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Ultrasonic Degradation of Aspirin in Mixed Solvent Systems

T. E. NEEDHAM, Jr. and ROBERT J. GERRAUGHTY

Abstract □ The effect of ultrasonic energy on the degradation of aspirin in ethanol–water, diethyl ether–water, and diethylene glycol–water solvent systems at various concentrations and temperatures was studied. It was found that the application of ultrasound to a system undergoing degradation would cause an increase in the rate, but would maintain the same kinetic order as in the control system. The heat of activation seems to be lowered by the mechanical vibrations of the ultrasonic energy. It is postulated that the ultrasonic vibration increases molecular collisions and the movement of the products away from each other, thereby producing a change in the overall rate of reaction. As the concentration ratio was increased in the diethylene glycol system, the subsequent increase in viscosity had a damping effect on the ultrasonic vibration.

Keyphrases □ Aspirin—ultrasonic degradation □ Ultrasonic degradation—aspirin, mixed solvent systems □ Solvent system effect—ultrasonic degradation, aspirin □ UV spectrophotometry—analysis

Ultrasound energy, at frequencies of 20 kc. or above, has been used to affect the rate and yield of a number of chemical reactions. Several hydrolysis reactions can be accelerated by an ultrasonic field including the degradation of procaine (1), ethyl acetate (2), and aspirin (3). Edwards, in a series of papers (4, 5) reported studies of the mechanism of aspirin degradation in aqueous systems in the absence of ultrasound, and found that the overall rate of aspirin hydrolysis followed a pseudo-first-order rate. In the absence of ultrasound, Garrett later studied the effect of alcohol–water and dioxane–water combinations on the hydrolysis of aspirin (6, 7). He reported that as the ethanol concentration was increased, the rate of hydrolysis also increased. He established a mechanism which showed that ethyl acetate was found in the presence of ethanol, causing an increase in the hydrolysis rate. Mario and Gerraughty studied the influence of ultrasound on the degradation of aspirin in an aqueous system (8) and reported that the ultrasonic energy would produce acceleration of the rate and that variation in temperature or pH still produced a pseudo-first-order kinetic rate.

In this study, the effect of ultrasonic energy on the degradation of aspirin dissolved in mixtures of water and ethanol, water and diethylene glycol, and water and ether was investigated. It was decided to study each system at different temperatures so that by using the Arrhenius equation the energies of activation could be calculated for each of the three systems.

EXPERIMENTAL

Equipment—The ultrasonic energy was supplied by a 100-kc. generator,[1] operated at the maximum plate voltage of 1,000 v. The transducer consisted of a mounted barium titanate crystal. Fitted to the inner wall of the ultrasonic bath was a round copper coil connected through an inlet-outlet pump arrangement to a separate constant-temperature water bath,[2] and controlled so that the temperatures of the two baths were both constant and identical, within the limits of ±0.2°, during all individual runs.

Systems and Temperatures Employed—The concentrations of the ethyl alcohol–water solutions were 10, 30, 50, and 70% (v/v), and the three temperatures used were 20, 30, and 40°.

The concentrations of the diethyl ether–water solutions were 1, 3, and 5% (v/v) due to the limited solubility of the ether in water. The temperatures used were 20, 25, and 30°, since higher temperatures were not feasible due to the low boiling point of diethyl ether. Also, condensers were attached to the reaction flasks to prevent volatilization of the ether.

The concentrations of the ethylene glycol–water solutions were 5, 10, 30, and 50% (v/v) and the temperatures used were 20, 30, and 40°.

Procedure—The same procedure was used for the alcohol–water, ether–water, and ethylene glycol–water systems. Two sets of duplicate samples of aspirin buffered to an apparent pH of 3.67 with acetic acid–sodium acetate were used for all degradations. Each sample contained 5.0×10^{-4} moles of aspirin. Of the duplicate samples involved in each degradation, one was subjected to the ultrasound waves, and the other was used as a control by immersing it in the second bath.

After the samples were placed in their respective baths, they were allowed to equilibrate to the selected temperature before a zero time reading was taken. Aliquots were withdrawn from the reaction vessels at accurately measured intervals of time and the absorption values recorded. Since instrumental efficiency could be affected dur-

[1] McKenna model 100 generator, McKenna Laboratories, Santa Monica, Calif.
[2] Catalog No. 3052, Labline Instruments Inc., Chicago, Ill.

Table I—Effect of Ultrasonic Energy on the Degradation of Aspirin in Solutions of Ethanol

Ethyl Alcohol, %[a]	Temperature, °C.	Control: $K \times 10^2$ (hr.$^{-1}$)[b]	Control: Activation Energy (K/cal.)[c]	Ultrasound: $K \times 10^2$ (hr.$^{-1}$)	Ultrasound: Activation Energy
10	20	0.48	17.59	0.74	16.81
	30	1.58		2.72	
	40	3.22		4.60	
30	20	0.53	19.19	0.94	15.71
	30	1.86		3.13	
	40	4.60		5.52	
50	20	0.76	19.19	1.01	17.55
	30	2.07		4.14	
	40	5.98		6.67	
70	20	1.40	16.26	1.75	15.57
	30	3.91		5.52	
	40	8.28		9.30	

[a] All runs contained 10% concentration of buffer. [b] Each K rate is the average of at least two runs. [c] The activation energy is calculated from the average K rates.

ing extended operation, some highly stable samples could only be followed until 10% complete.

