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# Effect of Ultrasonic Waves on the Stability of Selected Surface-Active Agents, Sulfonamides, and *p*-Aminobenzoic Acid

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**Data are presented showing the effect of ultrasonic waves on the stability of certain surface-active agents, sulfonamides, and *p*-aminobenzoic acid. Under the experimental conditions employed, the surface-active agents were stable and the breakdown of the sulfonamides and *p*-aminobenzoic acid was greater than could be accounted for on the basis of peroxide formation.**

BEAL and Skauen have reported that the viscosity of several surface-active agents is reduced upon exposure to ultrasonic waves (1). This suggests the possibility of a decrease in molecular weight of these agents as a result of depolymerization or some other type of chemical decomposition. Similar breakdown of large molecules has been reported by several authors (2–5). Araujo has reported the decomposition of procaine penicillin G and sulfathiazole in an ultrasonic field (6). The authors have noted similar decomposition of procaine and buteth-amine hydrochlorides. This decomposition was apparently of an oxidative nature and was prevented by the use of sodium bisulfite as an antioxidant (7). A number of authors have reported the formation of peroxides in aqueous solutions as a result of treatment with ultrasonic waves (8–11). In view of these investigations, it was deemed to be of value to determine if surface-active agents are stable in an ultrasonic field and if peroxide formation is responsible for the breakdown of sulfonamides and similar compounds. This communication reports the effect of ultrasonic waves at a frequency of 400 kilocycles per second upon the stability of selected surface-active agents. This should give an indication as to the advisability of using these agents when preparing emulsions or suspensions by ultrasonics. The amount of peroxides formed as a result of exposure to ultrasonic waves of this frequency was determined. The effect of similar amounts of peroxide alone on the stability of one of the sulfonamides was compared with the effect of ultrasonic waves upon stability. This should indicate if the breakdown due to ultrasonic waves is caused primarily by the formation of peroxides.

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## EXPERIMENTAL

**Calibration of the Generator.**—The ultrasonic generator employed in this study was constructed at Purdue University and was designed for use with a barium titanate transducer. The generator is rated at 250 watts with a variable frequency range. A Hypersonic Transducer, model BU-305,[1] with a focused bowl of barium titanate was employed. The generator was calibrated by determining the wattage produced at various rheostat settings by multiplying the power amplifier voltage and the power amplifier current as shown by appropriate meters on the generator. All of the experiments involving insonation were conducted at a frequency of 400 kilocycles per second and an energy level of approximately 150 watts.

**Stability of Selected Surface-Active Agents.**—The surface-active agents chosen for this part of the study were Myrj 45,[2] G-2159,[2] Aerosol AY,[3] Tween 80,[2] Span 80,[2] and Triton X-200.[4] Solutions of these surfactants were insonated for extended periods of time. The hydroxyl and saponification

[1] Marketed by Brush Development Co., Cleveland, Ohio.
[2] Marketed by Atlas Powder Co., Inc.
[3] Marketed by American Cyanamid Co., Inc.
[4] Marketed by Rohm and Haas Co. Inc.

TABLE I.—SAPONIFICATION AND HYDROXYL VALUES OF SAMPLES OF INSONATED AND NONINSONATED SURFACE-ACTIVE AGENTS

| Surface-Active Agent | Hydroxyl Value | | Saponification Value | |
|---|---|---|---|---|
| | Noninsonated Sample | Insonated Sample | Noninsonated Sample | Insonated Sample |
| Myrj 45 | 107.2 | 103.6 | 93.8 | 91.8 |
| | 102.9 | 102.3 | 92.9 | 92.8 |
| G-2159 | 19.0 | 18.9 | [a] | [a] |
| | 19.1 | 19.1 | | |
| Aerosol AY | 0 | 0 | 304.1 | 303.8 |
| | 0 | 0 | 305.3 | 304.2 |
| Tween 80 | 77.8 | 77.2 | 52.3 | 52.6 |
| | 75.3 | 74.4 | 52.4 | 52.7 |
| Span 80 | 193.3 | 188.2 | 156.4 | 157.3 |
| | 190.7 | 186.0 | 154.6 | 156.3 |
| Triton X-200 | 21.7 | 19.7 | [b] | [b] |
| | 21.1 | 19.7 | | |

[a] Not determined, due to lack of change in hydroxyl value. [b] Not determined, since compound lacks ester group.

