 25 | <i>53.1</i> | 25 | <i>51.6</i> | 34 | <i>95.4</i> | 2 | <i>50.3^a</i> | 1 | <i>53.5^a</i> | 39 | <i>46.5</i> |
| 22 | 15 | <i>57.7</i> | 19 | <i>56.6</i> | 7 | <i>95.8</i> | 19 | <i>53.4</i> | 2 | <i>53.8^a</i> | 5 | <i>47.2^a</i> |
| 23 | 31 | <i>57.9</i> | 15 | <i>56.6</i> | 20 | <i>95.9</i> | 30 | <i>56.5</i> | 30 | <i>58.7</i> | 38 | <i>49.2</i> |
| 24 | 19 | <i>58.1</i> | 31 | <i>58.6</i> | 21 | <i>96.6</i> | 38 | <i>58.9</i> | 15 | <i>60.0</i> | 2 | <i>49.3^a</i> |
| 25 | 18 | <i>59.6</i> | 30 | <i>61.3</i> | 19 | <i>96.7</i> | 39 | <i>60.6</i> | 38 | <i>60.4</i> | 30 | <i>52.4</i> |
| 26 | 17 | <i>61.0</i> | 9 | <i>61.9</i> | 31 | <i>97.4</i> | 15 | <i>61.5</i> | 31 | <i>60.9</i> | 35 | <i>52.8</i> |
| 27 | 30 | <i>62.5</i> | 17 | <i>62.3</i> | 30 | <i>102.0</i> | 31 | <i>61.9</i> | 9 | <i>61.4</i> | 36 | <i>57.9</i> |
| 28 | 9 | <i>64.0</i> | 18 | <i>62.3</i> | 10 | <i>106.1</i> | 9 | <i>63.4</i> | 39 | <i>62.2</i> | 9 | <i>58.4</i> |
| 29 | 10 | <i>69.1</i> | 10 | <i>67.4</i> | 15 | <i>106.2</i> | 35 | <i>63.4</i> | 35 | <i>63.0</i> | 15 | <i>58.6</i> |
| 30 | 38 | <i>73.2</i> | 38 | <i>70.9</i> | 11 | <i>114.4</i> | 36 | <i>67.5</i> | 36 | <i>69.6</i> | 31 | <i>59.9</i> |
| 31 | 35 | <i>78.1</i> | 35 | <i>77.0</i> | 35 | <i>114.8</i> | 37 | <i>71.2</i> | 37 | <i>70.8</i> | 37 | <i>60.6</i> |
| 32 | 36 | <i>78.2</i> | 36 | <i>78.4</i> | 38 | <i>119.2</i> | 18 | <i>76.4</i> | 18 | <i>74.7</i> | 22 | <i>69.5</i> |
| 33 | 39 | <i>82.7</i> | 39 | <i>80.5</i> | 22 | <i>120.5</i> | 10 | <i>78.4</i> | 10 | <i>76.9</i> | 10 | <i>77.8</i> |
| 34 | 37 | <i>84.1</i> | 37 | <i>82.0</i> | 36 | <i>127.0</i> | 17 | <i>78.5</i> | 22 | <i>78.0</i> | 18 | <i>79.0</i> |
| 35 | 22 | <i>90.7</i> | 22 | <i>85.7</i> | 37 | <i>129.1</i> | 22 | <i>83.8</i> | 17 | <i>79.1</i> | 23 | <i>79.0</i> |
| 36 | 32 | <i>92.3</i> | 32 | <i>90.8</i> | 29 | <i>129.3</i> | 32 | <i>90.6</i> | 23 | <i>90.0</i> | 17 | <i>82.5</i> |
| 37 | 29 | <i>93.6</i> | 29 | <i>92.2</i> | 39 | <i>132.1</i> | 23 | <i>91.2</i> | 32 | <i>90.1</i> | 32 | <i>83.6</i> |
| 38 | 23 | <i>98.2</i> | 23 | <i>94.5</i> | 32 | <i>133.8</i> | 29 | <i>96.9</i> | 29 | <i>92.8</i> | 29 | <i>88.8</i> |
| 39 | 11 | <i>114.8</i> | 11 | <i>112.7</i> | 23 | <i>140.5</i> | 11 | <i>111.9</i> | 11 | <i>113.3</i> | 11 | <i>104.7</i> |

PFOA labels shown in bold, relative G values (in kJ/mol at 298.15 K) shown in italics

^a Estimated value using the corresponding gas–octanol correlation (M06-2X, B3LYP, PM6) or gas–water correlation (B97D) with details shown in Table S5 (some anions became decarboxylated during the gas-phase optimization)

method that most resembles the M06-2X distribution {0, 2, 4}. Next are LC- ω PBE {1, 2, 3} and B97D {1, 3, 2}. They are ranked as much more stable by B3LYP than by any of the other methods {2, 4, 0}. The results obtained for the

seven least branched PFOSs (PFOSs **83–89**), if arranged in groups {A, B, C} of 30 isomers, have a lot in common with the PFOA results. M06-2X {2, 5, 0} predicts these isomers to be much less stable than does B3LYP {7, 0, 0} [28].