Since the breakdown of aspirin yields salicylic acid in a mole for mole ratio, the rate of degradation could be followed by measuring the amount of salicylic acid that was formed spectrophotometrically at 298 mμ as shown in previous papers (4–8). Beer's law relationships were prepared for all concentrations of each solvent that was used.

All the trials were made at least twice with the different concentrations of the three solvents and the various temperatures. The agreement of duplicate runs was good and indicated that the experimental technique was reproducible.

RESULTS AND DISCUSSION

Each of the three systems produced a distinct pseudo-first-order rate at all concentrations and temperatures. As seen in Tables I to III, the rate increased in all cases when the degradation was carried out under exposure to ultrasound. The lower heat of activation required for those systems subjected to ultrasound would indicate that the mechanical vibrations caused by the ultrasonic energy contributed to the total energy required by the system to effect degradation. Since the thermal energy was kept constant for both ultrasonified and control systems, it was apparent that the ultrasonic energy was responsible for the increase in the kinetic rates.

The portion of the energy causing degradation of a system which is contributed by ultrasound can be affected by the viscosity of the solvent medium. This is illustrated in Fig. 1 and Table IV for the variation of viscosity in the ethylene glycol system. Laidler (9) states, "The reaction of two molecules in solution can be thought of as occurring in three well defined stages: (*a*) diffusion of the molecules to each other; (*b*) the actual chemical transformation; (*c*) the diffusion of the products away from each other." He later states that diffusion is not the rate-determining step in a reaction, and

Table II—Effect of Ultrasonic Energy on the Degradation of Aspirin in Solutions of Diethyl Ether

Concn. Diethyl Ether, %[a]	Temperature, °C.	Control: $K \times 10^2$ (hr.$^{-1}$)[b]	Control: Activation Energy (K/cal.)[c]	Ultrasound: $K \times 10^2$ (hr.$^{-1}$)	Ultrasound: Activation Energy
1	20	0.51	18.90	0.99	14.93
	25	0.68		1.20	
	30	1.25		1.90	
3	20	0.48	19.60	0.74	18.12
	25	1.00		1.35	
	30	1.37		1.89	
5	20	0.37	19.72	0.60	17.6
	25	0.77		1.13	
	30	1.30		1.65	

[a] All runs contained 10% concentration of buffer. [b] Each K rate is the average of at least two runs. [c] The activation energy is calculated from the average K rate.

Table III—Effect of Ultrasonic Energy on the Degradation of Aspirin in Solutions of Diethylene Glycol

Concn. Diethylene Glycol[a], %	Temperature, °C.	Control: $K \times 10^2$ (hr.$^{-1}$)[b]	Control: Activation Energy (K/cal.)[c]	Ultrasound: $K \times 10^2$ (hr.$^{-1}$)	Ultrasound: Activation Energy
5	20	0.58	16.80	4.60	3.66
	30	1.73		5.06	
	40	3.54		7.65	
10	20	0.68	16.40	2.99	7.57
	30	1.62		5.02	
	40	3.75		6.72	
30	20	0.92	17.00	2.12	13.10
	30	2.53		4.60	
	40	5.82		8.05	
50	20	1.24	18.79	1.60	17.63
	30	3.32		5.00	
	40	8.80		11.50	

[a] All runs contained 10% concentration of buffer. [b] Each K rate is the average of at least two runs. [c] The activation energy is calculated from the average K rates.

that the viscosity of a solvent system does not affect the chemical reaction rate. The fact that the effect of viscosity on a chemical degradation in the absence of ultrasound is negligible can be seen in Fig. 1. Although the degradation rate of the control increases because of uneven temperature, the slope remains positive throughout each temperature range. However, the slope of the ultrasonically

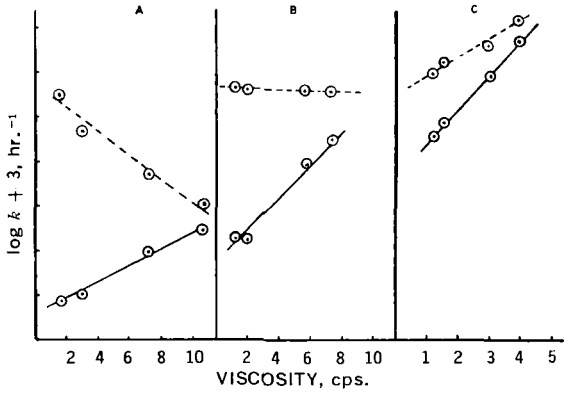

Figure 1—*Comparison of viscosity with the log of the rate of degradation of aspirin for 5, 10, 30, 50% ethylene glycol in water. Key:* A, *20°;* B, *30°;* C, *40°;* —, *without ultrasound;* - - -, *with ultrasound.*

energized degradations changes from a minus slope at 20° to a positive slope at 40°. At 20° the viscosity of the diethylene glycol system changes from 1.95 cps. at 5% to 10.45 cps. at 50%. The increase in viscosity causes a distinct reduction in the degradation