TABLE II.—PER CENT SULFAPYRIDINE REMAINING AFTER ULTRASONIC IRRADIATION

| Time, Hr. | Insonated at 25°C. | | | Controls at 25°C. | | |
|---|---|---|---|---|---|---|
| | Sample 1 | Sample 2 | $\bar{x}$[a] | Sample 1 | Sample 2 | $\bar{x}$[a] |
| 1 | 98.7 | 99.1 | 98.7 | 100.0 | 100.0 | 100.0 |
| 2 | 98.3 | 98.3 | 98.3 | 100.0 | 100.0 | 100.0 |
| 3 | 97.8 | 98.3 | 98.0 | 100.0 | 100.0 | 100.0 |
| 4 | 97.4 | 97.6 | 97.5 | 100.0 | 100.0 | 100.0 |
| 5 | 97.3 | 97.8 | 97.6 | 100.0 | 100.0 | 100.0 |
| 6 | 97.4 | 97.4 | 97.4 | 100.0 | 100.0 | 100.0 |

[a] Arithmetic mean.

values of both insonated and noninsonated samples were determined. Hydroxyl values were determined by the method of Ogg, Porter, and Willits (12), while the saponification values were determined by the official method of the American Oil Chemists' Society (13). A decrease in the saponification value would indicate that ester hydrolysis had occurred while an increased hydroxyl value would indicate either ester or ether hydrolysis, or both, had occurred. The temperature was held at 25° ± 0.5° by circulating cold water through the transducer cooling coil. Table I shows the values obtained for these agents under these conditions.

**Stability of Selected Sulfonamides and *p*-Aminobenzoic Acid.**—The drugs selected for this portion of the study were sulfanilamide, sulfapyridine sodium, sulfathiazole sodium, and *p*-aminobenzoic acid. Solutions of 0.050 *M* concentration were prepared. To each 0.050 mole of sulfanilamide 0.025 mole of sodium hydroxide was added to give a salt to acid ratio of 1:1, and to each 0.050 mole of *p*-aminobenzoic acid, 0.050 mole of sodium hydroxide was added to form the sodium salt. The solutions were prepared using a pH 10.43 phosphate buffer of such composition that the resulting solutions had ionic strengths of 1.0. The buffer was composed of 11.40 Gm./L. of $Na_3PO_4 \cdot 12\ H_2O$ and 74.28 Gm./L. of $Na_2HPO_4 \cdot 7\ H_2O$. Sample volumes of 30 ml. were exposed to ultrasonic irradiation for time periods of from one to six hours at a temperature of 25° ± 0.5°, maintained by circulating the transducer coupling fluid from a constant temperature bath. Noninsonated control samples were held at the same temperature for equal time periods. For sulfanilamide, control samples were also run at 75° and 100° ± 0.5°. A 25.0-ml. sample of each of the insonated and control samples was then analyzed for remaining drug by the potentiometric titration of LaRocca and Waters (14). The amount of drug present in the samples before treatment was also determined by this method. Table II and Fig. 1 show typical results, while Table III summarizes the findings.

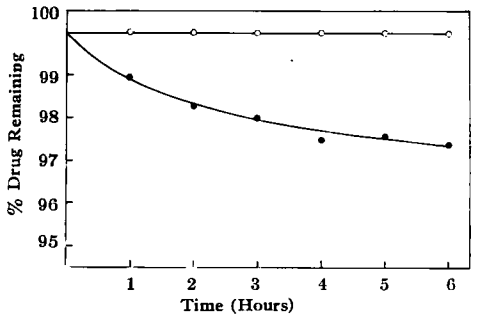


Fig. 1.—Per cent sulfapyridine remaining after ultrasonic irradiation; ●, insonated sample; ○, control sample.