Table 3 Average label identifying the 39 PFOA isomers (neutrals and anions) in each of the three stability groups in the gas phase

| | M06-2X/ 6-311++G(3df,3p) | | M06-2X/ 6-31++G(d,p) | | PM6 | | LC- ω PBE/ 6-31++G(d,p) | | B97D/ 6-31++G(d,p) | | B3LYP/ 6-31++G(d,p) | |
|----------------------|-----------------------------|-------|-------------------------|-------|---------|-------|-----------------------------------|-------|-----------------------|-------|------------------------|-------|
| | Neutral | Anion | Neutral | Anion | Neutral | Anion | Neutral | Anion | Neutral | Anion | Neutral | Anion |
| Group A ^a | 13 ^d | 12 | 13 | 12 | 14 | 12 | 19 | 14 | 19 | 17 | 22 | 19 |
| Group B ^b | 22 | 21 | 22 | 21 | 22 | 21 | 20 | 22 | 20 | 18 | 22 | 19 |
| Group C ^c | 24 | 27 | 24 | 27 | 23 | 27 | 21 | 24 | 21 | 23 | 16 | 22 |

^a Thirteen most stable PFOA isomers

^b Thirteen PFOA isomers with intermediate stability

^c Thirteen least stable PFOA isomers

^d Thirteen is the average label of the thirteen most stable neutral PFOAs at the M06-2X/6-31++G(d,p) level of theory (labels in this group: **24**, **5**, **13**, **16**, **3**, **33**, **12**, **6**, **2**, **28**, **27**, **1**, **4**; see Table 1)

Given that the PFOA label (**n**) used to identify these isomers is related to their degree of branching, we can use the average of the labels of the isomers in a particular group to get an overall idea of the performance of the different methods applied to the 39 PFOA isomers. The notation (**n**-Mean_(A), **n**-Mean_(B), **n**-Mean_(C)) denotes the average **n** value of the isomers in the groups A, B and C previously described. The larger the label **n**, the less branched the PFOA isomer in general, and the larger the aliphatic chain attached to the head group (see Table S1). However, there are groups of isomers that have very similar degrees of branching and differ only regarding the position of the same type of substituents, e.g., PFOAs **6–11**, **12–18**, **21–23**, **24–33** and **34–38**, but without doubt, the group of PFOAs **12–18** has a much greater degree of branching than PFOAs **34–38**. Table 3 displays this information for neutral and anionic PFOAs in the gas phase at different levels of theory. The same overall tendencies previously noticed for the reduced group of least branched PFOA isomers can be observed. The M06-2X distribution of average labels of neutral isomers per group (13, 22, 24) is very similar to the PM6 distribution (14, 22, 23), which indicates that these methods predict more branched isomers to be more thermodynamically stable than less branched ones. This stability ranking resembles that of alkanes. The opposite general prediction is made by B3LYP (22, 22, 16), while an intermediate situation is equally described by LC- ω PBE and B97D (19, 20, 21). Somehow similar M06-2X and B3LYP behaviors can be observed when examining the PFOSs data for the 89 neutral isomers in the gas phase when arranged in groups of 30 isomers, as previously described [28]. In the PFOSs case, the PM6 results (43, 47, 46) are in between the M06-2X (52, 51, 32) and B3LYP (66, 46, 23) results, perhaps because the PM6 optimized structures were obtained by another group [20] following a different procedure than the one followed in present and previous studies by our group [18, 28].

Interesting observations from Table 1 are that PFOA **24** is predicted as the most stable neutral species by all methods (except PM6, for which it comes up as the second most stable), while PFOA **11** appears as the least stable (PM6 predicts it as the third least stable). PFOA **24** is also predicted as the most stable for the anions (see Table 2) (except regarding PM6, for which it comes up as the third most stable).

Figures 1 and 2 display the gas-phase relative *G* values for neutral and anionic PFOAs, respectively, as calculated using the M06-2X, PM6, LC- ω PBE, B3LYP and B97D methods. Another point of view for comparisons comes from visualizing differences in relative *G* values between a particular method (M06-2X is the chosen one in this study) and the others. Tables S6 to S6c show the calculated differences in relative *G* values between M06-2X and other methods (PM6, LC- ω PBE, B3LYP and B97D) for neutral and anionic PFOAs in the three environments considered. Figures 3 and 4 display these values in the gas phase for neutral and anionic PFOAs, respectively. The M06-2X and B3LYP comparisons in *n*-octanol and water are also shown, and it can be seen how similar these curves are to that in the gas phase in both cases (neutrals and anions), a result in agreement with our previous discussion and the previous PFOSs study [28]. The mean absolute differences (MADs) of the calculated differences are 13.4–14.9 kJ/mol (see Table S6b). These values are 8.6–9.8 and 9.4–10.4 kJ/mol when comparing M06-2X with LC- ω PBE (see Table S6a) and with B97D (see Table S6c), respectively. The M06-2X, LC- ω PBE, B97D and B3LYP methods predict consistent average differences in relative *G* values for neutrals and anions in the three environments.

The main difference between Figs. 1 and 2 (and Figs. 3, 4) has to do with the PM6 calculations. The PM6 relative *G* values are larger than the M06-2X values in most cases (see Table S6). These two methods are closest in performance for neutral PFOAs with MADs of 8.8–11.0 kJ/mol in the three environments, a result somewhat in agreement

