Modeling the hydrolysis of the polymeric brominated flame retardants BC-58 and FR-1025

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Abstract

The SPARC software program was used to estimate the acid-catalyzed, neutral, and base-catalyzed hydrolysis rate constants for the polymeric brominated flame retardants BC-58 and FR-1025, as well as the hydrolyzable daughter products of BC-58. Relatively rapid hydrolysis of BC-58, producing 2,4,6-tribromophenol and tetrabromobisphenol A as the hydrolytically stable end products from all potential hydrolysis reactions, is expected in both environmental and biological systems with starting material hydrolytic half lives ($t_{1/2,hydr}$) ranging from less than one hour in marine systems, several hours in cellular environments, and up to several weeks in slightly acid fresh waters. Hydrolysis of FR-1025 to give 2,3,4,5,6-pentabromobenzyl alcohol is expected to be slower ($t_{1/2,hydr}$ less than 0.5 years in marine systems up to several years in fresh waters) than BC-58, but is also expected to occur at rates that will contribute significantly to environmental and in vivo loadings of this compound.

Keywords: brominated flame retardants, polymers, hydrolysis, environmental fate

A range of monomeric brominated flame retardants (BFRs) are employed commercially and have been reported in environmental samples [1][2]. The leaching of monomeric additive BFRs from consumer products, their subsequent presence in the environment, and associated toxicological concerns have led to increased usage of polymeric BFRs such as BC-58 (**1**; a phenoxy-terminated carbonate oligomer of tetrabromobisphenol A (TBBPA)) and FR-1025 (**2**) (Figure 1) [3][4]. Under mild thermal stress, Gouteaux et al. [4] found that various brominated benzene and phenol derivatives were released from these polymeric BFRs. However, there does not appear to be any information available on potential products resulting from other modes of physicochemical degradation for BC-58 and FR-1025. Thus, we have investigated their potential hydrolytic behavior in aqueous environmental and biological systems using the SPARC software program (http://ibmlc2.chem.uga.edu/sparc/; September 2009 release w4.5.1529-s4.5.1529). Hydrolytic degradation of polymeric BFRs such as BC-58 and FR-1025 is relevant for exposure conditions in landfills, in vivo transformations, ambient atmospheric exposure in sufficiently humid environments, and where smaller pieces of the polymeric substrate enter fresh and marine waters either intentionally via direct disposal, or indirectly through degradation and transport of the parent product.

Two potential terminal hydrolytic cleavage modes ('a' and 'b') are available for **1**, yielding 2,4,6-tribromophenol (**3**) and the terminal 2,4-dibrominated carbonate ester of the parent polymeric model (**4**) via pathway 'a', as well as the 2,4,6-tribromophenyl carbonate ester (**5**) and the terminal 2,4-dibromophenol of the parent polymeric model (**6**) via pathway 'b' (Figure 2). Compound **4** can be subsequently hydrolyzed to give **6** and carbonic acid (Figure 3). Compound **5** can also be hydrolyzed to **3** and carbonic acid (Figure 4). In addition to the terminal hydrolysis of **4** to give **6**, both **4** and **6** can be hydrolyzed at the adjacent internal carbonate ester linkage. Hydrolysis of **4** at the adjacent internal carbonate ester linkage gives the mono-carbonate ester of TBBPA (**7**) (pathway 'a' in Figure 5) and the di-carbonate ester of TBBPA (**8**) (pathway 'b' in Figure 5), as well as the corresponding **4** and **6** with loss of the terminal TBBPA moiety (termed **4**(n-1) and **6**(n-1), respectively). Compound **8** can be

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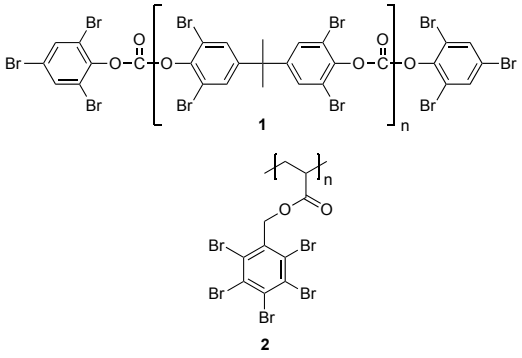

