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Applications of 1,3,5-trimethoxybenzene as a derivatizing agent for quantifying free chlorine, free bromine, bromamines, and bromide in aqueous systems†

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Free chlorine and free bromine (*e.g.*, HOCl and HOBr) are employed as disinfectants in a variety of aqueous systems, including drinking water, wastewater, ballast water, recreational waters, and cleaning products. Yet, the most widely used methods for quantifying free halogens, including those employing *N*,*N*-diethyl-*p*-phenylenediamine (DPD), cannot distinguish between HOCl and HOBr. Herein, we report methods for selectively quantifying free halogens in a variety of aqueous systems using 1,3,5-trimethoxybenzene (TMB). At near-neutral pH, TMB reacted on the order of seconds with HOCl, HOBr, and inorganic bromamines to yield halogenated products that were readily quantified by liquid chromatography or, following liquid–liquid extraction, gas chromatography-mass spectrometry (GC-MS). The chlorinated and brominated products of TMB were stable, and their molar concentrations were used to calculate the original concentrations of HOCl (method quantitation limit (MQL) by GC-MS = 15 nmol L^{-1} = 1.1 μg L^{-1} as Cl_2) and HOBr (MQL by GC-MS = 30 nmol L^{-1} = 2 μg L^{-1} as Cl_2), respectively. Moreover, TMB derivatization was efficacious for quantifying active halogenating agents in drinking water, pool water, chlorinated surface waters, and simulated spa waters treated with 1-bromo-3-chloro-5,5-dimethylhydantoin. TMB was also used to quantify bromide as a trace impurity in 20 nominally bromide-free reagents (following oxidation of bromide by HOCl to HOBr). Several possible interferents were tested, and iodide was identified as impeding accurate quantitation of HOCl and HOBr. Overall, compared to the DPD method, TMB can provide lower MQLs, larger linear ranges, and selectivity between HOCl and HOBr.

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1. Introduction

Free chlorine and free bromine serve as disinfectants (or are generated *in situ*) in drinking water, wastewater, spas, pools, ballast water in ships, as well as in household and industrial cleaning products.[1–3] Free chlorine (*i.e.*, free available chlorine) describes all aqueous chlorine species in the +1 or 0 oxidation state (except chloramines).[4] Examples of free chlorine species include HOCl, ClO^-, Cl_2, and Cl_2O.[4,5] Solutions of free chlorine are commonly generated by dosing water with NaOCl(aq), $Ca(OCl)_2$(s), Cl_2(g), or stabilized chlorine, including various organic chloramines.[1,6] Free bromine (*i.e.*, free available bromine) refers to all aqueous bromine species in the +1 or 0 oxidation state (except bromamines).[7] Examples of free bromine species include HOBr, BrO^-, Br_2, BrCl, Br_2O, and BrOCl.[7] Free bromine can be produced *via* hydrolysis of liquid bromine (Br_2) or organic bromamines, as well as by *in situ* oxidation of bromide (*e.g.*, by HOCl, eqn (1)).[1,7,8]

$$HOCl + Br^- \rightleftharpoons BrCl + OH^- \rightleftharpoons HOBr + Cl^- \quad (1)$$

Ozone and hydrogen peroxide/peroxidase systems are also capable of oxidizing bromide into free bromine.[9,10] At pH 7, hypochlorous acid (HOCl, pK_a = 7.58 at 20 °C)[11] and hypobromous acid (HOBr, pK_a = 8.70 at 20 °C)[12] are the most abundant forms of free chlorine and free bromine, respectively.

Accurate quantification of free halogen residuals in disinfected waters is important for protecting human and environmental health. At doses on the order of 1–4 mg L^{-1}, free halogens are capable of inactivating pathogens in drinking water, wastewater, and recreational waters.[1] Higher concentrations (*e.g.*, 10 to >10 000 mg L^{-1}) of free chlorine are employed for disinfection processes associated with food service, medical/mortuary settings, and decontamination of biological warfare agents.[13–16]

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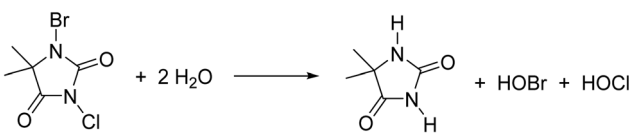
Monitoring of free halogens in disinfected waters is also important due to the propensity of free halogens to react with organic matter to form chlorinated and brominated disinfection byproducts (DBPs).[17,18] Brominated DBPs are generally more toxic than their chlorinated analogues,[19] which underscores the need for analytical methods capable of selectively quantifying free chlorine and free bromine as precursors of DBPs. Quantification of free halogens is also important in laboratory settings, including experiments investigating disinfection efficacy and DBP (trans)formation.[20–22] Such studies frequently employ solutions containing mixtures of free chlorine and free bromine generated *via* oxidation of bromide (*e.g.*, from NaBr) by excess free chlorine.[23] Free chlorine/bromine mixtures are also generated in waters (*e.g.*, spas and toilet tanks) disinfected with 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH, Scheme 1),[1] as well as in chlorinated solutions amended with salts (*e.g.*, NaCl) in which bromide is present as an impurity.[24]

Several methods exist for quantifying free halogen residuals in aqueous samples, including iodometric titration, amperometric titration, and, perhaps most commonly, colorimetric methods employing *N*,*N*-diethyl-*p*-phenylenediamine (DPD).[26,27] Methods of quantifying free chlorine involving chemiluminescent reactions[28] and quantum dots[29–31] have also been reported. None of these methods, however, are able to selectively and concurrently quantify free chlorine and free bromine in samples containing mixtures of these analytes.

To distinguish between free chlorine and free bromine, electron-rich aromatic compounds can serve as derivatizing agents (*i.e.*, probes) for these free halogens. Such methods leverage the propensity of aromatic compounds containing "activating" substituents (*e.g.*, hydroxy and methoxy) to form organohalides *via* electrophilic substitution.[32,33] When selecting among possible probes, several characteristics of the candidate probe and of its halogenated products need to be considered, including water solubility, nucleophilicity, stability, ease of analysis, molecular symmetry, acid/base behavior, and toxicity. Probes (and their halogenation products) must be sufficiently water soluble so as to preclude precipitation. Probes should demonstrate adequate nucleophilicity in reactions with free halogens so as to promote stoichiometric conversion of free halogens to the corresponding organohalides in reasonable time frames (ideally on the order of seconds). Candidate probes must generate stable halogenated products amenable to selective quantitation (*e.g.*, by liquid chromatography (LC) and/or gas chromatography (GC)) so that non-halogenated, chlorinated, and brominated probe species can be individually quantified. Probes with higher degrees of symmetry have fewer unique substitution positions, generate fewer products, and thereby simplify analysis of product mixtures compared to probes of lower symmetry. Acid–base behavior (if any) should be chosen so as to enhance (or, at a minimum, not diminish) the probe's performance in terms of water solubility, nucleophilicity, and ease of analysis. Importantly, probes should also be selected so as to minimize toxicity hazards.