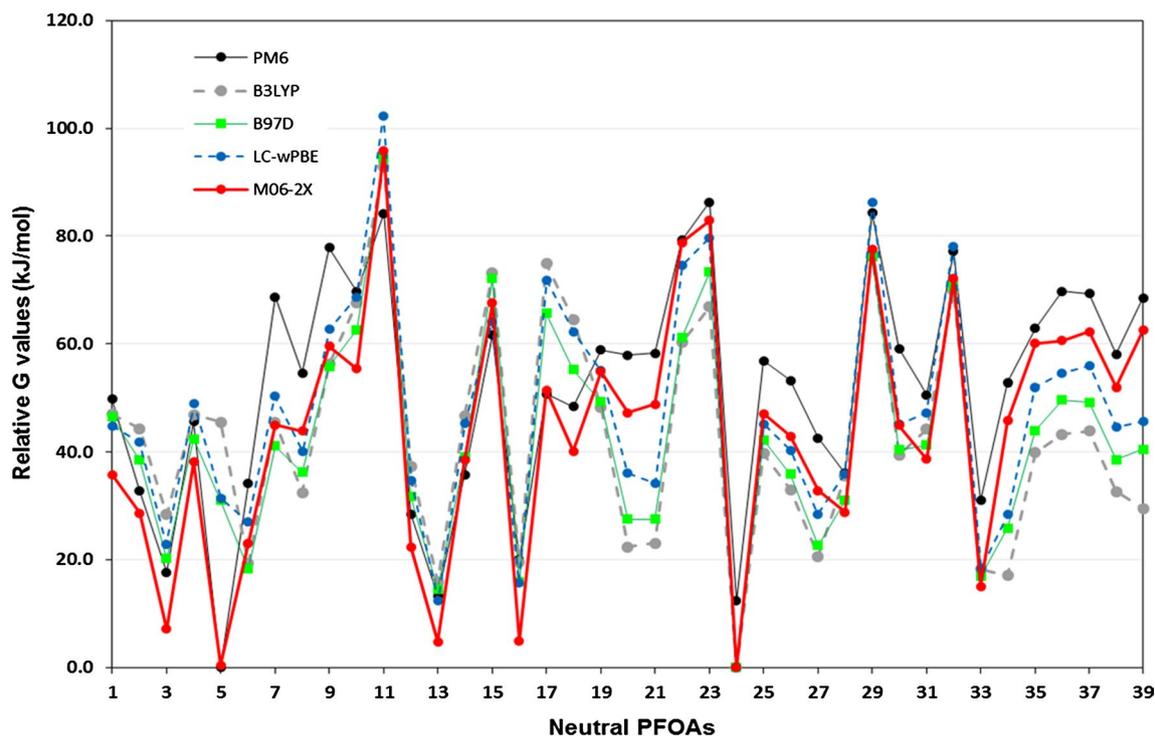


Fig. 1 Comparison of relative G values of neutral PFOA isomers in the gas phase using several methods

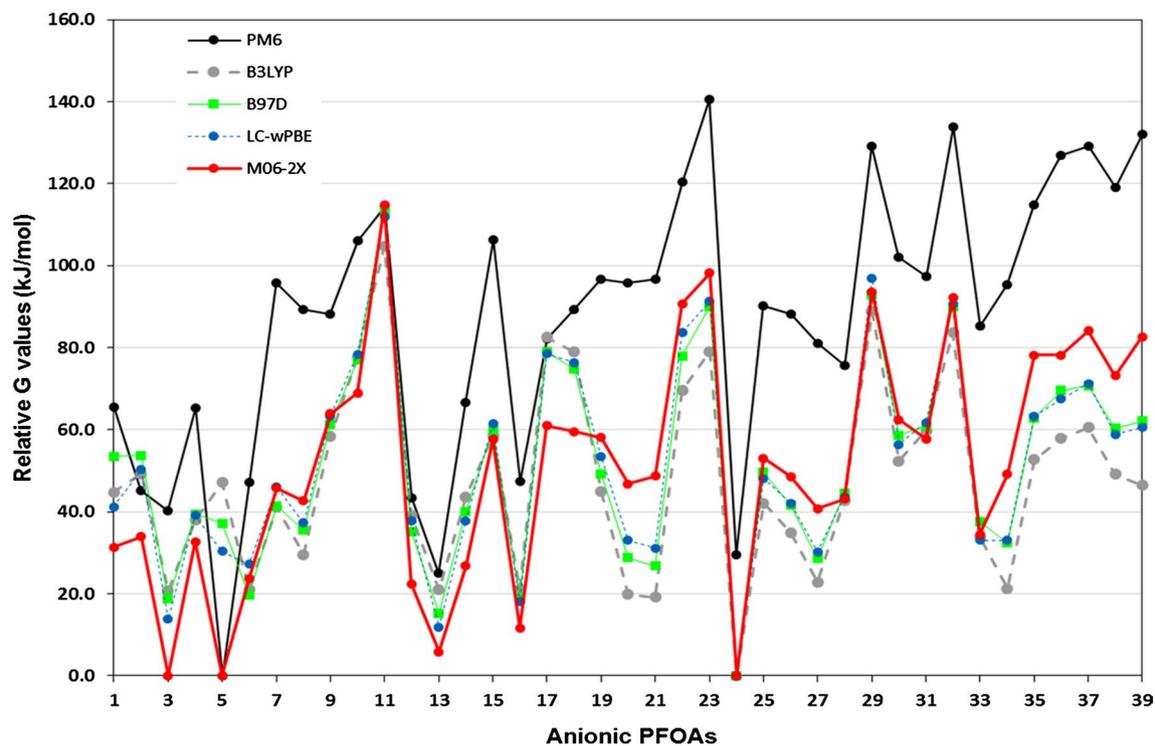


Fig. 2 Comparison of relative G values of anionic PFOA isomers in the gas phase using several methods