Table IV—Effect of Viscosity and Ultrasonic Energy on the Degradation of Aspirin in Solutions of Ethylene Glycol

Ethylene Glycol, %	Temperature, °C.	Viscosity, cps.[a]	Control, $K \times 10^2$ (hr.$^{-1}$)	Ultrasound, $K \times 10^2$ (hr.$^{-1}$)
5	20	1.950	0.58	4.60
	30	1.438	1.73	5.06
	40	1.103	3.54	7.65
10	20	2.890	0.68	2.99
	30	2.086	1.62	5.02
	40	1.525	3.75	6.72
30	20	6.670	0.92	2.12
	30	4.678	2.53	4.60
	40	3.215	5.82	8.05
50	20	10.450	1.24	1.60
	30	7.270	3.32	5.00
	40	4.905	8.80	11.50

[a] Viscosity taken from literature values.

rate and may be attributed to decreased effectiveness of ultrasonic vibration. As the temperature increases, the difference in viscosity between 5 and 50% samples becomes less and the slope of the degradation approaches that of the control. In the ethanol and diethyl ether solvent systems, there are not significant enough differences in viscosity to produce this effect. Since the differences in viscosity in these two systems are very small, the slope of the ultrasonically effected degradation approaches that of the control throughout the temperature range.

SUMMARY AND CONCLUSIONS

1. Under the conditions stated in this study, the application of ultrasonic energy to a system undergoing degradation will cause an increase in kinetic rate in ethanol–water, diethyl ether–water, and diethylene glycol–water systems.

2. The lowering of the heat of activation is apparently due to the mechanical vibrations of ultrasonic energy applied to the degrading system, since the thermal energy is kept constant.

3. The ultrasonic vibration appears to increase the effect that the movement of the molecules toward each other and the movement of the products away from each other have on the overall rate.

4. As the concentration ratio is increased in an ethylene glycol–water system, the subsequent increase in viscosity apparently reduces the effect on the movement of molecules caused by ultrasonic vibration.

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Photoinduced Interaction of Phenothiazine Drugs with a Lecithin Monomolecular Film

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Abstract □ Monomolecular films of dipalmitoyl lecithin (DPL) were spread onto an aqueous phase into which a potential photosensitizing drug had been dissolved. Chlorpromazine, promazine, triflupromazine, prochlorperazine, and trifluoperazine were the drugs used. The drug-film system was exposed to ultraviolet irradiation and resultant changes in the drug-film interaction determined. The interaction of chlorpromazine and prochlorperazine with the DPL film was found to increase after irradiation. The film interaction of trifluoperazine showed an initial decrease, while that of promazine and triflupromazine was not affected by the irradiation. Thus the substituent in the 2-position of the phenothiazine nucleus appears to be critical in the photosensitized interaction. A phototoxic index was calculated and related to *in vivo* data.

Keyphrases □ Phenothiazine compounds—photosensitivity □ Lecithin monomolecular films-phenothiazines—irradiation □ UV light—film-drug irradiation □ Phototoxic index—determination □ Photoreaction—halogen substitution

The cutaneous edema and erythema that develops in mammals, exposed to sunlight subsequent to treatment with a photosensitizing drug, is indicative of increased cell-membrane permeability. It appears likely then that, at least in some instances, photosensitized reactions and their consequent symptoms are the result of an interaction of a photoproduced species with one or more of the structural elements which maintain membrane integrity. On the basis of this postulation recently proposed was the use of monomolecular films of phospholipids and other cell membrane constituents as a model system for the investigation of photosensitized reactions (1).

In this paper the interaction of a series of UV-irradiated phenothiazine drugs with a monomolecular film of dipalmitoyl lecithin (DPL) is reported. A "phototoxic index" is calculated and related qualitatively to some limited clinical data from the literature.

EXPERIMENTAL

Materials—The *l*-α-dipalmitoyl lecithin (DPL) was chromatographically pure.[1] The following phenothiazine derivatives were used without further purification: chlorpromazine hydrochloride, prochlorperazine hydrochloride, and trifluoperazine dihydrochloride[2]; promazine hydrochloride[3]; and triflupromazine hydrochlo-

[1] Mann Chemical Co., New York, N. Y.
[2] Smith Kline & French, Philadelphia, Pa.
[3] Wyeth Laboratories, Philadelphia, Pa.