Previous studies have demonstrated the ability of electron-rich aromatic compounds (including phenol, 2,6-dimethylphenol, 2,6-dichlorophenol, and 3,5-dimethyl-1*H*-pyrazole (DMPyr), Fig. 1) to serve as probes of free chlorine and/or free bromine *via* quantification of their halogenated products by LC or GC.[34–39] Notably, all of these compounds are ionizable, with greater nucleophilicity under alkaline conditions[40–44] whereas the electrophilicity of free chlorine and free bromine increases under acidic conditions.[45,46] Collectively, these factors can complicate pH-optimization efforts for electrophilic aromatic substitutions involving ionizable nucleophiles. Use of 2,6-dichlorophenol as a derivatizing agent for free bromine was also confounded by precipitate formation in systems disinfected with peracetic acid; precipitation was not observed in systems disinfected with free chlorine or ozone.[34] Recently, DMPyr was shown to provide an exceptionally low method quantitation limit (MQL = 18 pmol L^{-1}) as a probe for free bromine and other reactive bromine species in conjunction with LC-tandem mass spectrometry; however, the ability of DMPyr to concurrently quantify free chlorine and free bromine was not investigated.[39]

Herein, we propose a derivatization method wherein the aromatic ether 1,3,5-trimethoxybenzene (TMB) serves as a free halogen trap (Scheme 2). The water solubility of TMB (estimates ranging from 4.6 to 19 mmol L^{-1} at 25 °C)[47] is sufficient to permit its use as a derivatizing agent across a wide range of free halogen concentrations. The presence of three methoxy groups activates TMB toward electrophilic substitution.[33] The D_{3h} symmetry of TMB minimizes the number of possible regioisomeric products that can form *via* electrophilic aromatic substitution. The absence of proton donor/acceptor (*e.g.*, hydroxy or amino) groups renders the nucleophilicity of TMB



Scheme 1 Hydrolysis of 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH) yielding HOBr and HOCl. Whether BCDMH exists principally as 1-bromo-3-chloro-5,5-dimethylhydantoin or as 3-bromo-1-chloro-5,5-dimethylhydantoin has been discussed in the literature.[25]

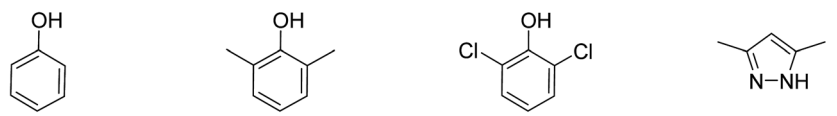
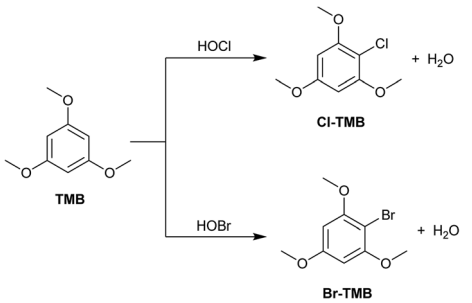


Fig. 1 Examples of aromatic compounds previously examined as probes of free chlorine and free bromine.[34–39]



Scheme 2 Derivatization of free chlorine (HOCl) and free bromine (HOBr) by TMB to give Cl-TMB and Br-TMB, respectively.

essentially invariant as a function of pH and permits quantification of TMB and its products by both LC and GC.

Previous studies demonstrated that TMB reacts with HOCl ($k_{TMB,HOCl}$ (20 °C) = 697 M^{-1} s^{-1}) and monochloramine (k_{TMB,NH_2Cl} (20 °C) ≈ 3 × 10^{-3} M^{-1} s^{-1}) to give 1-chloro-2,4,6-trimethoxybenzene (Cl-TMB).[5,21] Reaction of TMB with HOBr is more rapid ($k_{TMB,HOBr}$ (20 °C) = 3.35 × 10^6 M^{-1} s^{-1}) and yields 1-bromo-2,4,6-trimethoxybenzene (Br-TMB).[21] In waters containing mixtures of free bromine and ammonium ions (*e.g.*, recreational waters disinfected with free bromine or chlorinated wastewater containing bromide), bromamines can form.[48] The reactivity of TMB toward bromamines has not been previously characterized and is examined herein. Previous work in our laboratory demonstrated that TMB can be used to selectively quench and quantify free chlorine and free bromine;[21] however, these studies were limited to synthetic waters whose matrices were notably less complex than natural or recreational waters.

The purpose of this study is to develop methods for using TMB as a probe to (1) quantify residual free halogens in synthetic waters, chlorinated surface waters, municipal drinking water, and pool water; (2) monitor free halogens generated by BCDMH present in disinfecting tablets designed for spas; and (3) quantify bromide as an impurity in ostensibly bromide-free reagents upon oxidation by HOCl to HOBr. Overall, this work affords selective and sensitive methods for concurrent quantification of HOCl and HOBr that are amenable to either LC or GC analysis.