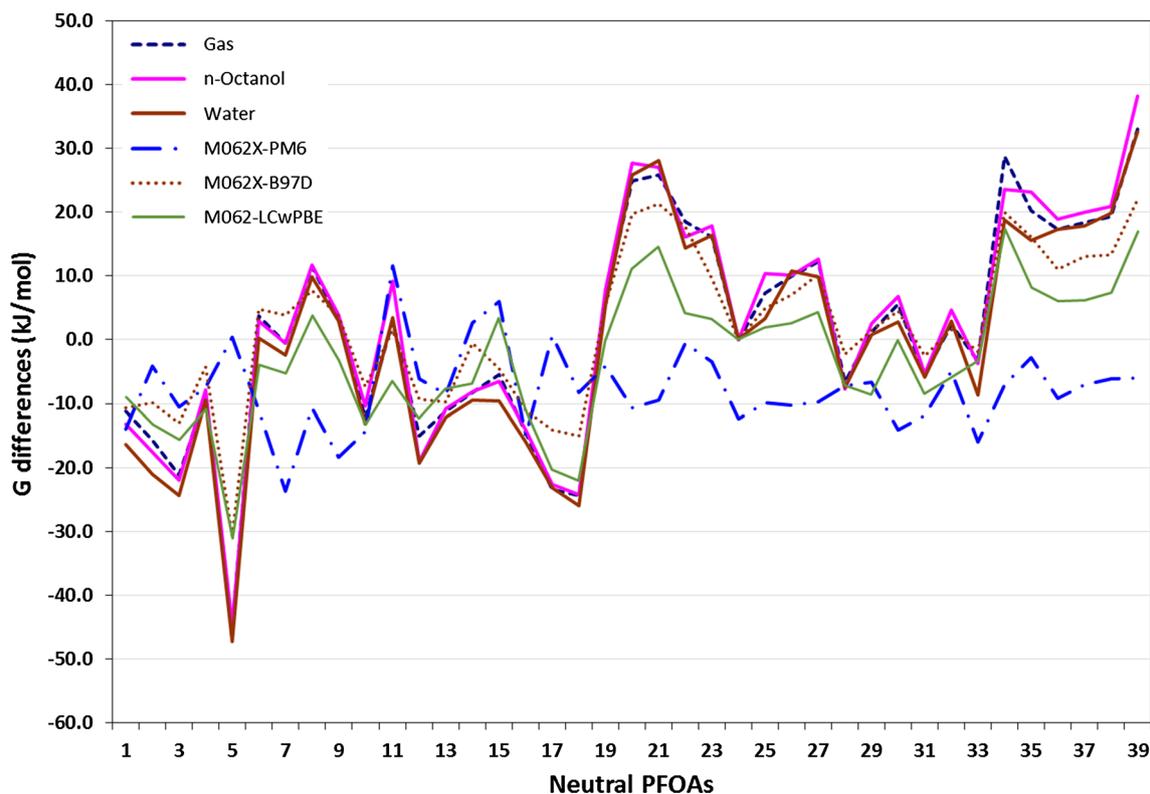


Fig. 3 Relative G differences between isomers of neutral PFOA calculated by M06-2X and B3LYP methods in three environments, shown along with gas-phase differences between M06-2X and LC- ω PBE, B97D and PM6 for comparison

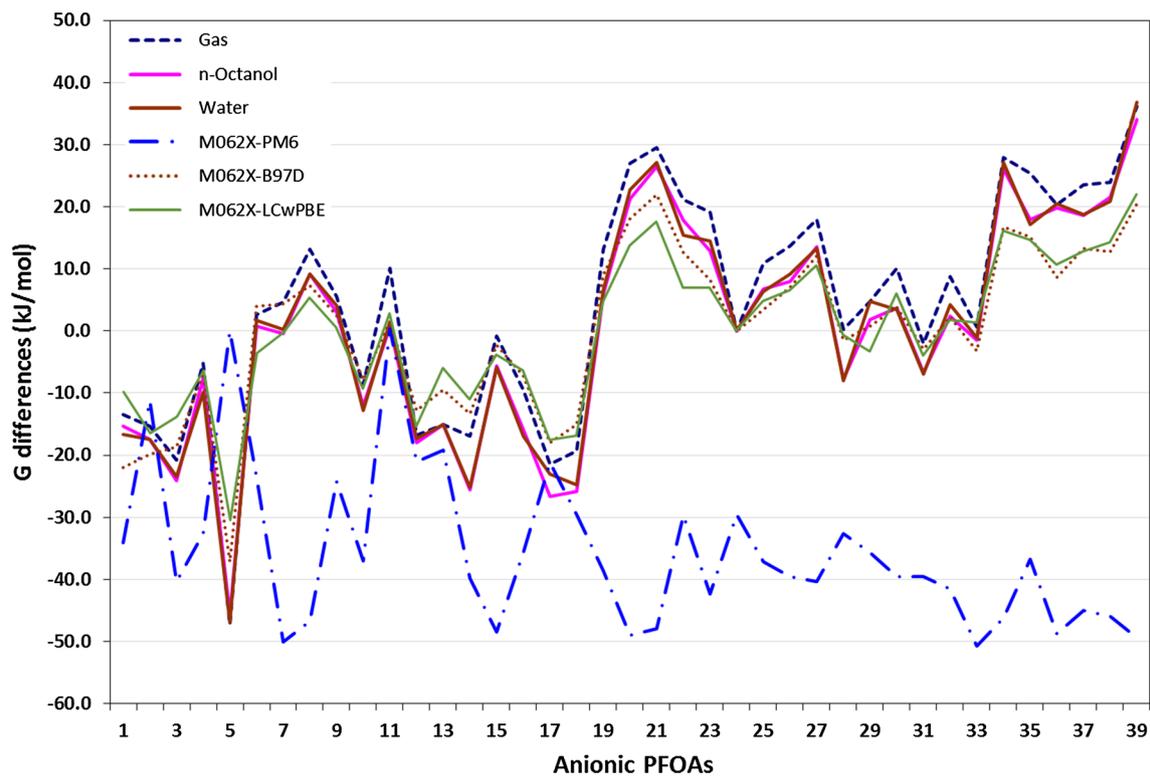


Fig. 4 Relative G differences between isomers of anionic PFOA calculated by M06-2X and B3LYP methods in three environments, shown along with gas-phase differences between M06-2X and LC- ω PBE, B97D and PM6 for comparison

with the previously mentioned observations by Rayne and Forest regarding the PFOSs **83–89** family [46]. However, when considering anions, the MAD values are significantly greater (24.7–35.4 kJ/mol) than the MADs between M06-2X and any of the other methods applied. Hence, the discussion that follows will ignore the PM6 results.

