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Chloral hydrate as an accelerant for the Weissler reaction

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Abstract

The Weissler reaction, in which a potassium iodide aqueous solution is oxidized to produce triiodide ion, is a conventional means of quantifying ultrasound-induced inertial cavitation. The reaction is commonly accelerated by saturating the solution with carbon tetrachloride, thereby increasing triiodide ion yields for any given ultrasound exposure. Chloral hydrate, being less toxic and easier to handle, is an alternative accelerant that was characterized. Observed triiodide ion levels were around 11–15% of that produced with carbon tetrachloride. Chloral hydrate was shown to be less susceptible to accelerant exhaustion for prolonged measurements. Spectrophotometric measurement of triiodide ion is typically performed through absorbance measurements at 350 nm; however, there is a separate absorption peak at 288 nm. Measurements at 288 nm were strongly correlated with 350 nm measurements. Due to the greater molar absorptivity at 288 nm, Weissler reaction measurements in the future may be preferably conducted at this alternative wavelength regardless of the means of acceleration.

KEYWORDS

carbon tetrachloride, cavitation, chloral hydrate, dosimetry, Weissler reaction

1 | INTRODUCTION

Inertial cavitation is defined as the process in which cavitational bubbles are formed and subsequently implode.[1] When cavitational bubbles collapse, extreme conditions are generated, with local energies equivalent to temperatures around 5,000 K, pressures over 1,000 atm, and temperature changes at rates around 10^{10} K/s.[2] This cavitational activity may be measured using physical or chemical means. A physical approach uses hydrophones or other transducers to detect the broadband signal formed by collapsing bubbles.[3] Related to that is the use of an imaging transducer to detect bubble presence.[4] Chemical approaches rely on the extreme conditions generated to drive various reactions, after which reaction product is quantified in various dosimeters. The Fricke dosimeter[5–8] measures Fe^{2+} oxidation to Fe^{3+}. The terephthalate dosimeter, developed previously for measuring radiation, uses fluorescence to measure the 2-hydroxyterephthlate generated from starting terephthalate.[9,10] A third approach uses the conversion of 2,2-diphenyl-1-picrylhydrazyl (DPPH) to 2,2-diphenyl-1-picrylhydrazine ($DPPH_2$) and its subsequent spectrophotometric measurement.[11] Nevertheless, the Weissler reaction is one of the most studied and is easily employed.

The Weissler reaction forms the basis of a chemical dosimeter, which measures the level of inertial cavitation present within an aqueous volume.[12] A dissolved solution of potassium iodide is oxidized by inertial cavitation, and quantities of reaction products indicate cavitation levels. Older literature refers to the measured product as iodine.[13] The addition of carbon tetrachloride (CCl_4) to the solution dramatically increases iodine levels formed for a given amount of cavitation, and carbon tetrachloride is commonly used today as a reaction accelerant.[14]

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Nowadays, the measured reaction product is typically triiodide ion (I_3^-), which is usually quantified through spectrophotometric measurement at 350 nm. Morison and Hutchinson[15] provide an excellent description of the chemistry and relation between iodine and triiodide ion measurements and how the literature somewhat confusingly conflates the two terms. The use of the reaction in measuring hydrodynamic cavitation is limited by the presence of a consumption reaction that degrades I_3^-.[15] In ultrasonic cavitation, a consumption reaction is significant at high power and frequency,[16] and in neutral and alkaline[17] solutions. Nevertheless, potassium iodide dissolved in distilled water is adequate for measurements without additional pH control.[18] The concentration of potassium iodide used is typically 0.1 M. [15,19–22]

Triiodide ion levels are linearly related to levels of cavitation that occur for any given insonation frequency. Triiodide ion has a separate absorbance peak at 288 nm with a higher absorptivity[23] than the peak at 350 nm. The absorbance at 288 nm can be measured using a spectrophotometer capable of measuring the spectrum's ultraviolet portion and a quartz cuvette. In this paper, spectrophotometric absorbances measured at 288 nm are compared to absorbances measured at the traditional 350 nm to verify the suitability of using 288 nm to quantify triiodide ion levels. The higher absorptivity at 288 nm suggests that measurements at that wavelength would be more sensitive than those at 350 nm.