Figure 1: Structures of BC-58 (**1**) and FR-1025 (**2**).

hydrolyzed to **7**, which can subsequently be hydrolyzed to TBBPA (**9**) (Figure 6). Similarly, hydrolysis of **6** at the adjacent internal carbonate ester linkage can give **9** directly (pathway 'a' in Figure 7) or **7** (pathway 'b' in Figure 7), which can be subsequently hydrolyzed to **9**, as well as **4**(n-1) and **6**(n-1). Collectively, these hydrolytic pathways indicate that **3** and **9** are the final hydrolytically stable end products from the polymeric BFR BC-58. Hydrolysis of FR-1025 (**2**) gives 2,3,4,5,6-pentabromobenzyl alcohol (**10**) and the secondary alkylcarboxylic acid (**11**) (Figure 8).

Prior to estimating the hydrolytic rate constants for these degradation pathways of BC-58 and FR-1025, we validated the SPARC software program for the hydrolysis kinetics of related compounds. In a previous study, we validated SPARC estimated hydrolysis rate constants for a range of carboxylic acid esters [5]. Less experimental work has been conducted on the hydrolysis of carbonate esters. Stjerndahl and Holmberg [6] reported hydrolytic half-lives ($t_{1/2,hydr}$; but not individual rate constants for the acid [k_A] and base [k_B] catalyzed and neutral [k_N] mechanisms) for two linear and branched carbonate esters and the corresponding carboxylic acid esters (Table 1). Good agreement was found between the experimental and SPARC estimated $t_{1/2,hydr}$ for all compounds, with all errors within an order of magnitude (-20%, -33%, 762%, and -60%, respectively).

Ostergaard and Larsen determined k_A, k_N, and k_B values for a suite of carbonate ester model prodrugs with fatty acid structures (Table 2) [7]. Excellent agreement was obtained between the experimental and SPARC estimated k_A and k_B values. The $k_N$values reported by these authors are in poor agreement with the SPARC estimates and general structure-activity expectations. However, even at pH 7, where the contribution of the neutral hydrolysis mechanism is often maximized, this pathway is unlikely to play an important role in the hydrolysis of carbonate esters. Even with the large differences between the experimental and SPARC $k_N$values, SPARC $t_{1/2,hydr}$ estimates at pH

Table 1: Comparison of experimental and SPARC estimated hydrolytic half-lives ($t_{1/2,hydr}$) for the linear and branched carbonate esters and carboxylic acid esters at 20°C and pH 12 reported by Stjerndahl and Holmberg [6].

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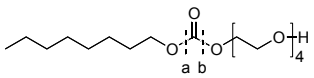
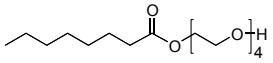
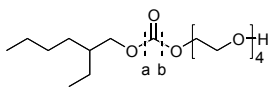
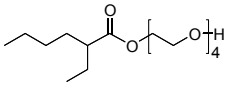
	21 min	16 min
	24 min	16 min
	13 min	112 min
	10 h	4.0 h

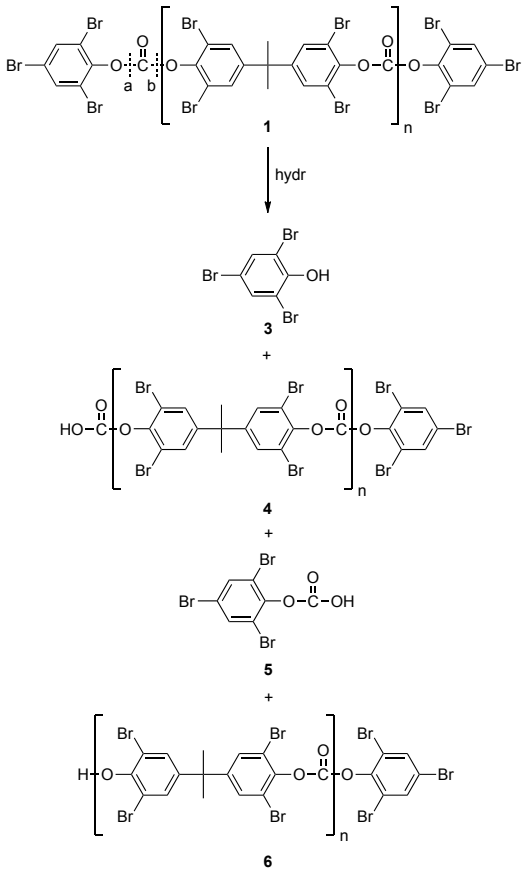


Figure 2: Terminal hydrolysis products for BC-58 (**1**).