The LC- ω PBE, B97D and B3LYP methods tend to yield consistent, similar differences relative to the M06-2X calculations (see Figs. 1, 2, 3, 4), while the LC- ω PBE and B97D results fall between the B3LYP and M06-2X calculations. The calculated differences in relative G values of these three functionals relative to M06-2X reveal three regions, shown in Figs. 3 and 4. One region contains the most branched isomers (PFOAs **1–18**), which generally display lower relative G differences. The calculated differences generally increase in relation to the second (made of PFOAs **19–33**) and third regions (made of the linear and monomethyl isomers, PFOAs **34–39**). A similar general pattern was previously identified when comparing M06-2X and B3LYP relative G differences in PFOSs [28]. The B3LYP results for both neutral and anionic PFOAs show the largest differences with M06-2X. Hence, the next paragraph will deal briefly with their comparison for neutral PFOAs in the gas phase.

B3LYP relative G values are consistently higher than the M06-2X prediction (with the exception of PFOAs **6**,

8, **9** and **11**, see Figs. 1, 3 and Table S6b) for almost the first half of the PFOA family, from PFOS **1** to PFOS **18**, the most branched PFOAs. However, the opposite situation is observed (with the exception of PFOAs **28**, **31** and **33**) for the remaining, least branched PFOAs (PFOA **19**–PFOA **39**). As previously seen with the PFOS family [28], M06-2X consistently calculates more branched (least branched) isomers as more (less) thermodynamically stable than does B3LYP, which modestly aligns with the well-accepted (although not clearly understood and still in debate) idea that degree of branching is inversely related to thermodynamic stability. Figure 5 combines the gas-phase relative G values of neutral PFOAs and PFOSs [28] using both the M06-2X and B3LYP functionals. Additional discussion dealing with solvation methods and basis sets used can be found in Appendix A of the SI section.

3.2 Structure and relative stability of PFOA isomers: M06-2X predictions

The fact that some subgroups of isomers with an apparently similar degree of branching (e.g., PFOAs **6–11**, **12–18**, **21–23**, **24–33** and **34–38**) have different relative thermodynamic stabilities, impels us to explore the relationship between relative G -value trends and patterns

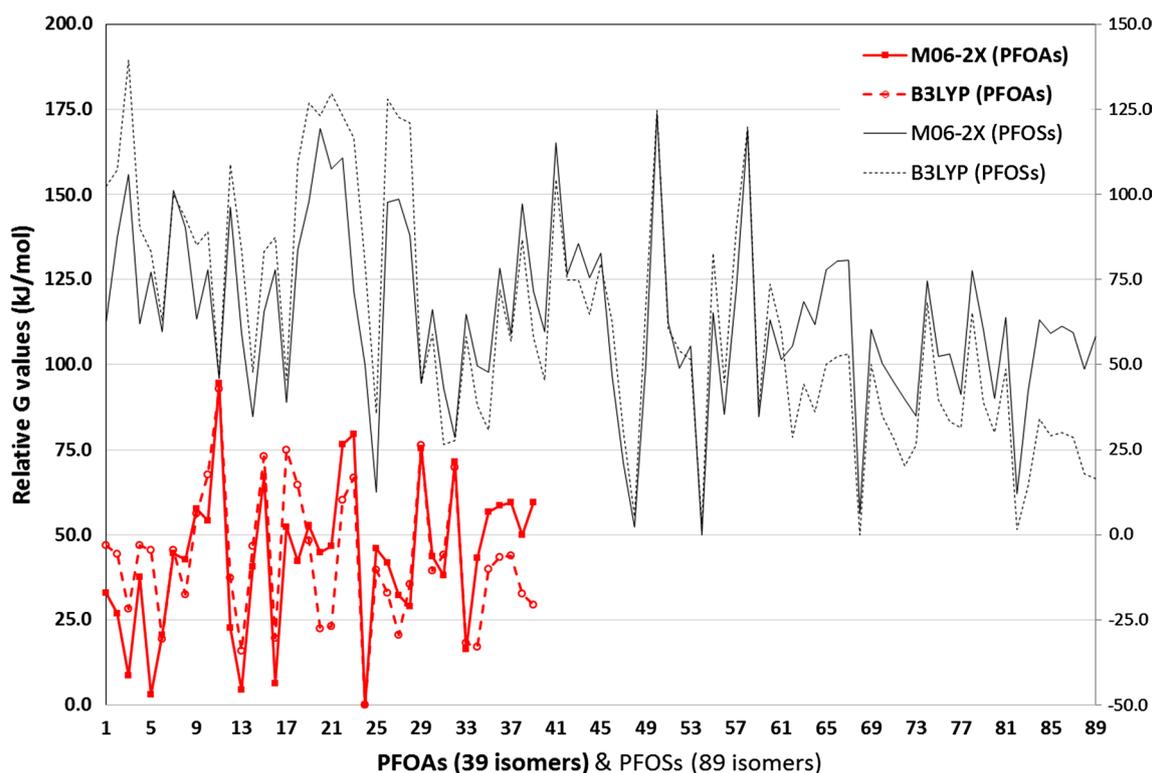


Fig. 5 Relative G values of neutral PFOA (left y-axis) and PFOS (right y-axis, taken from Ref. [28]) isomers in the gas phase using the M06-2X and B3LYP functionals

of substitution (indicated by the types and positions of the substituents) on the main chain that contains the head group ($-\text{COOH}$ or $-\text{COO}^-$) within this family of 39 isomers. These trends are qualitatively very similar for both neutrals and anions in the three environments under all tested methods. As previously mentioned, to facilitate data analysis, the 39 PFOA isomers are divided into three groups (A, B and C), each containing thirteen isomers. The following discussion will concentrate on

trends within groups A, B and C rather than on local differences between isomers, focusing on the M06-2X/6-311+G(3df,3p) results.