Carbon tetrachloride is a liver toxin[24] and also damages the ozone layer.[25] It is a volatile liquid that is only slightly soluble in water, and it may erode polyethylene films.[26] Chloral hydrate ($Cl_3CCH(OH)_2$) has also been used to increase iodide oxidation upon insonation in the Weissler reaction.[26–28] Chloral hydrate is a solid at room temperature that is soluble in water. It is much less toxic and is used as a drug for sedation.[29] However, the effectiveness of chloral hydrate as a Weissler reaction accelerant has not been characterized. In this paper, we characterize chloral hydrate as a Weissler reaction accelerant at differing concentrations and compare the results to those obtained using saturated carbon tetrachloride. Chloral hydrate is reported as being "incompatible" with iodide ion,[30] suggestive of a competing self-reaction in the absence of ultrasound. The advantages and drawbacks of using each reaction accelerant are subsequently discussed.

2 | RESULTS AND DISCUSSION

2.1 | Comparison of chloral hydrate and carbon tetrachloride

Triiodide yields were spectrophotometrically measured for two ultrasonic setups. Absorbances are directly proportional to the levels of triiodide ion (Beer–Lambert Law). The two setups used were (a) an ultrasonic horn and (b) an ultrasonic cleaning bath. Horn exposures were for 1 min per sample. Bath exposures were for 10 min to produce sufficient reaction product for analysis.

The use of saturated carbon tetrachloride as a reaction accelerant produced absorbance differences to which chloral hydrate results were compared (Table 1). Observed absorbance differences at 288 and 350 nm for both the ultrasonic horn and cleaning bath as a function of chloral hydrate concentration were plotted (Figure 1) and were compared to values obtained with saturated carbon tetrachloride.

Slope values were consistent with corresponding cleaning bath data, as found using the Real Statistics Resource Pack, indicating a lack of detectable difference in reaction acceleration levels (Table 2). In other words, reaction acceleration levels for a given concentration of chloral hydrate were consistent between the ultrasonic horn and the cleaning bath. They were also consistent regardless of the wavelength of measurement as expected. Cleaning bath data had substantial variability; the addition of chloral hydrate did not increase reaction yield to a statistically significant degree. However, the degree of reaction acceleration is nevertheless consistent with ultrasonic horn data. The acceleration is likely independent of ultrasonic frequency and intensity. The ultrasonic horn operated at 20 kHz while the cleaning bath operated at 37 kHz. Average ultrasonic intensities were 71.4 and 0.50 W/cm^2, respectively, spanning more than two orders of magnitude. The reaction times were 1 and 10 min, with the latter case selected to obtain sufficient product for analysis. Sonochemical reactions almost always produce highly variable yields, and the observed variability here is no exception.

Sakai, Sadaoka, and Takamaru reported that ultrasound decomposes chloral hydrate with a reaction rate proportional to the chloral hydrate concentration's square root.[31] Acceleration of the Weissler reaction by chloral hydrate requires that ultrasound decompose chloral hydrate as an initial step. The level of Weissler reaction acceleration reported here readily fits a linear model,

TABLE 1 Saturated carbon tetrachloride as accelerant

Spectrophotometric wavelength λ (nm)	Ultrasonic horn (20 kHz for 1 min, $n = 3$)	Cleaning bath (37 kHz for 10 min, $n = 2$)
288	0.073 ± 0.004	0.131 ± 0.008
350	0.051 ± 0.004	0.082 ± 0.004

Note: Absorbance differences (after–before) using saturated carbon tetrachloride as the reaction accelerant (numbers denote mean ± 1 SD).