2. Experimental

All aqueous solutions were prepared using deionized water further purified with a NANOpure system (Thermo Scientific) to a resistivity ≥ 18 MΩ cm. Laboratory-grade sodium hypochlorite (NaOCl, ~6% w/w, Fisher Scientific) served as the source of free chlorine and was standardized *via* iodometric titration.[26] Working solutions of free chlorine were prepared fresh daily by diluting 6% w/w NaOCl solution with 11 mM NaOH and were standardized *via* UV-vis spectrophotometry (ε_{OCl^-} = 365.8 ± 0.7 M^{-1} cm^{-1}, T = 21 ± 1 °C, see ESI,† for more details). Additional reagents are described in Table S1 and Fig. S1–S4 of the ESI.†

Under most experimental conditions employed herein, TMB is added in sufficient excess of the total free halogen concentration so as to render di- and tri-halogenation of TMB negligible (≤0.3% of the initial concentration of TMB). Under such conditions, the TMB mass balance can be calculated as:

$$[TMB]_{tot} = [TMB] + [Cl\text{-}TMB] + [Br\text{-}TMB] \quad (2)$$

Measured concentrations of Cl-TMB and Br-TMB can be used to determine the residual free chlorine ($[HOCl]_{res}$) and free bromine ($[HOBr]_{res}$) concentrations, respectively, in the original samples.

$$[HOCl]_{res} = [Cl\text{-}TMB] \quad (3)$$

$$[HOBr]_{res} = [Br\text{-}TMB] \quad (4)$$

We note, however, that when free chlorine is dosed to solutions containing bromide, the mass balance of total free chlorine must account for the conversion of free chlorine into free bromine (eqn (1)). In such instances, the total (added) free chlorine ($[HOCl]_{tot}$) mass balance is given by:

$$[HOCl]_{tot} = [Cl\text{-}TMB] + [Br\text{-}TMB] \quad (5)$$

When free chlorine is added in excess of the initial bromide concentration, bromide can be stoichiometrically converted into free bromine and, upon addition of TMB, into Br-TMB. Thus, Br-TMB can serve as a useful surrogate for the bromide originally present in a sample treated with free chlorine (assuming that free bromine does not appreciably react with components of the system other than TMB). Additional considerations pertaining to mass balances are provided in the ESI.†

As described below, concentrations of TMB and its halogenated products can be determined by high-performance liquid chromatography (HPLC) and, following extraction into toluene, by gas chromatography-mass spectrometry (GC-MS). Analyte concentrations determined by these methods were corrected for any sample preparation steps resulting in dilution or preconcentration.

2.1 Comparison of free halogen quantification by TMB and DPD

The utility of quantifying HOCl and HOBr *via* derivatization with TMB was compared to the DPD method[26] using laboratory solutions of free chlorine/bromine as well as chlorinated swimming pool water. Laboratory solutions of free chlorine/bromine (25 mL) were prepared in 40 mL amber glass vials containing borate buffer (20 mM, adjusted to pH 6.0 or 7.0 using HNO_3), $NaNO_3$ (90 mM), NaCl (10 mM), and NaBr (0 or 40 μM). $NaNO_3$ served as an ionic strength adjuster. NaCl was added to maintain a uniform $[Cl^-]$, noting that the speciation of free chlorine and free bromine can vary with $[Cl^-]$.[49,50] After dosing with NaOCl (20 μM), reactors were incubated in a circulating water bath at 20.00 ± 0.01 °C for ~4 min to permit thermal equilibration and (for solutions amended with NaBr) bromide oxidation.

Pool water samples were obtained in 250 mL clear plastic bottles from an indoor swimming pool (volume ≈ 900 m^3) in Baltimore County, Maryland, whose treatment includes

filtration and UV irradiation followed by chlorination. Water samples were collected 0.3 m below the surface when no swimmers were present; the pool had not been occupied for 21 h prior to sampling. Samples were stored in a cooler chilled with ice during transit back to the laboratory and were analyzed for free chlorine/bromine within 1 h of sampling.

For TMB workup, triplicate aliquots of free halogen solutions (1.00 mL) were transferred to 4 mL amber glass vials pre-amended with methanolic TMB solution (0.15 mL at 2.62 mM to give a diluted TMB concentration of 342 μM). The 4 mL vials were capped and shaken manually for 10 s. After all samples were quenched with TMB, toluene (0.50 mL, containing 2-chlorobenzonitrile at 10.2 μM as the internal standard) was added to each 4 mL vial as the extraction solvent. Vials were capped and shaken manually for 30 s. After phase separation was re-established, an aliquot of the toluene phase (0.20 mL) was transferred to a 0.3 mL glass insert seated inside an amber glass 2 mL autosampler vial. The 2 mL vials were capped with a screw-top plastic cap fitted with a PFTE-lined septum. Concentrations of TMB and its halogenated products in toluene extracts were determined using GC-MS (see ESI, Table S2,† for additional GC-MS method details). Example GC-MS chromatograms are shown in Fig. S5.†

For DPD workup, triplicate aliquots of free halogen solutions (3.9 mL) were added to amber glass vials (capacity = 4.4 mL) pre-amended with 0.2 mL of DPD indicator solution and 0.2 mL of phosphate buffer (0.5 M, pH 7.0). Vials were capped, shaken manually for 10 s, and allowed to stand for 30 s to permit development of a magenta color. Absorbance measurements at 515 nm were obtained using a Cary 60 UV-vis spectrophotometer following established methods.[26]

2.2 Assessing the reactivity of TMB with aqueous combined bromine

The reactivity of TMB towards inorganic combined bromine (*i.e.*, bromamines) was assessed using batch reactors. Reactor solutions (total volume = 25 mL) were prepared in 40 mL amber glass vials containing borate buffer (20 mM, pH 8.0), $NaNO_3$ (90 mM), NaCl (10 mM), and NaBr (100 μM). Reactors were incubated at 20.00 ± 0.01 °C in a circulating water bath for 4 min prior to dosing with NaOCl, which was added to the reactor vial to achieve a final concentration of 150 μM. The vial was capped, shaken manually for 10 s, and returned to the water bath for 5 min to allow bromide oxidation to HOBr by the 1.5 molar excess of free chlorine. Following this equilibration period, NH_4Cl was added (as a source of $NH_4^+ + NH_3$) to the reactor vial to achieve a final concentration of 300 μM. The vial was capped, shaken manually for 10 s, and returned to the water bath for 2 min to permit bromamine formation *via*:[48]

$$\begin{aligned} &NH_3(aq) + HOBr_{tot}(aq) \rightleftharpoons NH_2Br(aq) + H_2O \\ &\log K_{eq} = 9.3 \pm 1.1 \\ &k_{HOBr} = (5.5 \pm 0.5) \times 10^7 \ (24 \pm 2\ ^\circ C) \end{aligned} \quad (6)$$

At $t = 0$, a spike of methanolic TMB solution (0.150 mL at 100 mM) was added to the reaction solution such that $[TMB]_o$ in the reaction solution was 630 μM. Aliquots (0.800 mL) were obtained periodically and transferred to 4 mL amber glass vials pre-amended with aqueous $Na_2S_2O_3$ (0.075 mL at 10 mM) to quench residual halamines.