**Peroxide Formation by Ultrasonics.**—In this portion of the study, samples of a pH 10.43 phosphate buffer with an ionic strength of 1.0 were

TABLE III.—PER CENT OF DRUG REMAINING AFTER ULTRASONIC IRRADIATION

| Drug | 1 Hr. | 2 Hr. | 3 Hr. | 4 Hr. | 5 Hr. | 6 Hr. |
|---|---|---|---|---|---|---|
| Sulfanilamide | 98.9 | 97.6 | 96.7 | 96.3 | 95.6 | 95.4 |
| Sulfapyridine | 98.9 | 98.3 | 98.0 | 97.5 | 97.6 | 97.4 |
| Sulfathiazole | 98.6 | 98.2 | 97.8 | 97.6 | 97.4 | 97.4 |
| *p*-Aminobenzoic acid | 99.1 | 98.5 | 98.3 | 97.4 | 97.1 | 96.9 |

insonated at a temperature of 25° ± 0.5° for varying periods of time. The buffer was composed of 11.29 Gm./L. of $Na_3PO_4 \cdot 12H_2O$ and 73.43 Gm./L. of $Na_2HPO_4 \cdot 7\ H_2O$. One-milliliter portions were withdrawn and analyzed for hydrogen peroxide, using a Beckman model B spectrophotometer, by the method of Patrick and Wagner (15). Table IV shows the results of this segment of the study.

TABLE IV.—PEROXIDE FORMATION IN PHOSPHATE BUFFER AS A RESULT OF ULTRASONIC IRRADIATION

| Time, Hr. | Absorbance | Moles/L. × $10^5$ |
|---|---|---|
| 0.5 | 0.029 | 0.15 |
| 1.0 | 0.085 | 0.4 |
| 1.5 | 0.164 | 0.8 |
| 2.0 | 0.505 | 2.5 |
| 2.5 | 1.08 | 5.3 |
| 3.0 | 1.35 | 6.6 |

**Effect of Hydrogen Peroxide on the Stability of Sulfanilamide.**—Dilutions of varying concentrations of hydrogen peroxide in a pH 10.43 phosphate buffer which, when used to prepare 0.050 *M* sulfanilamide solution, gave an ionic strength of 1.0 were prepared. The hydrogen peroxide concentration ranged from $2 \times 10^{-5}$ moles/L. to $2 \times 10^{-3}$ moles/L., or up to about 40 times the amount shown to be produced by ultrasonic waves. These concentrations of hydrogen peroxide had no measurable effect on the stability of sulfanilamide.

## DISCUSSION

These data would indicate that the surface-active agents chosen were stable, in terms of ether and ester hydrolysis, to prolonged periods of ultrasonic irradiation. No danger of breakdown would be anticipated if these agents were employed in emulsions or suspensions prepared by ultrasonics.

The stability of the sulfonamides and the *p*-aminobenzoic acid is decreased by exposure to ultrasonic waves. The amount of peroxides formed, however, is not sufficient to account for the observed decomposition of these drugs. It would also appear that very high temperatures would be required to produce a similar degree of decomposition. It seems reasonable to state that other factors must be involved in the ultrasonic decomposition of these drugs. Possible local heating effects or mechanical effects may be partially responsible.

## SUMMARY AND CONCLUSIONS

1. The purposes of this study were to determine if selected surface-active agents are subject to ester or ether hydrolysis in an ultrasonic field and if the amount of peroxide formed by ultrasonic irradiation is sufficient to account for the observed decomposition of certain sulfonamides and *p*-aminobenzoic acid.

2. No ester or ether hydrolysis of selected surface-active agents was induced by exposure to ultrasonic waves, as noted by determination of hydroxyl and saponification values.

3. The amount of hydrogen peroxide shown to be formed by ultrasonics is not sufficient to account for the observed decomposition of selected sulfonamides and *p*-aminobenzoic acid. The decreased stability of the sulfonamides and *p*-aminobenzoic acid as well as the amount of hydrogen peroxide formed as a result of ultrasonic irradiation was noted. No decrease in the stability of sulfanilamide with up to 40 times this amount of hydrogen peroxide was noted without insonation.

4. Under the experimental conditions described in this paper, the stability of the surface-active agents investigated was not affected by ultrasonic waves. The effect on the stability of the sulfonamides and *p*-aminobenzoic acid cannot be accounted for by the amounts of hydrogen peroxide shown to be formed by ultrasonic irradiation. Local thermal or mechanical effects, or some other factors must be involved.

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