Table 4 combines the stability order of neutral PFOA isomers in the gas phase, the length of the main chain and the type of substitution (taking both type and positions of substituents into account) in each isomer. Table S8 displays the same information for anions. The averages of chain length (defined here as the average of the longest linear backbone

Table 4 Stability order and substitution pattern of the 39 neutral PFOA isomers in the gas phase (M06-2X)

| PFOA n n | Stability order | Chain length ^a | ACL ^b | Type of substitution (position of the substitution) | | | | | | | | | | | | | |
|----------------|--------------------|------------------------------|------------------|---|--------------------------------|---------------------------------|---------------------------------|-----------------------------------|---|--|---|---|---|---|--|--|---|
| | | | | CH ₃ (α) | CH ₃ (β) | CH ₃ (γ) | CH ₃ (δ) | CH ₃ (ϵ) | CH ₃ CH ₂ (α) | CH ₃ CH ₂ (β) | CH ₃ CH ₂ (γ) | (CH ₃) ₂ CH ₂ (α) | CH ₃ CH ₂ CH ₂ (α) | | | | |
| 24 | 1 | 5 | | 2 | | | | | | | | | | | | | |
| 5 | 2 | 3 | | 2 | 2 | | | | | | | | | | | | |
| 13 | 3 | 4 | | 2 | | 1 | | | | | | | | | | | |
| 16 | 4 | 4 | | 1 | | 2 | | | | | | | | | | | |
| 3 | 5 | 3 | | | 2 | | | | | 1 | | | | | | | |
| 33 | 6 | 5 | | | | | 2 | | | | | | | | | | |
| 12 | 7 | 4 | 3.9 | 2 | 1 | | | | | | | | | | | | |
| 6 | 8 | 4 | | 1 | | | | | | 1 | | | | | | | |
| 2 | 9 | 3 | | 1 | 1 | | | | | 2 | | | | | | | |
| 28 | 10 | 5 | | | 2 | | | | | | | | | | | | |
| 27 | 11 | 5 | | 1 | | | 1 | | | | | | | | | | |
| 1 | 12 | 3 | | | | | | | | 2 | | | | | | | |
| 4 | 13 | 3 | | | 1 | | | | | | | | | 1 | | | |
| 14 | 14 | 4 | | 1 | 2 | | | | | | | | | | | | |
| 31 | 15 | 5 | | | | 2 | | | | | | | | | | | |
| 18 | 16 | 4 | | | 1 | 2 | | | | | | | | | | | |
| 26 | 17 | 5 | | 1 | | 1 | | | | | | | | | | | |
| 8 | 18 | 4 | | | | 1 | | | | 1 | | | | | | | |
| 30 | 19 | 5 | | | 1 | | 1 | | | | | | | | | | |
| 7 | 20 | 4 | 4.7 | | 1 | | | | | 1 | | | | | | | |
| 34 | 21 | 6 | | 1 | | | | | | | | | | | | | |
| 25 | 22 | 5 | | 1 | 1 | | | | | | | | | | | | |
| 20 | 23 | 4 | | | | | | | | | | | | | | | 1 |
| 21 | 24 | 5 | | | | | | | | 1 | | | | | | | |
| 17 | 25 | 4 | | | 2 | 1 | | | | | | | | | | | |
| 38 | 26 | 6 | | | | | | 1 | | | | | | | | | |
| 19 | 27 | 4 | | | | | | | | | | | | 1 | | | |
| 10 | 28 | 4 | | | 1 | | | | | | | 1 | | | | | |
| 9 | 29 | 4 | | 1 | | | | | | | | 1 | | | | | |
| 35 | 30 | 6 | | | 1 | | | | | | | | | | | | |
| 36 | 31 | 6 | | | | 1 | | | | | | | | | | | |
| 37 | 32 | 6 | | | | | 1 | | | | | | | | | | |
| 39 | 33 | 7 | 5.0 | | | | | | | | | | | | | | |
| 15 | 34 | 4 | | 1 | 1 | 1 | | | | | | | | | | | |
| 32 | 35 | 5 | | | | 1 | 1 | | | | | | | | | | |
| 29 | 36 | 5 | | | 1 | 1 | | | | | | | | | | | |
| 22 | 37 | 5 | | | | | | | | | 1 | | | | | | |
| 23 | 38 | 5 | | | | | | | | | | 1 | | | | | |
| 11 | 39 | 4 | | | | 1 | | | | | 1 | | | | | | |

The position of the substitution is represented by α (carbon next to the $-\text{COOH}$ group, position one), β , γ , δ and ϵ (positions 2, 3, 4 and 5 after the $-\text{COOH}$ group, respectively); colored numbers represent the number of substitutions (yellow and clear background represents a substitution either in position α or at the tail, and blue represents a substitution elsewhere)

^a Length of the unsubstituted backbone

^b Average chain length

for each isomer, ignoring substituents) for the neutrals (anions) in groups A, B and C are 3.9, 4.7 and 5.0 (3.8, 4.5 and 5.2), respectively. These observations agree with previous discussions indicating that with M06-2X, the most branched isomers (with a smaller chain length) are in general ranked as more thermodynamically stable than the least branched isomers, in agreement with what is well accepted for alkanes.

The thirteen most stable (group A, see Table 1) neutral PFOAs in the gas phase are predicted to be $24 > 5 > 13 > 16 > 3 > 33 > 12 > 6 > 2 > 28 > 27 > 1 > 4$ (4 has relative

G values of 38.2, 39.1 and 38.6 kJ/mol in the gas phase, n -octanol and water, respectively, as shown in Table S2). The thirteen least stable (group C, see Table 1) neutral PFOAs in the gas phase are $11 < 23 < 22 < 29 < 32 < 15 < 39 < 37 < 36 < 35 < 9 < 10 < 19$ (11 has relative G values of 95.8, 97.7 and 95.1 kJ/mol in the gas phase, n -octanol and water, respectively, as shown in Table S2). Figures 6 and 7 display the structures of the nine most and least stable neutral isomers in the gas phase, respectively; relative G values are shown in parentheses.