After all samples were quenched, liquid–liquid extractions as described in Section 2.1 were performed, using 0.80 mL of toluene containing 2-chlorobenzonitrile (10.2 μM) as the internal standard. TMB and halogenated products were analyzed *via* GC-MS (Table S2†).

2.3 Quantification of free halogens in chlorinated surface waters and drinking water

The ability of TMB to derivatize free halogens was investigated in surface waters amended with free chlorine and in chlorinated municipal tap waters. Surface water samples were collected from four different water bodies: the Loch Raven Reservoir (freshwater, near Timonium, Maryland, on 6 Jun 2017), the Susquehanna River (freshwater, near Havre de Grace, Maryland, on 6 Jun 2017), the Chesapeake Bay (brackish, at Cove Point, Maryland, on 5 Jun 2017), and the Atlantic Ocean (at Bethany Beach, Delaware, on 6 Jun 2017). A summary of water quality metrics for each water source is provided in Table S3.† Surface water samples were obtained approximately 0.3 m below the water surface and within 3 m of the shore in 2 L clear glass bottles with plastic caps. The 2 L bottles were pre-rinsed with free chlorine followed by 18 MΩ cm water prior to sampling. At each sampling location, bottles were rinsed with surface water several times before samples were obtained (volume = 2 L, collected in triplicate). Samples were stored in a cooler chilled with ice-packs during transit. Upon arrival at Towson University, samples were stored at 4 °C prior to use.

Aliquots of surface water (25.0 mL) were added to 40 mL amber glass vials and placed in a recirculating water bath at 20.00 ± 0.01 °C for 4 min to permit thermal equilibration. Vials containing Loch Raven Reservoir water and Susquehanna River water, respectively, were amended with NaBr (150 μM) to normalize bromide content between the two waters. Vials were dosed with NaOCl (100 μM), capped, and shaken manually for 10 s before being returned to the water bath. Triplicate aliquots (0.90 mL) were obtained at each sampling time over 1 h and added to vials pre-amended with TMB (0.332 mL at 2.60 mM in methanol). Vials were capped and shaken manually for 10 s to facilitate derivatization. After all samples were derivatized, similar liquid–liquid extractions as described in Section 2.1 were performed, using 1.00 mL of toluene containing 2-chlorobenzonitrile (10.2 μM) as the internal standard. TMB and its halogenated products were analyzed *via* GC-MS (Table S2†).

Municipal drinking water samples were obtained from three locations on Towson University's main campus in Towson, Maryland (Table S4†). Samples were stored in a cooler chilled with ice-packs during transit back to the laboratory and were treated with TMB within 1 h of sampling. Water samples were obtained in 125 mL clear plastic bottles covered in aluminum foil. Aliquots (1.00 mL) were added to clear glass 2 mL HPLC autosampler vials pre-amended with TMB solution (0.238 mL at 2.60 mM in methanol) and quenched at room temperature (21

± 1 °C). Vials were capped and shaken manually for 10 s. Concentrations of unreacted TMB and Cl-TMB were determined using HPLC with a diode array detector (DAD). Additional method details are available in the ESI (Fig. S6†).

2.4 Determination of trace bromide in laboratory salts and acids

The ability of TMB to react with free bromine to generate Br-TMB was utilized to detect trace bromide impurities in 20 reagents, including salts, acids, and bases (Table S5†). Solutions (25.0 mL) of each reagent were prepared in 40 mL amber glass vials with initial concentrations ranging from 0.31 to 1.4 M (Table S5†). An aliquot of a NaOCl primary dilution (0.45 mL at 7.5 mM) was added to each 40 mL vial; vials were capped, shaken manually for 10 s, and allowed to stand for 5 min at room temperature (21 ± 1 °C) to permit bromide oxidation. Aliquots from these vials (0.700 mL) were transferred to 4 mL amber glass vials containing methanolic TMB solution (0.150 mL at 2.60 mM). The 4 mL vials were capped, shaken manually for 30 s, and allowed to stand for 2 min to facilitate derivatization.

To assess whether nominally bromide-free salts can interfere with quantification of bromide, experiments were performed in which 25 mL solutions were prepared in 40 mL amber glass vials containing NaBr (30.0 μM, obtained from a 1003 mg Br^- L^{-1} certified standard solution) and a second (background) salt, typically at 1.0 M (Table 1). Examined background salts included NaCl (99.999%), $NaHCO_3$ (99.7+%), Na_2SO_4 (99.9%), $NaNO_3$ (99.0+%), and $NaI \cdot 2H_2O$ (99+%). To each 25 mL solution containing a background salt was added NaOCl (0.20 mL at 12.5 mM). Vials were capped, shaken manually for 10 s, and allowed to stand at room temperature (21 ± 1 °C) to permit bromide oxidation. Control experiments were performed with each background salt in the absence of added NaBr. Three aliquots (0.800 mL each) were obtained from each salt + NaOCl solution and transferred to individual 4 mL amber glass vials, which were pre-amended with TMB (0.175 mL at 2.24 mM in methanol). The 4 mL vials were capped, shaken manually for 30 s, and allowed to stand for 2 min to facilitate reaction of TMB with free bromine and residual free chlorine.

After all samples were derivatized, similar liquid–liquid extractions as described in Section 2.1 were performed, using 0.80 mL of toluene containing 2-chlorobenzonitrile (10.2 μM) as the internal standard. TMB and halogenated products were analyzed *via* GC-MS (Table S2†).

2.5 Quantification of halogens generated by spa disinfecting tablets

The ability of TMB to serve as a probe of halogens was assessed using simulated spa solutions treated with disinfecting tablets containing BCDMH. Simulated spa solutions (30 L) were prepared in a 39 L clear glass aquarium containing municipal (chlorinated) tap water. Simulated spa solutions were left open to the air and incubated in a circulating water bath at 39.0 ± 0.1 °C for 1 h prior to dosing with one spa disinfecting tablet (Clorox spa brominating tablet, 28 g, 96.0 wt% BCDMH). After tablet addition (at $t = 0$), solutions were gently stirred manually for 20 s. Aliquots (1.00 mL) were obtained prior to addition of a disinfecting tablet and hourly thereafter over 8 h. Prior to each sampling event, solutions were stirred manually for 10 s. Four aliquots were obtained at each time point; two aliquots were added to separate 2 mL vials pre-amended with TMB (0.14 mL at 5.56 mM in methanol), and two aliquots were added to separate 2 mL vials pre-amended with 2,6-dichlorophenol (0.13 mL at 6.04 mM in methanol). Following addition of an aliquot, the 2 mL vials were capped and shaken manually for 10 s. After all samples were derivatized, TMB, 2,6-dichlorophenol, and their halogenated products were quantified by HPLC-DAD (see ESI† for method details).