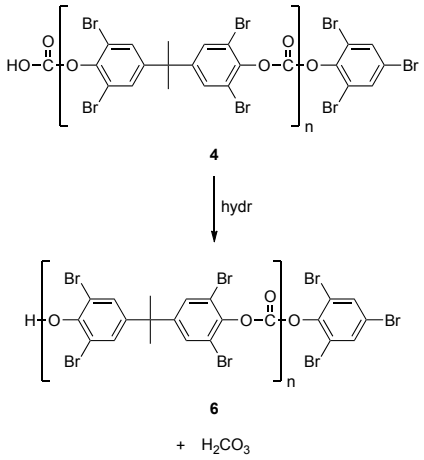


Figure 3: Terminal hydrolysis products for (**4**).

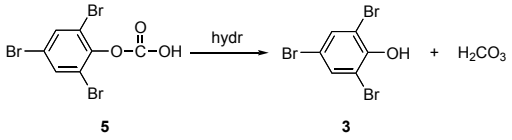


Figure 4: Hydrolysis products for (**5**).

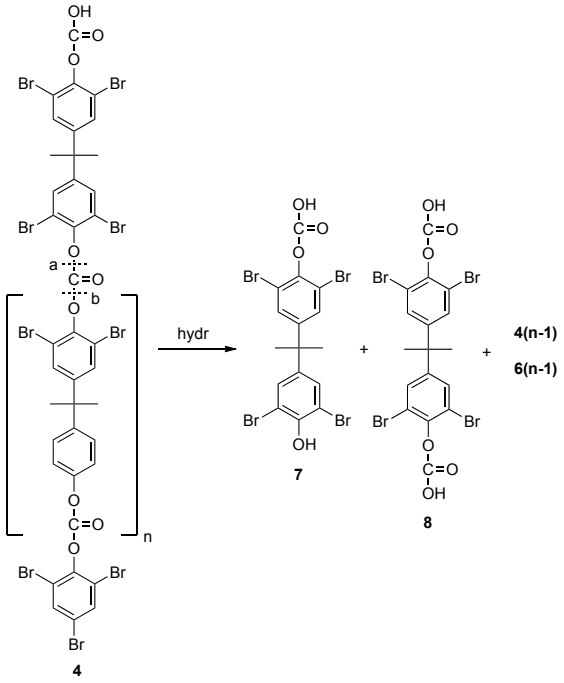


Figure 5: Internal hydrolysis products for (**4**).

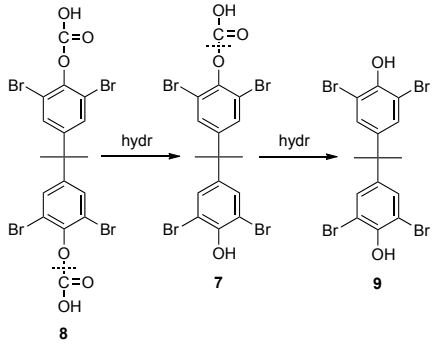


Figure 6: Hydrolysis products for (**8**).