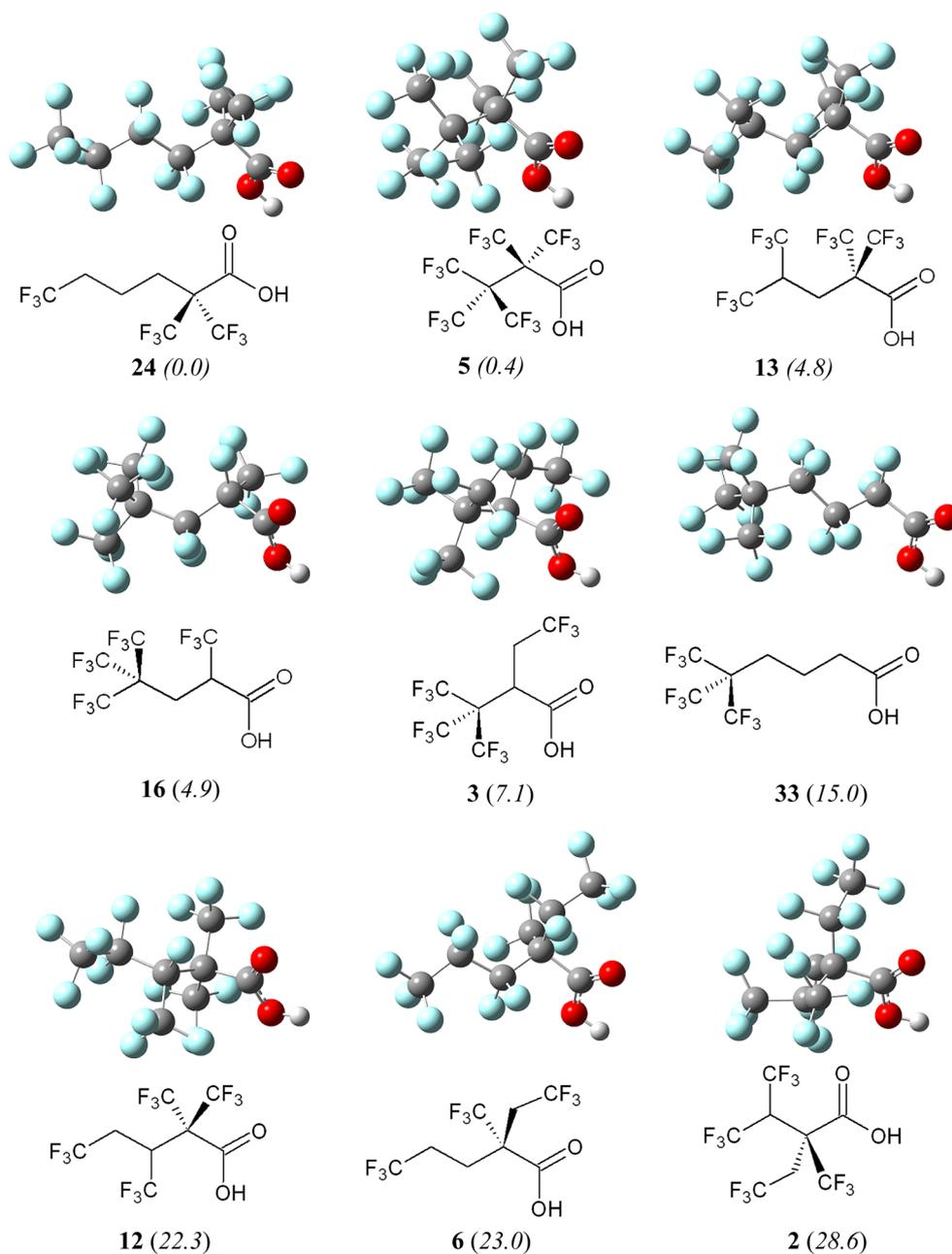


Fig. 6 Most stable gas-phase neutral isomers with their relative G values in kJ/mol at 298.15 K [M06-2X/6-311++G(3df,3p)] results; all main-chain carbons are perfluorinated but depicted as simple carbons for simplicity