3. Results and discussion

Many traditional methods of quantifying free halogens are unable to distinguish between free bromine and free chlorine.[26,51] The principal goal of this work was to design methods for selectively quantifying free chlorine and free bromine in a variety of aqueous systems *via* derivatization with TMB. As is common in the disinfection literature, mass-based

Table 1 Experimental systems investigating the effects of background salts on quantification of bromide as Br-TMB following oxidation by NaOCl

System #	Background salt	$[\text{Background salt}]_o$ (mM)	$[NaBr]_o$ (mM)	$[NaOCl]_o$ (mM)
1a	None	Not applicable	0.0300	0.100
1b			None added	
2a	NaCl	1.00×10^3	0.0300	0.100
2b			None added	
3a	$NaHCO_3$	1.00×10^3	0.0300	0.100
3b			None added	
4a	Na_2SO_4	1.00×10^3	0.0300	0.100
4b			None added	
5a	$NaNO_3$	1.00×10^3	0.0300	0.100
5b			None added	
6a	$NaI \cdot 2H_2O$	0.0300	0.0300	0.100
6b		0.200	0.0300	
6c		0.200	None added	

Table 2 Comparison of method detection limits (MDL), method quantitation limits (MQL), and instrument upper limits of linearity (LOL) of selected free halogen quantification methods[a]

Analyte	Method	MDL (μM)	MQL (μM)	LOL (μM)	Ref.
Free chlorine	Cl-TMB by HPLC[b]	1.4	5	600	Current work
	Cl-TMB by GC-MS[b]	0.010	0.03	120	Current work
	2,4,6-Trichlorophenol by HPLC[c]	5	18	600	Current work
	Cl-DMP by GC-MS[d]	8×10^{-4}	0.003	59	37
	DPD[e]	0.06	0.19	70	51
Free bromine	Br-TMB by HPLC[b]	1.0	3	600	Current work
	Br-TMB by GC-MS[b]	0.017	0.06	100	Current work
	4-Bromo-2,6-dichlorophenol by HPLC[c]	6	19	600	Current work
	Br-DMP by GC-MS[d]	4×10^{-4}	0.0014	11	37
	Br-DMPyr by LC-MS[f]	6×10^{-6}	1.8×10^{-5}	0.12	39
Bromide	Br-TMB by GC-MS[b]	0.017	0.06	100	Current work

[a] MDL (3 s m^{-1}) and MQL (10 s m^{-1}) values account for preconcentration (*e.g.*, associated with liquid–liquid extraction prior to GC-MS analysis) and extraction efficiencies (Table S2). Uncertainties denote 95% confidence intervals. [b] MDL, MQL, LOL, and slope values for TMB are provided in Table S6. [c] This method involves the use of 2,6-dichlorophenol to derivatize free chlorine (yielding 2,4,6-trichlorophenol) and free bromine (yielding 4-bromo-2,6-dichlorophenol). [d] This method pertains to the use of 2,6-dimethylphenol (DMP) to derivatize free chlorine (yielding 4-chloro-2,6-dimethylphenol, Cl-DMP) and free bromine (yielding 4-bromo-2,6-dimethylphenol, Br-DMP) in aquarium seawater treated with ozone. [e] The DPD method is not selective between free chlorine and free bromine. For a more extensive list of free chlorine detection methods, including comparisons of MDL values, see ref. 51. [f] This method pertains to the use of 3,5-dimethyl-1*H*-pyrazole (DMPyr) to derivatize free bromine and other reactive bromine species (yielding 4-bromo-3,5-dimethyl-1*H*-pyrazole, Br-DMPyr); the use of DMPyr to derivatize free chlorine was not reported in ref. 39.

concentrations of both free chlorine and free bromine are expressed herein as mg (or μg) of Cl_2 per L.

3.1 Comparison of free halogen quantification by TMB and DPD

In Table 2, analytical metrics associated with the TMB GC-MS and TMB HPLC methods are compared with those of three previously reported methods, including the DPD method. For HOCl and HOBr, the TMB GC-MS method provides substantially lower MQLs relative to the TMB HPLC method, due in part to the preconcentration step associated with the GC-MS method. The MQL for GC-MS determination of free chlorine by TMB is a factor of 7 lower than that of the DPD method. The MQL associated with free bromine derivatization by TMB (60 nM by GC-MS) is greater than that previously reported for 2,6-dimethylphenol (1.4 nM by GC-MS)[37] and for DMPyr (0.018 nM by LC-MS/MS).[39]

The TMB GC-MS method and the DPD method were compared (with respect to measured total free halogen concentrations) using synthetic waters containing free chlorine, free bromine, an equimolar mixture of free chlorine + free bromine, as well as chlorinated pool water (Table 3). Overall, treatment with TMB or DPD did not yield significantly different results at the 95% confidence level, which suggests that the TMB method performs comparably to the DPD method for quantifying free halogens. Furthermore, the use of both methods permitted recovery of approximately 100% of free bromine and/or free chlorine in synthetic waters.

Table 3 Summary of paired Student's *t* test results between DPD and TMB GC-MS methods[a]

Sample	Average measured total free halogen concentration (μM)			Significantly different at 95% confidence level?
	DPD method	TMB method	Difference	
Synthetic water HOCl only[b]	14.72	16.31	−1.59	No (p-value = 0.11)
	15.70	16.15	−0.46	
	15.62	16.38	−0.75	
Synthetic water HOBr only[c]	21.85	20.61	1.24	No (p-value = 0.06)
	21.74	21.07	0.67	
	21.79	20.07	1.72	
Synthetic water HOCl + HOBr[d]	19.77	20.75	−0.98	No (p-value = 0.07)
	19.94	20.36	−0.42	
	19.50	19.99	−0.49	
Chlorinated pool water[e]	27.92	28.13	−0.21	No (p-value = 0.70)

[a] Conditions (unless specified otherwise): pH = 7.0, [phosphate buffer] = 20 mM, $[HOCl]_{tot,o} \approx 20$ μM, [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, T = 20.0 °C. Total free halogen concentration by the TMB method calculated as [Cl-TMB] + [Br-TMB]; p-values are two-tailed. [b] No NaBr added. [c] $[NaBr]_o$ = 40 μM. [d] $[NaBr]_o$ = 10 μM. [e] Pool water samples obtained from an indoor swimming pool in Baltimore County, Maryland. Conditions: pH = 7.4, T = 21 °C. Values denote averages of four sampling locations in the pool that were measured in triplicate. The full data set is provided in Table S7.