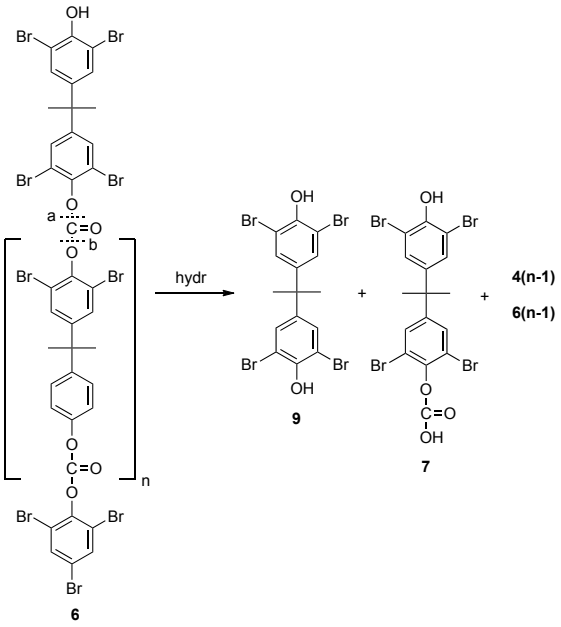


Figure 7: Internal hydrolysis products for (**6**).

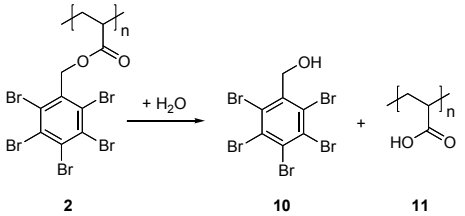
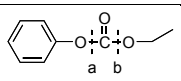
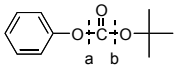
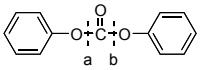
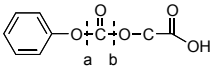
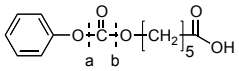
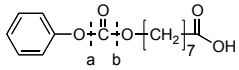
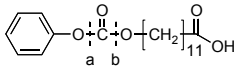
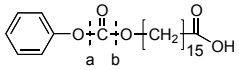
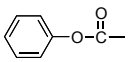


Figure 8: Hydrolysis products for (**2**).

Table 2: Comparison of experimental and SPARC estimated k_A, k_N, k_B, and $t_{1/2,hydr}$ (pH 7) for the carbonate ester model prodrugs with fatty acid structures and for phenyl acetate at 37°C reported by Ostergaard and Larsen [7].

	k_A		k_N		k_B		$t_{1/2,hydr}$ (pH 7)	
	expt[a]	SPARC	expt	SPARC	expt	SPARC	expt	SPARC
 a b	1.4×10^{-6}	a: 2.3×10^{-5} b: 6.9×10^{-5}	6.8×10^{-8}	a: 1.7×10^{-13} b: 2.0×10^{-17}	1.3	a: 0.7 b: 1.4	41 d	57 d
 a b	n/i[b]	n/i	n/i	n/i	0.03	a: 0.1 b: 0.3	n/a	n/a
 a b	n/a[c]	3.0×10^{-5}	1.2×10^{-5}	6.1×10^{-15}	13	18	n/a	4.4 d
 a b	n/a	a: 2.0×10^{-5} b: 4.7×10^{-5}	4.7×10^{-6}	a: 4.0×10^{-13} b: 4.6×10^{-16}	1.0	a: 1.3 b: 38	n/a	2.1 d
 a b	1.7×10^{-6}	a: 1.0×10^{-5} b: 5.7×10^{-5}	6.5×10^{-8}	a: 2.0×10^{-13} b: 1.9×10^{-17}	1.0	a: 0.6 b: 1.2	49 d	65 d
 a b	n/a	a: 1.9×10^{-5} b: 5.7×10^{-5}	n/a	a: 2.0×10^{-13} b: 1.9×10^{-17}	1.0	a: 0.6 b: 1.2	n/a	67 d
 a b	n/a	a: 1.9×10^{-5} b: 5.7×10^{-5}	n/a	a: 2.0×10^{-13} b: 1.9×10^{-17}	1.0	a: 0.6 b: 1.2	n/a	68 d
 a b	n/a	a: 1.9×10^{-5} b: 5.7×10^{-5}	n/a	a: 2.0×10^{-13} b: 1.9×10^{-17}	1.0	a: 0.6 b: 1.2	n/a	68 d
	3.2×10^{-4}	1.9×10^{-4}	3.9×10^{-8}	5.0×10^{-8}	4.1	1.6	18 d	38 d

[a] expt data acquired at μ=0.50M ionic strength. [b] not included in analysis as the mechanisms are thought to be different than for the other carbonate esters due to the t-butyl substitution. [c] not available.