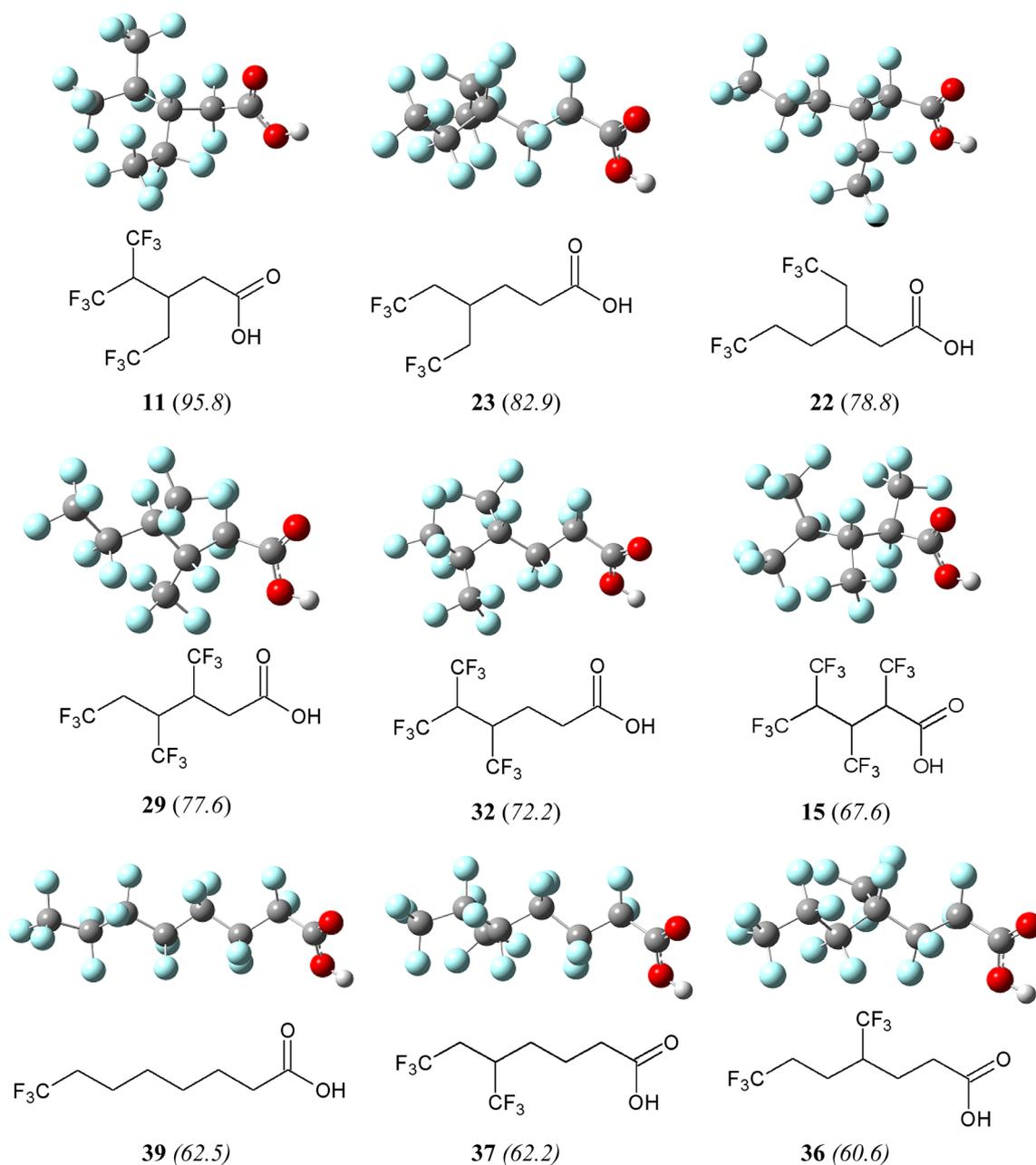


Fig. 7 Least stable gas-phase neutral isomers with their relative G values in kJ/mol at 298.15 K [M06-2X/6-311++G(3df,3p)] results; all main-chain carbons are perfluorinated but depicted as simple carbons for simplicity

There are no major differences when the most stable anions and neutrals in the three media considered are compared. The thirteen most stable anions (see Table 2) in the gas phase are $24 \approx 5 \approx 3 > 13 > 16 > 12 > 6 > 14 > 1 > 4 > 2 > 33 > 2$ (27 has relative G values of 40.7, 35.6 and 34.3 kJ/mol in the gas phase, n -octanol and water, respectively, as shown in Table S3), while the thirteen least stable are $11 < 23 < 29 < 3 < 22 < 37 < 39 < 36 < 35 < 38 < 10 < 9 < 30$ (11 has relative G values of 114.0, 104.0 and 100.0 kJ/mol in the gas phase, n -octanol and water, respectively, as shown in Table S3).

The most stable isomers (group A) have a predominance of (at least one but sometimes several) substituents (mostly methyl groups, but also ethyl and isopropyl) next to the head group (α position) or at the tail (see Fig. 6 and the yellow-colored cells shown in Tables 4 and S8). Because this type of substitution sometimes appears in isomers in groups B or C, it does not seem to significantly increase thermodynamic stability. However, substitutions that occur somewhere in the middle of the main chain (see Fig. 7 and the blue-colored cells shown in Tables 4 and S8)

predominate in the least stable group of isomers (group C). This type of substitution is almost absent in isomers of group A (PFOAs **12** and **28** are exceptions). Isomers with ethyl substitutions other than next to the head group or the tail (such as PFOAs **9**, **10**, **11**, **22** and **23**) belong to group C. The protobranching effect [53], which can describe differences in thermodynamic stability between structural isomers due to branching through electron correlation, could be used to explain the observed relative stability among the 39 PFOA isomers.

The general relationships previously mentioned between thermodynamic stability and patterns of substitution were also observed in the family of 89 PFOSs isomers [28]. Significant deviations from the helical conformation of the main chain due to the nature and position of substituents were identified as a feature present in the least stable PFOSs when studied with the B3LYP functional [18]. However, inspecting the M06-2X structures of PFOSs [28] and PFOAs does not seem to reveal any significant relationship between helical shape and stability.

A discussion on enthalpy and entropy contributions to the calculated standard Gibbs free energies of formation of the neutral PFOAs in the gas phase can be found in Appendix B of the SI section.

4 Conclusions

The relative thermodynamic stability of the family of 39 PFOAs isomers (neutrals and anions) has been studied in the gas phase, *n*-octanol and water using several methods (M06-2X, LC- ω PBE, B97D, B3LYP and PM6). The PM6 results closely resemble the M06-2X results for neutral PFOAs, while the discrepancies between these methods when studying the anions are huge. However, LC- ω PBE and B97D follow the M06-2X and B3LYP results qualitatively, and from a quantitative point of view, the LC- ω PBE and B97D results are somewhere in between the M06-2X and B3LYP stability results.

Various similarities with the PFOS study [28] applying the M06-2X and B3LYP functionals have been identified. The general stability trends are independent of the type of species (neutral or anionic) and the environment (gas phase, *n*-octanol or water). M06-2X seems to produce results that could be better trusted: more branched isomers tend to be predicted as more stable in general. These isomers are calculated to have lower M06-2X relative standard Gibbs free energies of formation than predicted with B3LYP, and the opposite is observed for the least branched isomers, which in a way resembles well-known trends for alkanes. The M06-2X results emphasize isomers with substituents close to the head group and tail ends of the molecule as a factor in stability, while substitution patterns on the middle

carbons tend to decrease stability within the PFOA family of isomers. The difference in stability for these compounds is mostly enthalpic.

The calculation of various physico-chemical quantities of PFOAs (acid dissociation constants and various partition coefficients), work currently in progress, will reveal any obvious structure–property patterns and help us to compare the thermodynamic data generated by the methods applied here.

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