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Measuring log K_{ow} coefficients of neutral species of perfluoroalkyl carboxylic acids using reversed-phase high-performance liquid chromatography[☆]

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ABSTRACT

Accurate measuring *n*-octanol/water partition coefficients (log K_{ow}) of perfluoroalkyl carboxylic acids (PFCAs) using experimental approach has been proven to be very difficult due to their special properties. The ionizable carboxyl groups in PFCAs make their log K_{ow} dependent on pH. In this study, the log K_{ow} values of neutral species of PFCAs ($C_{4\leq n\leq 14}$) were measured based on reversed-phase high-performance liquid chromatography (RP-HPLC) with the mobile phase pH varying in the range of 1.09–5.00. The relationship between log K_{ow} and retention times was established using some reference compounds (including agrochemicals, polycyclic aromatic hydrocarbons) with known log K_{ow} values, and then validated with alkyl fatty acids, which have similar chemical structures as PFCAs. The apparent log K_{ow} (i.e., log D_{ow}) of the C_{4-14} PFCAs were calculated based on their retention times using the established model, and they displayed a negative linear relationship with the mobile phase pH in the range of 1.09–4.00. Consequently, the log D_{ow} values were converted to the corresponding log K_{ow} values (1.05–7.19) based on the relationship of log $D_{ow} =$ log K_{ow} + pK_a − pH. The log K_{ow} increased with perfluorinated carbon chain length with a greater rate for C_4 to C_5 PFCAs than for C_{5-14} PFCAs.

1. Introduction

Perfluoroalkyl carboxylic acids (PFCAs) are a family of surfactants and additives used in various applications including electroplating, firefighting, surface treatment, because they repel water, oil and grease (Prevedouros et al., 2006; Wang et al., 2013). PFCAs are currently ubiquitous in the environment all over the world and much attention has been paid on their bioavailability, toxicity and fate, which are highly dependent on their physicochemical properties, particularly hydrophobicity (Cousins, 2015; Greaves et al., 2012; Jin et al., 2016; Wang et al., 2014; Zhang et al., 2013). Many previous studies reported that the partitioning between solid and aqueous phases, bioaccumulation, biomagnification of PFCAs were correlated with their hydrophobicity (Martin et al., 2004; Fang et al., 2014). The *n*-octanol-water partition coefficient (log K_{ow}) of a compound is usually obtained by a classical shake-flask or slow-stirring method, and widely applied to quantitatively describe its hydrophobicity (OECD, 1995; OECD, 2006). However, it is difficult to use these classical methods to measure the log K_{ow} coefficients of PFCAs due to their surface-active properties (Hidalgo and Mora-Diez, 2015). PFCAs are strong acids (p$K_a = 0.37–0.52$ for C_{4-14} PFCAs) with a carboxylic acid group at the end of perfluorinated carbon chain due to the strong electronegativity of fluorine atoms, and are mainly present as anionic ions in natural water system (SciFinder, 2017; Ding and Peijnenburg, 2013). In the meanwhile, the perfluorinated carbon chain makes PFCAs hydrophobic as well as lipophobic (Ding and Peijnenburg, 2013). As a result, many studies tried to estimate their log K_{ow} values using theoretical models such as COSMOtherm, ALOGPS, EPI Suite, etc., based on the molecular structure descriptors of compounds (Gomis et al., 2015; Nguyen et al., 2016; Wang et al., 2011a; Wang et al., 2011b; ALOGPS 2.1, 2005). However, these estimated log K_{ow} values of PFCAs based on different models vary within 2–3 logarithmic units (in Table 1). Moreover, the estimated log K_{ow} values might suffer poor accuracy due to inadequate database and lack of efficient validation (Liang and Lian, 2015). Besides the theoretical approaches, some

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Table 1
Comparison of log K_{ow} of PFCAs in literature and the present study.

Compounds	Reported log K_{ow}					Reported log k_w at pH 6.8	Reported log k_w at pH 2.2	log K_{ow} in the present study
	via ion-transfer cyclic voltammetry method	via RP-HPLC on C_{18} column	via calculation based on COSMOtherm	via ACD/Labs Software	via ALOGPS 2.1 program			
PFBA	−0.68	2.41	2.82	3.93	2.57	1.90	1.56	1.05 ± 0.12
PFPeA	n.m.	3.05	3.43	5.29	2.93	2.54	n.m.	3.19 ± 0.27
PFHxA	0.54	3.76	4.06	5.97	3.37	3.24	2.97	3.99 ± 0.23
PFHpA	1.15	4.44	4.67	6.86	3.93	3.92	3.27	4.40 ± 0.21
PFOA	1.76	5.00	5.30	7.75	4.29	4.48	3.92	4.67 ± 0.26
PFNA	2.37	5.46	5.92	8.64	4.55	4.93	4.61	5.02 ± 0.31
PFDA	2.98	5.94	6.50	9.53	4.85	5.41	5.41	5.44 ± 0.31
PFUnDA	3.59	6.50	7.15	10.42	5.24	5.97	5.9	5.65 ± 0.29
PFDoDA	4.20	7.09	7.77	11.31	5.58	6.56	6.27	6.03 ± 0.25
PFTriDA	n.m.[a]	7.62	8.25	12.19	5.80	7.10	n.m.	6.65 ± 0.20
PFTeDA	n.m.	n.m.	8.90	13.08	5.95	n.m.	6.6	7.19 ± 0.25
References	Jing et al., 2009	Hammer et al., 2017	Wang et al., 2011b	ACD/Labs V12.01, 2010	ALOGPS 2.1, 2005	Hammer et al., 2017	de Voogt et al., 2012	