7 for these compounds are in strong agreement with the available experimental values (only able to be reliably calculated where Ostergaard and Larsen [7] report k_A, k_N, and k_B values for a given compound), with $t_{1/2,hydr}$ (pH 7) errors ranging from 33% to 39% (factors of 1.3- to 1.4-fold). Overall, the validation results suggest that SPARC may reliably estimate the hydrolytic behavior of carbonate esters.

SPARC estimated k_A, k_N, and k_B values at 25°C for the polymeric BFR hydrolysis reactions shown in Figures 2 through 8, along with corresponding I-values, are provided in Table 3. With the exception of highly acidic conditions (pH less than 3 to 4), where the acid catalyzed mechanisms will begin to play a significant role, the base catalyzed mechanisms are expected to dominate under all relevant environmental and biological conditions. The estimated rate constants for these compounds are consistent with both the qualitative and quantitative structure-activity trends for carbonate/carboxylic acid ester hydrolysis rates reported in the literature, and in particular, the reduction in k_A and increase in k_B with electron withdrawing groups (EWGs) near the reaction center (the carbonyl moiety) [8].

With these estimated k_A, k_N, and k_B values, expected hydrolytic half-lives ($t_{1/2,hydr}$) can be calculated for pH values between 1 and 13 at 25°C using the following equations,

$$t_{1/2,hydr}=\ln 2/k_{hydr} \quad \ldots \quad (1)$$

$$k_{hydr}=k_A[H_3O^+]+k_N[H_2O]+k_B[OH^-] \quad \ldots \quad (2)$$

$[H_3O^+]=10^{-pH}$ ... (3)

$[OH^-]= 10^{-pK_w}/10^{-pH}$ ... (4)

where $[H_3O^+]$ and $[OH^-]$ are the concentrations of hydronium and hydroxide ions, respectively, and the concentration of water ($[H_2O]$) is assumed constant at 55 mol L^{-1} under all conditions (where k_N is given in units of s^{-1} throughout, we have included the concentration of water in the rate constant estimate).

Variations in $t_{1/2,hydr}$ as a function of pH at 25°C for the 11 pathways are provided in Figure 9. For compounds with more than one possible hydrolysis pathway (i.e., **1** ['a' and 'b'], **4** [terminal, internal 'a', and internal 'b'], and **6** ['a' and 'b']), changes in pH are not expected to alter the dominant mechanistic pathway except for **4** under highly acidic conditions (pH less than 3, where the terminal hydrolysis pathway will dominate). Compounds **1**, **4**, **5**, **6**, **7**, and **8** exhibit very similar hydrolytic behavior between pH 4 and 13. Compound **2** has a $t_{1/2,hydr}$ consistently several orders of magnitude higher than the other compounds over this pH range, reflecting the absence of EWGs proximate to the reaction center that would promote the dominant base-catalyzed hydrolysis mechanism. At pH 3, all compounds are expected to have comparable $t_{1/2,hydr}$ between 2000 and 7000 days (~6 to 20 years). The rapidly declining $t_{1/2,hydr}$ with increasing pH in near-neutral through basic solutions suggests BC-58 (**1**) and its daughter products will be efficiently hydrolyzed under these conditions. Exposure to strongly alkaline solutions (either as cleaning products/commercial treatments or waste treatment processes) will result in rapid hydrolysis of BC-58 and its relevant daughter products ($t_{1/2,hydr}$ ranging from about 1 minute at pH 10 down to the millisecond range at pH 13). FR-1025 (**2**) is expected to be more recalcitrant towards hydrolysis, maintaining a correspondingly much higher $t_{1/2,hydr}$ of 32 hours at pH 10 and 2 min at pH 13.