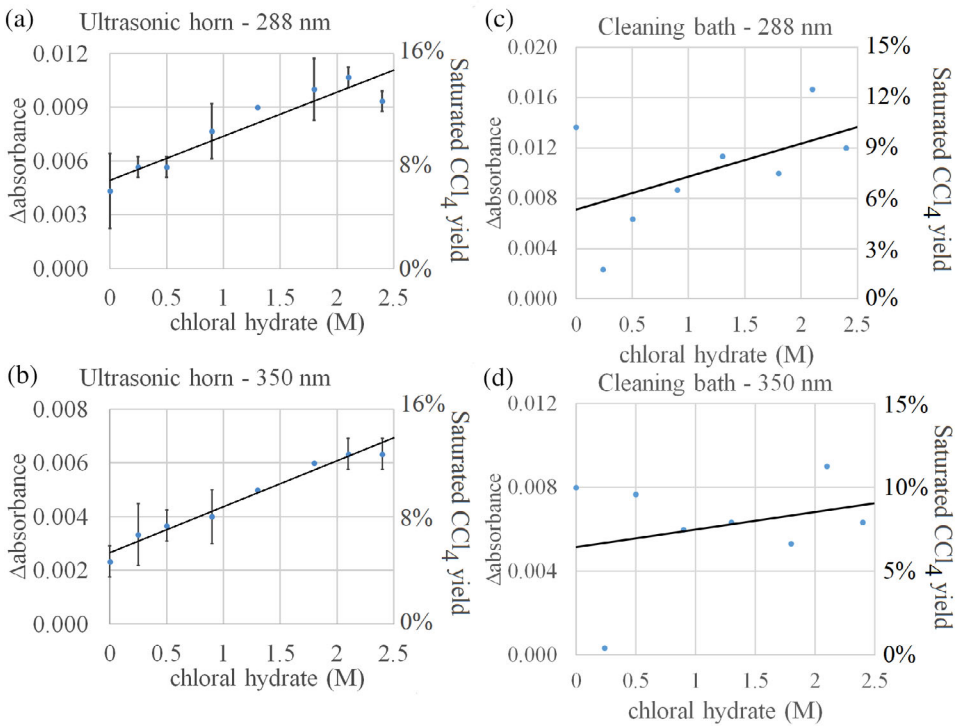

FIGURE 1 Comparison of measured absorbance differences, indicative of levels of triiodide ion produced in the Weissler reaction, using varying chloral hydrate concentrations as an accelerant. Data were fit to least-squares straight lines. (a, b) The ultrasonic horn yield (three measurements were made at each concentration) increased with increasing chloral hydrate concentration, up to a maximum of 12–15% of that obtained with CCl_4. Error bars denote ±1 SD. Points plotted without error bars indicate a lack of differences in measurements upon repetition. (c, d) The cleaning bath yield (one measurement per concentration) did not appreciably change with increasing chloral hydrate concentration due to relatively large measurement error. Maximum yields were 11–13% of those obtained from carbon tetrachloride. Subsequent analysis indicates that the increasing yields found with the horn are nonetheless consistent with cleaning bath data (see text)

TABLE 2 Fitted line slopes (% of saturated carbon tetrachloride yield vs. chloral hydrate concentration) for Figure 1 and the lack of statistical differences (differences considered significant for $p \leq .05$)

	Horn	Bath	Significant difference
288 nm	3.34 (2.46, 4.23)	1.99 (−1.23, 5.22)	No ($p = .3372$)
350 nm	3.27 (2.64, 3.89)	1.03 (−2.44, 4.49)	No ($p = .1334$)

and attempts to fit those results to a square root model were unsuccessful. This discrepancy can be explained by noting that their decomposition data include only data obtained at 0.1 M and lower concentrations, while this paper focuses on higher concentrations. Plots of square root functions covering higher abscissa (x-coordinate) values approach linearity, and experimental noise would easily render data impossible to fit a square root function.

Being a human drug, chloral hydrate is much safer in terms of environmental concerns and handling safety than carbon tetrachloride. However, the yields of triiodide ion are smaller than those obtained with saturated carbon tetrachloride, making it a less desirable accelerant when greater sensitivity is desired.

2.2 | Chloral hydrate and potassium iodide solution stability

A fresh aqueous solution of 0.1 M of potassium iodide and 0.9 M chloral hydrate was prepared to examine the extent to which a chloral hydrate and potassium iodide solution undergoes self-reaction where absorbing species are formed at 288 and 350 nm over time in the absence of ultrasound. Absorbances at both 288 and 350 nm were recorded over 120 min (Figure 2). A reaction was observed to occur, and average least-squares fitted lines for 288 and 350 nm wavelengths were respectively $8.597 \times 10^{-5}x + 0.019$ and $5.33 \times 10^{-5}x + 0.007$ with x denoting the time in minutes. Therefore, the absorbance difference over a 10 min experiment would be less than 0.001. This fact indicates that self-reaction-produced signal would significantly affect measurement results only for (a) lengthy ultrasound exposures or (b) long delays between exposure and measurement.