3.2 Assessing the reactivity of TMB towards aqueous combined bromine

To determine the inherent reactivity of TMB toward combined bromine, bromamines were prepared by dosing free bromine solutions (prepared from NaOCl + Br^-) with ammonium chloride at pH 8.0 and a $HOBr_{tot}$: $NH_{3,tot}$ molar ratio of approximately 1 : 3. The principal bromamine species formed in such solutions is anticipated to be monobromamine (NH_2Br, eqn (6)).

At near-neutral pH, solutions of ammonia and free bromine can also rapidly generate dibromamine, which can form *via* disproportionation of monobromamine.[9,48]

$$2NH_2Br(aq) + H^+(aq) \rightleftharpoons NHBr_2(aq) + NH_4^+(aq) \quad (7)$$

Similarly, disproportionation of dibromamine can generate tribromamine (NBr_3).

$$2NHBr_2(aq) \rightleftharpoons NBr_3(aq) + NH_2Br(aq) \quad (8)$$

Consequently, bromination of TMB in solutions containing bromamines will reflect the net reactivity of all active bromine species in solution, including free bromine species and various bromamines. Under our solution conditions, the equilibrium position of eqn (6) favors the products and $[NH_2Br(aq)]/[HOBr_{tot}(aq)]$ is calculated to be 4×10^4. The ratio of [Br-TMB] generated from bromamines to [Br-TMB] generated from free bromine ranges from 74–87% and does not appear to vary regularly as a function of sampling time (Table 4). These findings suggest that bromamines are reactive brominating agents towards TMB and that bromamination of TMB occurs under approximately the same timescale as bromination by free bromine (half-lives of seconds). Unlike bromamines, chloramines react sluggishly with TMB (half-lives of hours);[21] this result is consistent with previous reports of bromamines serving as more labile halogenating agents compared to their chlorinated counterparts.[48]

3.3 Quantification of free halogens in chlorinated surface waters and drinking water

Free chlorine was added to surface water samples to model disinfection of drinking water and saline ballast water. Following a free chlorine contact time of 30 s, aliquots were taken from each water sample and quenched with TMB. Recoveries of total free halogens in Chesapeake Bay and Susquehanna River water were somewhat less than recoveries in Atlantic Ocean and Loch Raven Reservoir water (Table 5), owing to possible reaction of free chlorine and free bromine with natural organic matter (NOM) or other nucleophilic species in each water source.[53] Free chlorine residuals measured in municipal drinking water ranged from 0.2–1.2 mg L^{-1} as Cl_2 (Table S4†), consistent with the range (0.2–4 mg L^{-1} as Cl_2) mandated by the U.S. Environmental Protection Agency.[54] Overall, these findings demonstrate the ability of TMB to facilitate selective quantification of HOCl and HOBr in chlorinated waters.

3.4 Background salt interference studies

The potential for nominally bromide-free background salts to interfere with the detection of bromide was examined with NaCl, $NaHCO_3$, Na_2SO_4, $NaNO_3$, and $NaI \cdot 2H_2O$ (Fig. 2). Compared to a reactor receiving no background salt, measured Br^- concentrations appeared to increase by 8% in the presence of NaCl (one-tailed p-value = 0.08) and decreased by ~10% in the presence of $NaHCO_3$, Na_2SO_4, and $NaNO_3$ (all present at 3.3×10^5 molar excess relative to NaBr; all one-tailed p-values < 0.05). The modest increase in the presence of NaCl could result from the presence of Br^- as an impurity in the NaCl, as

Table 5 Total free halogen recoveries measured in natural water during simulated disinfection[a]

Natural water source	$[HOCl]_{tot} + [HOBr]_{tot}$ recovery[b] (%)	Relative standard deviation (%)
Chesapeake Bay	91 ± 2	1.2
Atlantic Ocean	97 ± 4	2.6
Susquehanna River	92 ± 3	2.5
Loch Raven Reservoir	100 ± 4	2.7

[a] Conditions: contact time = 30 s, $[NaBr]_{added}$ = 150 μM (only in Susquehanna River and Loch Raven Reservoir water), $[HOCl_{tot}]_o$ = 100 μM. Error estimates represent 95% confidence intervals. [b] $[HOCl]_{tot} + [HOBr]_{tot}$ recovery = $\frac{[HOCl]_{TMB} + [HOBr]_{TMB}}{[HOCl]_{tot,o}} \times 100\%$..

Table 4 Summary of average Br-TMB yields from reactions of TMB with bromamines and with free bromine[a]

Sampling time	Average [Br-TMB] (μM)		
	TMB + bromamines	TMB + HOBr	$\frac{[Br-TMB]_{bromamines}}{[Br-TMB]_{HOBr}} \times 100$ (%)
10 s	77.4 ± 1.3	92.7 ± 1.3	83.5 ± 1.8
20 s	75 ± 2	93.3 ± 1.1	80 ± 2
30 s	65.6 ± 1.3	79.8 ± 1.6	74 ± 2
60 s	69.5 ± 1.6	83 ± 2	87 ± 3

[a] Conditions: pH = 8.0, [borate buffer] = 20 mM, $[NaBr]_o$ = 100 μM, $[NaOCl]_o$ = 155 μM, $[NH_4Cl]_o$ = 0 (HOBr reactors) or 300 μM (bromamine reactors), [NaCl] = 10 mM, $[NaNO_3]$ = 90 mM, T = 20.0 °C. Uncertainties denote 95% confidence intervals. The decreased recovery of bromine in the bromamine reactors compared to the free bromine reactors could result from irreversible decomposition of bromamines, which is subject to base catalysis.[9,52]