[a] n.m. = not mentioned.

alternative experimental methods such as ion-transfer cyclic voltammetry (CV), which is usually suitable for ionic compounds, were applied to estimate log K_{ow} values of PFCAs (Jing et al., 2009). Due to ionization of the carboxyl groups in PFCAs, the measured log K_{ow} values were for the perfluoroalkyl oxoanions rather than the neutral species under their experimental conditions (Chen and Lin, 2016; de Maagd et al., 1999). Determination of K_{ow} values of the neutral species of PFCAs based on experiments has proven to be a tough task. Lack of these data is still troubling the researchers who are trying to understand the real difference between the neutral and anionic species. Despite the completely dissociated anions of PFCAs in most natural environmental matrices, their fate and partitioning in some tissues, such as the human stomach, in which the pH (1.0–2.5) is extremely low (Evans et al., 1988), also attracts researchers' attention (D'eon, 2012).

As an alternative method, chromatographic methods have been proven to be an effective technique to estimate log K_{ow} values of non-ionic compounds, especially homologues (Burkhard and Kuehl, 1986; Gluck et al., 1996; González et al., 1992; Hackenberg et al., 2003; Wiczling et al., 2014; Yu et al., 2008). The partition of a solute between stationary and mobile phases can simulate the *n*-octanol/water partition process (Kaliszan, 1981; Valko et al., 2001). Chromatographic methods have some advantages over classical methods, such as time- and material-efficient, having less impact from impurities associated with the target solute, and usability over a wide log K_{ow} range (generally from 0 to 6) (Kaliszan, 1987; OECD, 2014; Valkó, 1984). However, it has some limitations for measuring log K_{ow} values of ionizable organic compounds, given that the neutral (K_{ow}) and ionic species ($K_{ow(i)}$) of an ionizable compound have different hydrophobicities (Bhal et al., 2007; Pieńko et al., 2016). The mobile phase pH should be adjusted to 2 pH units lower than the compounds' pK_a to accurately measure the log K_{ow} values of the neutral species of monoacid compounds (Berthod et al., 1999; Kraak et al., 1986; Valkó et al., 1997).

For strong acidic compounds, such as trifluoroacetic acid and pentafluoropropionic acid (the pK_a of which approaches zero at 25 °C, and ranges from 0.19 to 0.54) (Henne and Fox, 1951; Moroi et al., 2001), reversed-phase high-performance liquid chromatography (RP-HPLC) method is not suitable for measuring their log K_{ow} values directly because extremely acidic conditions are necessary, which is harmful to HPLC stationary phases (Eadsforth and Moser, 1983). To extend the application of RP-HPLC method on measuring the log K_{ow} of ionic chemicals, Berthod (1995) and Berthod et al. (1999) found that there was a sigmoidal curve relationship between the apparent partition coefficient (log D_{ow}) and mobile phase pH, and thus log K_{ow} of the neutral species could be extrapolated using the sigmoidal curve so that extremely low pH conditions are not necessary. Usually, for a monoacid HA, the sigmoidal curve is consisted of three phases: I, The log K_{ow} is constant and representative of that of neural molecular species (HA) at pH lower than a fixed value; II, As the pH increases, the compound is partially dissociated ($HA \rightleftharpoons A^- + H^+$), and the apparent log K_{ow} (i.e., log D_{ow}) displays a negatively linear correlation with pH values; III, When the pH further increases, the compound is completely dissociated, and the observed log K_{ow} is also constant and representative of the ionic species (A^-). The log K_{ow} of the neutral species of HA could be directly obtained by adjusting the mobile phase pH to a low enough value to get the Phase I of the sigmoidal curve; or indirectly converted based on the negative linear relationship in Phase II. Although current stationary phases of RP-HPLC can tolerate very low or high pH conditions (Walter, 2004), it is very hard to use the direct method to obtain the log K_{ow} of the neutral species of strong acid compounds, such as PFCAs, which have predicted pK_a in the range of 0.37–0.52 (listed in Table S1), since extremely low pH is required. Accordingly, it is possible to measure the log K_{ow} of the neutral species of PFCAs by the indirect method (Claessens and van Straten, 2004; Jandera and Janás, 2017; Liang and Lian, 2015).

de Voogt et al. (2012) made efforts to predict hydrophobicity of selected PFCAs (C_4–C_{14}) using the RP-HPLC method. However, they only obtained the chromatographic hydrophobicity parameter, log k_w, and the lowest pH adopted was 2.2, under which PFCAs were partially or completely dissociated. Later on, the same group advanced their study to estimate the log K_{ow} values of PFCAs using a fragment-based approach using ammonia acetate as ion-pair reagent (Hammer et al., 2017). Thus, the log K_{ow} values obtained under their conditions might not represent hydrophobicity of the neutral species of PFCAs, but could be those of PFC-NH_4 (i.e., ammonium perfluorocarboxylates) (Berthod et al., 1999).

The objectives of this study were to apply RP-HPLC method using a strong acidic mobile phase to experimentally measure the log K_{ow} values of selected PFCAs with carbon chain length of 4–14. Certain reference compounds (including agrochemicals as neutral compounds, polycyclic aromatic hydrocarbons (PAHs)) with known experimental log K_{ow} coefficients (ranging from 1.13 to 7.17) were selected to establish a quantitative relationship between the log K_{ow} values and capacity factors under the same conditions. A group of anionic compounds, saturated fatty acids (SFAs), which have similar chemical structures as PFCAs, were used to test reliability of the model. Then, the retention times of PFCAs (C_4–C_{14}) were