The classic carbon tetrachloride accelerated Weissler reaction is rate-limited by the ultrasonic decomposition of carbon tetrachloride into chlorine and other radicals, which then generates triiodide ion.[14,32] When chloral hydrate is used as the accelerant, ultrasound decomposes it into chloral hydrate radicals and peroxy radicals,[31] which proceed to generate triiodide ion. The lesser levels of triiodide ion formed with chloral hydrate, even at much higher concentrations when compared to carbon tetrachloride (water becomes saturated with carbon tetrachloride at a concentration around 5.3 mM) suggest that the radicals formed with chloral hydrate are less reactive or that they are formed at lower rates. This lesser reaction rate combined with chloral hydrate's much higher solubility has the potential advantage of being less likely to be consumed to any significant extent during lengthy measurements.

Accelerant consumption has been previously described as a problem with carbon tetrachloride[12] due to its low solubility and high volatility. As carbon tetrachloride is consumed, further reaction is accelerated less and less, resulting in a decreasing reaction rate during the dosimetric measurement process. The decreasing rate makes the dosimeter nonlinear, with the amount of triiodide ion generated no longer proportional to the amount of cavitation that occurred. We demonstrated accelerant consumption (Figure 3) for carbon tetrachloride and show that its effect is much reduced for chloral hydrate over lengthy measurements. The reduced reaction rate with carbon tetrachloride with added exposure may be attributed to its consumption or its volatility causing it to leave the solution.

For extremely lengthy measurements where self-reaction is no longer negligible, absorbance arising from the self-reaction between chloral hydrate and potassium iodide could be subtracted from final results.

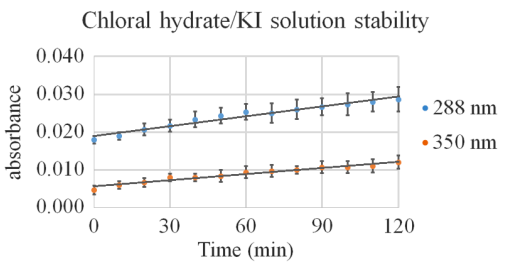

FIGURE 2 Stability of a combined chloral hydrate/potassium iodide solution over time. Absorbances were measured ($n = 3$) over time at both 288 and 350 nm. The plotted lines denote the average of three individual line fits over each measurement. While the absorbances rose with time, indicative of self-reaction, the self-reaction rate was small relative to the ultrasonically driven Weissler reaction rate in most cases

2.3 | pH, UV–Vis spectra, and 288 versus 350 nm measurements

Chloral hydrate solutions had pH measurements between 5 and 6 for all measured concentrations, with lower pH values found at higher chloral hydrate concentrations. Another advantage of chloral hydrate is that it acidifies the test solution; this acidification is demonstrated in this work. Possible external factors that would tend to make the test solution basic and thereby decompose formed triiodide ion are expected to play less of a role when chloral hydrate is used.

Chloral hydrate demonstrated a single, clear UV–Vis absorbance peak around 200–220 nm, with absorbances near-zero otherwise. These low values are readily subtracted from both the pre- and post-ultrasound exposure samples. At the higher concentrations examined, there was substantial evidence of nonlinearity at the strongly absorbing wavelengths. However, at the relevant wavelengths of 288 and 350 nm, the absorbances remain linear (Figure 4). These absorbances are absolute values rather than differences pre- and post-ultrasound