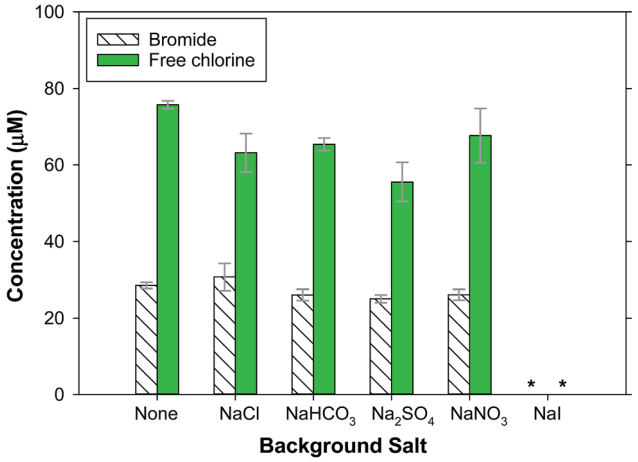


Fig. 2 Influence of background salts on quantification of bromide and total free chlorine *via* derivatization with TMB to give Br-TMB and Cl-TMB. Conditions: $[NaBr]_o$ = 30 μM, $[background\ salt]_o$ = 1.00 M (excepting NaI, which was added at 0.200 mM as $NaI \cdot 2H_2O$), $[NaOCl]_o$ = 0.100 mM. Free chlorine concentration was calculated as [Cl-TMB] + [Br-TMB] (eqn (5)). Error bars denote 95% confidence intervals. Asterisks (*) denote not detected. Data for control experiments performed in the absence of added NaBr are shown in Fig. S7.† Of the background salts examined in the absence of added NaBr, bromide was only detected in NaCl (Cl^-/Br^- molar ratio = 1.2×10^5, corresponding to a Br^- concentration in the NaCl of 11 ppm by weight).

evidenced by the detection of Br^- in a no-added NaBr control (Fig. S7†). Bromide was not detected in NaBr-free controls for any of the other examined background salts.

The modest decrease in bromide measured in the presence of large excesses of $NaHCO_3$, Na_2SO_4, and $NaNO_3$ could result from low-level impurities capable of scavenging free bromine. The apparent incomplete recovery of free chlorine in Fig. 2 is discussed in the ESI.†

NaI (0.200 mM) completely precluded detection of bromide (added at 0.030 mM) and free chlorine (added at 0.100 mM). When the concentration of NaI was decreased to 0.030 mM, 0.7 μM of bromide was measured (data not shown in Fig. 2), which corresponds to a bromide recovery of 2%. These results indicate that iodide can interfere with bromide quantification as Br-TMB. Iodide is a known reductant of free chlorine/bromine, which can generate free iodine (*e.g.*, HOI) and other electrophilic iodine species.[55,56] Free iodine can react with nucleophilic organic compounds,[57–59] including TMB,[60] to yield iodinated products. Thus, iodide could adversely impact free chlorine/bromine quantitation by (1) serving as a reductant of free chlorine/bromine and, subsequently, (2) generating free iodine, which could subsequently iodinate TMB (or other derivatizing agents) and their chlorinated/brominated products.

3.5 Determination of trace bromide in laboratory salts and acids

Reagents from chemical suppliers commonly report bromide as an impurity in salts such as NaCl and acids such as HCl. The presence of bromide as an impurity in these reagents can complicate experiments involving free chlorine, chloramines, and ozone due to the ability of these disinfectants to oxidize bromide into free bromine, which can be several orders of magnitude more inherently reactive as a halogenating agent relative to free chlorine.[22,53,61] Indeed, low levels of bromide introduced by NaCl have been shown to enhance rates of aromatic compound consumption in experiments involving free chlorine.[24,62] However, high background concentrations of anions (*e.g.*, chloride) can compromise the accuracy of some methods when measuring bromide.[63,64]

When solutions of 20 reagents (Table S5†) were treated with free chlorine followed by TMB, bromide impurity levels were greater than the MQL (60 nM = 0.005 ppm) in 7 of the 20 examined reagents (Table 6). The TMB method employed herein was capable of detecting ppm and sub-ppm levels of bromide present in a high chloride background (≥1 M) with relative standard deviations < 9%. Quantified bromide levels in high-purity NaCl (3 ppm Br^-) are approximately three times less than the upper limit reported by the manufacturer.

The ability of TMB to react with free bromine to yield a stable product in a high chloride background permits precise quantification of bromide as a trace impurity in a variety of laboratory reagents. Ion-selective electrodes (ISEs)[63] and ion chromatography (IC)[64] techniques can also be used to quantify bromide in solutions containing chloride. A bromide-ISE permits bromide quantification, but is limited to a maximum mole ratio of Cl^- : Br^- of 400 : 1 and a relatively high MQL (1 ppm).[63] Conversely, IC can accurately determine bromide levels in aqueous solutions containing a Cl^- : Br^- mole ratio of

Table 6 Summary of trace bromide impurity levels in reagent solutions treated with NaOCl and TMB[a]

Reagent	Description	[Br^-] (ppm) reported by manufacturer	Average [Br^-] (ppm) measured as Br-TMB	Relative standard deviation (%)
NaCl	Higher purity (99.999%)	<10	3	8.5
	Lower purity (99.0%)	<100	37	6.4
	Pool salt	Not reported	146	2.6
	Table salt	Not reported	167	2.6
HCl	Fisher Scientific	<50	34	7.8
	Fisher Chemical	<50	50	7.2
	J.T. Baker (ultra-pure)	Not reported	0.72	6.0

[a] Of the 20 examined reagents listed in Table S5, bromide levels exceeded the method quantitation limit (0.005 ppm) for the seven reagents shown above.

2500 : 1 (MQL = 30 ppb).[64] The solution conditions employed herein included relatively high concentrations of NaCl and HCl (~1.0 M) compared to the concentrations of bromide (3–167 μM); a lesser chloride concentration would be expected in typical halogenation studies mirroring surface water conditions (median $[Cl^-] = 0.3$ mM = 11 mg L^{-1}).[5,22] Accordingly, the ratio of Cl^- : Br^- in the examined salt solutions (~10^6 : 1) far exceeds the ratios observed in surface waters (~250 : 1; see Table S3†). Our results indicate that the TMB method described herein can afford trace quantitation of bromide in the presence of high chloride backgrounds without the need for more time-intensive methodologies (*e.g.*, standard addition).

3.6 Quantification of active halogens generated by spa disinfecting tablets

The ability of TMB to serve as a halogen trap was applied to tap water treated with spa disinfecting tablets. The active ingredient in the tablets was BCDMH, which hydrolyzes to yield free bromine and free chlorine (Scheme 1). In waters treated with BCDMH, TMB can conceivably be halogenated by free chlorine, free bromine, or by BCDMH itself. Accordingly, for such systems, Cl-TMB and Br-TMB serve as surrogates of active chlorine and active bromine, respectively, not just free chlorine and free bromine.