Estimated $t_{1/2,hydr}$ under representative environmental and in vivo conditions for compounds **1**, **2**, **4**, **5**, **6**, **7**, and **8** are shown in Table 4. In neutral, temperate freshwaters (pH 7, 15°C) and marine systems (pH 8.1, 15°C), BC-58 (**1**) and its daughter products are expected to have $t_{1/2,hydr}$ of less than one day. Corresponding rates are estimated to be about two orders of magnitude slower in mildly acidic temperate freshwaters (pH 5, 15°C). FR-1025 (**2**) is predicted to hydrolyze significantly more slowly than BC-58 (**1**) and its daughter products, with $t_{1/2,hydr}$ ranging from 120 days in temperate marine systems to several years in near-neutral fresh waters and up to several centuries in slightly acidic fresh waters. Rapid in vivo hydrolysis ($t_{1/2,hydr}$ of several hours) is predicted under cellular conditions (pH 7.4, 38°C) for BC-58 (**1**) and its daughter products. Conversely, FR-1025 (**2**) has a $t_{1/2,hydr}$ of 1.2 years in similar environments. The slow rates of acid-catalyzed hydrolysis for all compounds result in $t_{1/2,hydr}$ on the order 0.5 to 14 years in acidic regions of the gastrointestinal tract (pH 2, 38°C). Thus, hydrolysis of BC-58 (**1**) and its degradation products is expected to occur rapidly in the body, primarily in neutral and slightly alkaline regions, resulting in production of 2,4,6-tribromophenol (**3**) and TBBPA (**9**). FR-1025 (**2**) is expected to hydrolyze more slowly in vivo and will produce 2,3,4,5,6-pentabromobenzyl alcohol (**10**).

In slightly acidic through alkaline solutions, hydrolysis rates of **4**, **5**, **6**, **7**, and **8** are expected to be about 2 to 5-fold slower than that of the parent **1**, suggesting the steady-state accumulation of

Table 3: Estimated k_A, k_N, and k_B values and corresponding I-values at 25°C for compounds **1**, **2**, **4**, **5**, **6**, **7**, and **8**.

compound	k_A (L mol^{-1} s^{-1})	k_N (s^{-1})	k_B (L mol^{-1} s^{-1})	I^a_{AN}	I^b_{AB}	I^c_{NB}
1(a)	3.1×10^{-8}	4.2×10^{-11}	3.8×10^{2}	2.9	2.0	1.0
1(b)	3.3×10^{-8}	2.6×10^{-11}	1.5×10^{2}	3.1	2.2	1.2
2	1.1×10^{-6}	9.8×10^{-11}	6.0×10^{-2}	4.0	4.6	5.2
4-terminal	1.3×10^{-6}	1.7×10^{-11}	8.6×10^{1}	4.9	3.1	1.3
4-internal(a)	3.2×10^{-8}	5.9×10^{-13}	1.1×10^{2}	4.7	2.2	-0.3
4-internal(b)	3.6×10^{-8}	2.2×10^{-11}	1.6×10^{2}	3.2	2.2	1.2
5	1.3×10^{-6}	3.2×10^{-11}	2.0×10^{2}	4.6	2.9	1.2
6(a)	3.3×10^{-8}	5.8×10^{-13}	1.1×10^{2}	4.7	2.2	-0.3
6(b)	3.6×10^{-8}	2.2×10^{-11}	1.6×10^{2}	3.2	2.2	1.1
7	1.3×10^{-6}	1.7×10^{-11}	8.4×10^{1}	4.9	3.1	1.3
8	1.3×10^{-6}	1.7×10^{-11}	8.4×10^{1}	4.9	3.1	1.3

[a] $I_{AN}=\log(k_A/k_N)$. [b] $I_{AB}=1/2\times\log(k_A/k_Bk_w)$. $I_{NB}=\log(k_N/k_Bk_w)$.