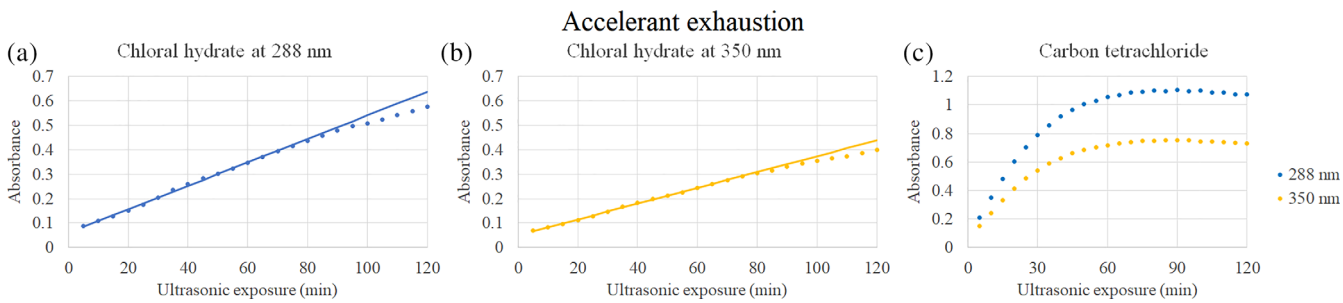

FIGURE 3 Demonstration of accelerant exhaustion. Here, a chloral hydrate based measurement (a, b) remained linear up to 70 min of ultrasonic horn exposure, with slight deviation from linearity with additional exposure. The linear regions are marked with solid lines. Their equations are $0.004343x + 0.076779$ and $0.003237x + 0.05033$, respectively, for measurements taken at 288 and 350 nm, with x denoting ultrasonic exposure in minutes. Using carbon tetrachloride (c) as the accelerant with this exposure produced no purely linear region

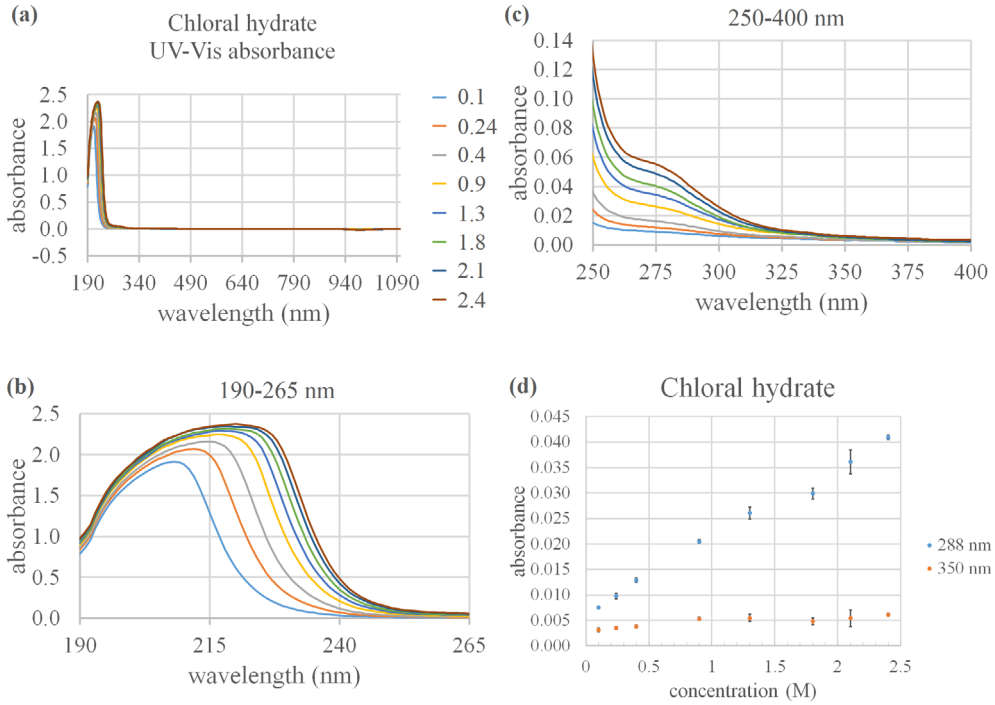

FIGURE 4 Chloral hydrate UV–Vis spectra. (a–c) The spectral absorbance peak of chloral hydrate is around 200–220 nm. Concentrations examined are sufficiently high to make absorbances in this peak region nonlinear relative to concentration. Different colored lines denote chloral hydrate concentrations in molar (M). (d) At the dosimetrically relevant wavelengths of 288 and 350 nm, absorbances are substantially lower and grow linearly with concentration ($R^2 = 0.987$ and 0.592, $p = 2.64 \times 10^{-22}$ and 1.1×10^{-5} respectively for each case) [Correction added on 10 July 2021, after first online publication: Figure 4 (c) and Figure 4 (d) were incorrectly swapped and have been updated in this current version.]