In the simulated spa water quenched with TMB, active bromine residuals increased continually over 8 h to a maximum of 79 μM (5.6 mg Cl_2 L^{-1}, Fig. 3A). In the same system, active chlorine residuals increased up to 40 μM (2.9 mg Cl_2 L^{-1}) over 8 h. When 2,6-dichlorophenol was used as the derivatizing agent for aliquots obtained from the same simulated spa water, the active bromine profile (Fig. 3B) was in strong agreement with that obtained from samples quenched with TMB. Indeed, a paired *t* test (two-tailed) indicated that the active bromine data obtained with TMB and with 2,6-dichlorophenol were not significantly different at the 95% confidence level ($p = 0.38$).

Notably, active chlorine was not detected in any of the samples treated with 2,6-dichlorophenol. The somewhat greater water solubility of 2,4,6-trichlorophenol (4.3 mM)[65] relative to 4-bromo-2,6-dichlorophenol (3.4 mM)[66] suggests that solubility limitations cannot account for the failure to detect active chlorine when 2,6-dichlorophenol served as the derivatizing agent. These results suggest that 2,6-dichlorophenol is less nucleophilic than TMB under the conditions of the simulated spa solutions (*e.g.*, pH 7.3). Under these conditions, 2,6-dichlorophenol ($pK_a = 6.78$, presumably corresponding to 25 °C)[67] exists predominantly in the more nucleophilic (anionic) form and HOCl ($pK_a = 7.46$ at 35 °C)[11] exists predominantly in the more electrophilic (neutral) form. Accordingly, the simulated spa conditions should ostensibly favor reactions between free chlorine and 2,6-dichlorophenolate. That 2,6-dichlorophenol was reactive toward active brominating (but not chlorinating) agents is consistent with the greater inherent electrophilicity of active bromine species compared to their chlorinated counterparts.[61] Overall, these findings illustrate the ability of the TMB method to selectively quantify active bromine and active chlorine in waters disinfected with BCDMH.

4. Summary of methodological advantages and limitations

TMB can be used to derivatize free chlorine and free bromine into stable chlorinated and brominated products that can be quantified using GC-MS and HPLC-DAD. TMB can be used to quantify free chlorine and free bromine in solutions of varying matrix complexity, including synthetic waters treated with NaOCl, drinking water, pool water, and a variety of chlorinated surface waters.

Performance of TMB as a free chlorine probe gave results that were on par with those of the traditional DPD method. Unlike the DPD method, however, the halogenation products of

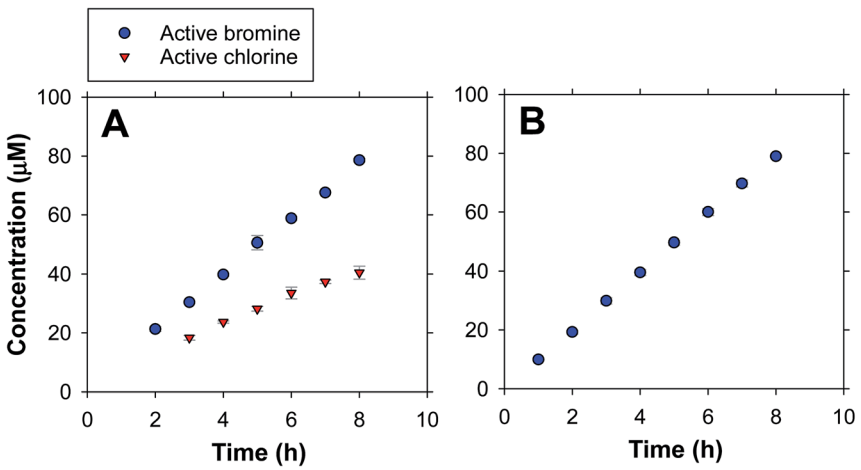


Fig. 3 Active halogen residuals generated by a spa disinfecting tablet (28 g, 96.0 wt% BCDMH) quantified using (A) TMB and (B) 2,6-dichlorophenol as the derivatizing agent. Tap water served as the reaction matrix. Error bars denote standard deviations ($n = 2$) and are smaller than symbols if not shown. Solution conditions: pH = 7.3, $T = 39.0 \pm 0.1$ °C, total volume = 30 L. Neither active chlorine nor active bromine were detected in the water prior to addition of the spa tablet. In frame A, active bromine and active chlorine were not detected until 2 h and 3 h, respectively, after tablet addition at $t = 0$. In frame B, active chlorine was not detected at any of the sampling times.

TMB are stable and therefore do not require immediate analysis. Moreover, while the DPD method cannot distinguish between free chlorine and free bromine, derivatization with TMB permits simultaneous and selective quantification in solutions containing both free halogens. The large linear range of the TMB method for free chlorine and for free bromine can be tailored to meet the requirements of individual samples by varying the extent of preconcentration (*i.e.*, during solvent extraction prior to GC-MS analysis) or dilution. For the GC-MS method reported herein, MDLs for free chlorine and free bromine are on the order of 1 μg L^{-1} as Cl_2.

The formation of Br-TMB in solutions treated with free chlorine can be used to quantify trace bromide present as an impurity in laboratory reagents with substantially lower MQLs than traditional assays. Unlike alternative methods (*e.g.*, ion-selective potentiometry and IC), the presence of high chloride backgrounds does not appear to limit the performance of the TMB method described herein when quantifying bromide.

While our results demonstrate that TMB is sufficiently nucleophilic to serve as a derivatizing agent for inorganic bromamines, TMB is unlikely to be able to distinguish between free bromine and inorganic bromamines. As with other derivatization methods relying on LC or GC,[37,68] the TMB method reported herein is not suitable for field applications requiring remote monitoring, continuous analysis, or in laboratories lacking access to both HPLC-DAD and GC-MS. The TMB method is also susceptible to interference by iodide, which is likely to affect other derivatizing agents that are reactive toward free iodine.

Together with our recent work,[21] this study establishes a range of applications by which TMB can be used to quantify free chlorine, free bromine, inorganic bromamines, and bromide. The potential utility of TMB as a derivatizing agent of aqueous free iodine and iodide (upon oxidation to free iodine) merits future investigation.

Conflicts of interest

There are no conflicts to declare.

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