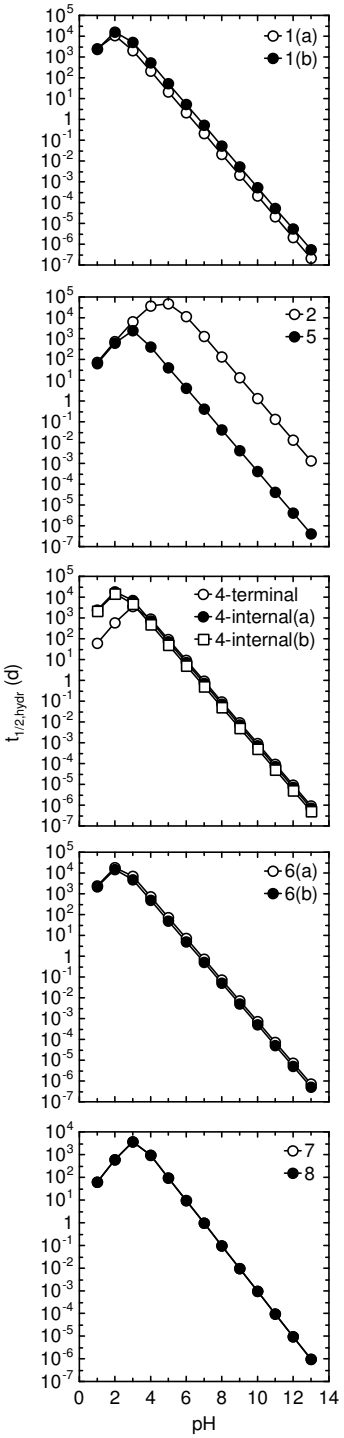


Figure 9: Variations in $t_{1/2,hydr}$ as a function of pH at 25°C for the hydrolysis of **1**, **2**, **4**, **5**, **6**, **7**, and **8**.

Table 4: Estimated $t_{1/2,hydr}$ under representative ambient environmental and in vivo conditions for compounds **1**, **2**, **4**, **5**, **6**, **7**, and **8**.

	25°C pH 7	15°C pH 5	15°C pH 7	15°C pH 8.1	38°C pH 2	38°C pH 7.4
1	5.1 h	17 d	4 h	0.3 h	13 y	3 h
2	3.6 y	212 y	4.1 y	120 d	200 d	1.2 y
4	12 h	41 d	10 h	1 h	158 d	6 h
5	10 h	38 d	9 h	43 min	164 d	4 h
6	12 h	41 d	10 h	47 min	14 y	6 h
7	23 h	90 d	22 h	1.7 h	158 d	10 h
8	23 h	90 d	22 h	1.7 h	158 d	10 h

partially hydrolyzed daughter products from BC-58. At pH 2 and below, hydrolysis rates of **1** will be competitive with or slower than those of its daughter products. At all pH values, hydrolysis of **1** by pathway 'a' is predicted to be about 2 to 3-fold faster than pathway 'b', indicating preferential formation of 2,4,6-tribromophenol (**3**) and the terminal 2,4-dibrominated carbonate ester of the parent polymeric model (**4**) as the major primary hydrolysis products. Compound **4** will then be relatively rapidly hydrolyzed to TBBPA (**9**) under most environmental and biological conditions.

Both 2,4,6-tribromophenol (**3**) and TBBPA (**9**) are well characterized from environmental and toxicological risk perspectives [9][10]. No information appears to be available on the expected biological or environmental fate of 2,3,4,5,6-pentabromobenzyl alcohol (**10**), but its SPARC estimated log P(octanol:water) is 5.1 with a pK_a of 13.2. Reductive debromination could result in lesser brominated derivatives that would be less likely to be retained in vivo. Enzymatic oxidation of the reactive benzylic position would yield 2,3,4,5,6-pentabromobenzoic acid (SPARC estimated pK_a of 1.0 and log D of 4.0 at pH greater than 4.5). We stress that the estimates provided herein assume effective freely dissolved behavior of all starting materials (i.e., surface area/wetting limitations to hydrolysis are absent), and therefore may overestimate the reactivity under actual field conditions. Experimental datasets on the hydrolytic behavior of these compounds are needed to validate or refute the SPARC predictions.