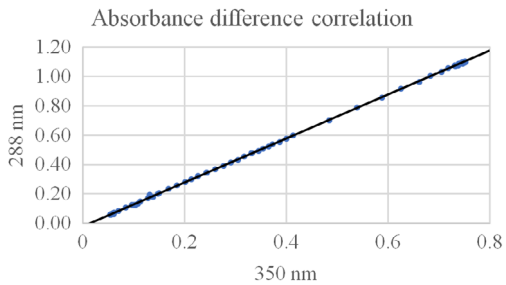

FIGURE 5 Correlation between measured absorbance differences at 288 versus 350 nm. For every sample ($n = 86$ overall), the absorbance difference at 288 nm is plotted versus the absorbance difference at 350 nm, and the results are fitted to a straight line. Summary statistics are as follows: $R^2 = 0.9999$, $p = 5.04 \times 10^{-172}$ which are indicative of an extremely strong linear relationship. This correlation verifies that measurements made at the 288 nm wavelength can be used in place of traditional measurements made at 350 nm

exposure; these values would be constant before and after any measurement.

There is an extremely strong correlation between absorbance differences found at 288 and 350 nm for any given sample (Figure 5). This result indicates that measurements at 288 nm may be used to quantify triiodide ion levels just as 350 nm measurements are typically used. Triiodide has a 52% larger molar attenuation coefficient of 3.52×10^4 L mol^{-1} cm^{-1} at 288 nm versus 2.32×10^4 L mol^{-1} cm^{-1} at 350 nm.[23] The 288 nm wavelength, therefore, may be a superior wavelength at which to measure triiodide levels regardless of their method of generation, subject to the limitation of using a spectrophotometer capable of measuring in the UV range and corresponding required quartz cuvettes.

3 | EXPERIMENTAL

3.1 | Ultrasonic horn and cleaning bath

The effect of chloral hydrate on the Weissler reaction was examined as follows. A polypropylene test tube had 30 ml of air-saturated water added to it. Potassium iodide (Katayama Chemical, Osaka, Japan) was added to the water to form a 0.1 M (molar or equivalently mol/L) KI solution. Chloral hydrate (Scharlab S. L., Senrmenat, Spain) was subsequently added to the solution to a concentration of 0.24 M. The spectrophotometric absorbances relative to pure water at both 288 and 350 nm were recorded using a spectrophotometer (CT-2800, E-Chrom Tech, Taipei, Taiwan) with a quartz cuvette with a 5 mm light path length. The solution was then sonicated at 20 kHz using a 3.2 mm diameter ultrasonic horn (QSonica, Newton, CT) running continuously for 1 min, at 50% amplitude (the horn tip displacement distance was 60 μm peak-to-peak). Post sonication, spectrophotometric absorbances at 288 and 350 nm

were again recorded, and differences from the values pre-sonication were noted. The procedure was subsequently performed using other dissolved chloral hydrate concentrations (0—control, 0.5, 0.9, 1.3, 1.8, 2.1, and 2.4 M) while maintaining KI concentration at 0.1 M. Experiments were repeated to assess measurement variability ($n = 3$ at each concentration). Finally, water saturated with carbon tetrachloride and also containing 0.1 M KI was sonicated using the above procedure for comparison ($n = 3$).

Chloral hydrate effects under conditions with substantially reduced ultrasonic intensity were examined by placing the above chloral hydrate and potassium iodide solutions into test tubes and measuring their absorbances at 288 and 350 nm. The test tubes were subsequently placed at the center of an ultrasonic cleaning bath (Elmasonic P30H, Singen, Germany) and exposed to 37 kHz continuous ultrasound at 100% power for 10 min. The longer exposure time of 10 min was selected to produce sufficient measurable cavitation at the lower ultrasound intensity produced compared to the ultrasonic horn. Afterward, resulting absorbances at 288 and 350 nm were recorded. Saturated carbon tetrachloride solutions were also likewise treated for comparison.

Differences in spectrophotometric absorbances at 288 and 350 nm before and after ultrasonic exposure were calculated at each chloral hydrate concentration and plotted for both the ultrasonic horn and cleaning bath. These values were then compared to results obtained with a saturated carbon tetrachloride solution. The triiodide ion yield relative to saturated carbon tetrachloride was empirically fitted to straight lines of the form $Ax + B$, with A and B denoting fitted constants using the Real Statistics Resource Pack software by Charles Zaiontz. Line slopes and their 95% confidence intervals were recorded. The slopes were subsequently compared using the SlopesTest function for values obtained at both wavelengths across setups (288 nm, horn vs. bath; 350 nm, horn vs. bath), with $p \leq .05$ considered the threshold for statistically significant differences.

3.2 | Chloral hydrate and potassium iodide solution stability

Three test tubes of water had 0.1 M of potassium iodide dissolved within them along with chloral hydrate at a concentration of 0.9 M to examine whether and to what degree combined potassium iodide and chloral hydrate solutions undergo self-reaction in the absence of ultrasound over time. Absorbances at 288 and 350 nm, relative to pure water, were measured at 10 min intervals from 0 to 120 min and recorded. Data points were plotted and fitted to straight lines to determine the extent self-reaction affects chloral hydrate accelerated measurements.

3.3 | Accelerant exhaustion in lengthy measurements

The effects of accelerant exhaustion in prolonged measurements were examined with chloral hydrate and carbon tetrachloride as follows. Test tubes containing 30 ml of water and 0.1 M of potassium iodide were prepared. Chloral hydrate at a concentration of 0.9 M was then added to a test tube. Test tube contents were preheated to 40°C, the equilibrium temperature previously found with lengthy ultrasonic exposure using the ultrasonic horn. The contents were then sonicated at 5 min intervals, and samples were removed and spectrophotometrically measured at both the 288 and 350 nm wavelengths using a 2 mm path length quartz cuvette. After each measurement, samples were readded to the test tube for additional sonication. This process was repeated until the test tube contents have been exposed to ultrasound for a total of 2 hr.

For the other test tube, carbon tetrachloride was added to produce a 5.3 mM solution after preheating to 40°C to minimize loss due to its volatility. Spectrophotometric measurements were likewise taken at 5 min intervals over 2 hr of ultrasonic exposure.

Measured absorbances were plotted versus ultrasonic exposure times for both cases. The linear region was identified as follows. The best-fitting least-squares line to all the data points was plotted, and fit residuals were examined. The number of positive and negative runs of the fit residuals was examined with the Wald–Wolfowitz runs test to determine if the residuals were randomly occurring at a 5% significance level (if the data truly fit a line, positive and negative residual values should randomly occur). If the residuals were not random, then the longest time point was removed and the process repeated until the residuals were random. If there was no identifiable purely linear region, as identified by uniformly decreasing differentials ($[p_2 - p_1] > [p_3 - p_2] > [p_4 - p_3]$ and so forth), then that fact was noted. Lines corresponding to the corresponding linear regions were plotted atop measured absorbances.

3.4 | Other measurements

The pH of chloral hydrate solutions at the following concentrations (0.1, 0.24, 0.5, 0.9, 1.3, 1.8, 2.1, and 2.4 M) was measured using paper test strips (Macherey-Nagel Gmbh & Co., KG, Düren, Germany). Their absorbance spectra were also measured from 190 nm to 1,100 nm and plotted to examine possible effects of high chloral hydrate concentration on resulting absorbances. Particular attention was paid to absorbances at 288 and 350 nm to detect possible nonlinearity at higher concentrations,

where the Beer–Lambert law no longer applies. Finally, absorbance differences at 288 and 350 nm for all measurements post ultrasonic exposure were plotted against each other to verify that both wavelengths linearly indicate triiodide ion levels.

4 | CONCLUSIONS

In this work, we characterized the use of chloral hydrate as an accelerant of the Weissler reaction, which is commonly used to assess inertial cavitation levels produced in various processes. Chloral hydrate is highly soluble in water, unlike the widely used carbon tetrachloride. Therefore, we first demonstrate that increasing chloral hydrate concentrations result in additional reaction acceleration. The acceleration is applicable across differing reaction setups. Although the acceleration obtained with chloral hydrate is less than that obtained with saturated carbon tetrachloride, chloral hydrate has the advantages of (a) being easier to handle, (b) being less toxic, (c) being less affected by reaction consumption, as well as (d) acidifying the test solution. Also, we show that spectrophotometric measurements of the Weissler reaction product triiodide ion made at the more sensitive 288 nm may be superior to the usually used 350 nm.

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