Efforts were made to obtain SPARC generated activation energies (E_a) for the k_A, k_N, and k_B values of **1**, **2**, **4**, and **5** by calculation of rate constants at 0°C and 100°C, analogous to the approach used in our prior work [5] on perfluorinated compounds that employed a previous version of SPARC (August 2007 release w4.0.1219-s4.0.1219). Apparently reliable E_a values were obtained for the acid-catalyzed (ranging from 75 to 80 kJ mol^{-1}) and neutral hydrolysis (ranging from 52 to 61 kJ mol^{-1}) mechanisms, however, negative E_a valu(from -3 to -16 kJ mol^{-1}) were predicted for **1**, **4**, and **5**, and a low value of 10 kJ mol^{-1} for **2**. In the context of the predicted substantial negative entropy of activation for formation of the tetrahedral intermediate in the base-catalyzed mechanism, and lack of clear literature support for negative E_a in the base-catalyzed hydrolysis of similar carboxylic acid or carbonate esters, we view the SPARC E_a estimates as unreliable. The absence of reliable predicted E_a values for **1**, **2**, **4**, and **5** prevents (at present) a more detailed kinetic analysis across a broader temperature range. In addition, we observed inconsistent rate constant predictions using SPARC at both temperature end members (i.e., repeated entries of the same SMILES molecular structure format occasionally yielded different results), further reducing confidence in the 0°C and 100°C values for the E_a calculations. We also examined whether the recent September 2009 update to SPARC (w4.5.1529-s4.5.1529) has led to a general E_a error for all carboxylic acid esters. Re-examination of our previously reported E_a values for the acid-catalyzed, neutral, and base-catalyzed hydrolysis mechanisms for fluorotelomer acrylates shows that the new September 2009 SPARC version (w4.5.1529-s4.5.1529) gives E_a values less than 2 to 3 kJ mol^{-1} different than the previous August 2007 SPARC release (w4.0.1219-s4.0.1219). As such, the apparent concerns regarding the SPARC estimated E_a values of compounds **1**, **2**, **4**, and **5** do not reflect a general change in SPARC between the 2007 and 2009 releases, but rather appear to be a specific issue with regard to the brominated compounds under investigation.

In conclusion, relatively rapid hydrolysis of the polymeric BFR BC-58 (**1**) is expected in both environmental and biological systems, producing 2,4,6-tribromophenol (**3**) and tetrabromobisphenol A (TBBPA; **9**). Hydrolysis of FR-1025 (**2**) is expected to be slower than BC-58, but is predicted to produce 2,3,4,5,6-pentabromobenzyl alcohol (**10**) at rates that may contribute significantly to environmental and in vivo loadings of this compound.

References

[1] M. Alaee, P. Arias, A. Sjodin, A. Bergman, An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release, Environ. Int. 29 (2003) 683–689.

[2] C. de Wit, An overview of brominated flame retardants in the environment, Chemosphere 46 (2002) 583–624.

[3] B. Gouteux, M. Alaee, G. Pacepavicius, D. Muir, Polymeric flame retardants: Potential sources for low molecular weight organobromine contaminants, BFR 2007 International Workshop on Brominated Flame Retardants (2007) Amsterdam, NL.

[4] B. Gouteux, M. Alaee, G. Pacepavicius, D. Muir, Polymeric brominated flame retardants: Are they a relevant source of emerging brominated aromatic compounds in the environment?, Environ. Sci. Technol. 42 (2008) 9039–9044.

[5] S. Rayne, K. Forest, Modeling the hydrolysis of perfluorinated compounds containing carboxylic and phosphoric acid ester functions and sulfonamide groups, J. Environ. Sci. Health A in press (2010) doi: 10.1080/10934520903538731.

[6] M. Stjerndahl, K. Holmberg, Hydrolyzable nonionic surfactants: Stability and physicochemical properties of surfactants containing carbonate, ester, and amide bonds, J. Colloid Interface Sci. 291 (2005) 570–576.

[7] J. Ostergaard, C. Larsen, Bioreversible derivatives of phenol. 2. Reactivity of carbonate esters with fatty acid-like structures towards hydrolysis in aqueous solutions, Molecules 12 (2007) 2396–2412.

[8] R. P. Schwarzenbach, P. M. Gschwend, D. M. Imboden, Environmental Organic Chemistry, John Wiley and Sons: New York, NY, U.S.A., 2003.

[9] A. Covaci, S. Voorspoels, M. Abdallah, T. Geens, S. Harrad, R. Law, Analytical and environmental aspects of the flame retardant tetrabromobisphenol-A and its derivatives, J. Chromatogr. A 1216 (2009) 346–363.

[10] P. Howe, S. Dobson, H. Malcolm, 2,4,6-Tribromophenol and Other Simple Brominated Phenols: Concise International Chemical Assessment Document 66., World Health Organization: Geneva, CH, 2005.