International Journal of Pharmaceutics, 51 (1989) 189–194
Elsevier

IJP 01732

The influence of sonic energy on the hydrolysis of procaine hydrochloride in aqueous buffer at pH 9.15

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(Received 15 August 1988)
(Accepted 5 October 1988)

Key words: Sonication; Sonic energy; Procaine hydrochloride; Hydroxyl radical

Summary

The hydrolysis of procaine hydrochloride in borate buffer solution pH 9.15 under sonication is described. Both sonicated and non-sonicated solutions follow first-order kinetics. Activation energy calculations indicate that sonication facilitates a free radical reaction pathway. Experiments are described which show that the rate of reaction is reduced when the hydroxyl radical scavengers glucose and *n*-propyl gallate are added to the procaine hydrochloride solution. Examination of the effects of temperature indicates that below 65°C the influence of hydroxyl radicals on the rate of reaction is important, since their formation is facilitated by low vapour pressure.

Introduction

Sonic energy has a large number of industrial applications including soldering, dental descaling, depolymerisation, laboratory apparatus cleaning and dissolution of solutes in pharmaceutical processes. This last application involves the use of small baths. These baths increase dissolution mainly by increasing temperature and agitation. Sonic energy from such baths has additional effects; microstreaming, sonic energy can propagate both longitudinal and transverse waves through liquids. However, fluids can only support compressional and tensile stress; shear waves rarely penetrate more than 1 μM (Blitz, 1971). Only longitudinal waves are of importance in this situation, where exponential reduction in amplitude occurs within a few wavelengths (Lighthill, 1978). Acoustic propagation is not strictly adiabatic, but most of the energy is absorbed by the fluid resulting in increases in kinetic energy and temperature. Frictional attenuation of longitudinal waves resulting from viscous retardation gives rise to energy dissipation in the boundary layers between solute and solvent increasing the rate of dissolution of the former.

Pressure variations occur due to compression and rarefaction of the fluid under sonication which result in a localised, transient increase in temperature; the movement thus created in the fluid reduces boundary layers and thus facilitates dissolution of the solute.

Cavitation is by far the most important effect of sonication unlike boiling and effervescence, the cavities undergo both expansion and contraction phases (Neppiras, 1980). There are two types of

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cavitation; (i) stable, in which the cavities oscillate about an equilibrium size and remain stable over several acoustic pressure cycles; (ii) transient, where the cavities have a 'life time' of less than one cycle, during which they grow to a maximum size and then implode into a mass of smaller bubbles. Transient bubbles create the most spectacular effects including momentary local pressures of several GPa and temperatures of up to 10^4 to 10^6 K. These effects are visible when the implosion occurs near to the surface of the fluid. Cavitation facilitates the dissolution of solids by the mechanisms previously discussed. In addition, cavitation produces increases in temperature which will influence the rate of chemical reactions. Sonication of water results in decomposition leading to the formation of hydroxyl radicals (Anbar and Pecht, 1967; Makino et al., 1982):

$$H_2O\ OH^{\cdot} + H_2O_2 + H_3O^+ + OH^- + e^-$$

(hydrated)

$$H_2O_2 \rightarrow OH^{\cdot} + OH^-$$

$$H^{\cdot}\ H_2O \rightarrow H_2 + {}^{\cdot}OH^{\cdot}$$

Thus the $OH^{\cdot}$ is the major radical formed in this reaction.

Procaine hydrochloride is a convenient model system being a water-soluble ester which is subject to hydrolysis at high pH. The objectives of the present work are to investigate the effect of sonic energy on the rate of hydrolysis of procaine hydrochloride in buffer at pH 9.15 and in addition to study the role of the hydroxyl radical in this sonic energy-accelerated reaction.

Materials and Methods

Chemicals

Boric acid B.P., Evans Pharmaceuticals, lot no. 8HQ 3740; D-glucose anhydrous, B.D.H. Analar, no. 10117; *n*-propyl gallate, Nipa Laboratories Ltd., potassium chloride, B.D.H. Analar, no. 10198; procaine hydrochloride, B.D.H. Analar, no. 29671.

Apparatus

Sonic generator and water bath, Kerry No. 1184 PUL 125; UV/visible spectrophotometer, Pye Unicam SP 550.

Degradation of procaine hydrochloride

Procaine hydrochloride (100 mg) was dissolved in Clark Lubs borate buffer pH 9.15. (Diem, 1962). An aliquot (5 cm^3) was added to buffer (44 cm^3) which had been heated to the predetermined temperature in a water bath (28, 40, 50, 65, 80 °C). The final volume was adjusted to 50 cm^3 to give a test solution of 0.01% w/v at the chosen temperature. The solution was agitated mechanically and a sample withdrawn. Further samples were taken at time intervals and assayed spectrophotometrically by the method of Higuchi et al. (1950). A series of assays were carried out at each of the temperatures listed above. A second series of experiments was carried out in which the agitation was provided by a sonic cleaning bath.

Additional experiments were carried out in which the Clark Lubs borate buffer was replaced by the same buffer containing 0.05% w/v of D-glucose in the final dilution. In this case agitation was provided separately by mechanical and sonic energy so as to afford two series of results.

Lastly an experiment was carried out at 28 °C in Clark Lubs borate buffer in which *n*-propyl gallate (0.05%) was incorporated into the final dilution.

Results and Discussion

Examination of Tables 1 and 2 shows that both the sonicated and non-sonicated reactions follow first-order kinetics. It is worth pointing out that below 50 °C (Table 1) the reactions also show good agreement with zero-order kinetics but the difference is small enough to be within the limits of experimental error. In both of these reactions the rate of hydrolysis increases with rises in temperature. Examination of Table 3 shows that the rate of reaction is greater in the sonicated system than in the control system at any one temperature, but the magnitude of this increase is not constant at all temperatures. Examination of Figs. 1 and 2

TABLE 1

Hydrolysis of procaine hydrochloride in Clark Lubs borate buffer pH 9.15 non-sonicated

Time (min)	80 °C 353 K		65 °C 338 K		50 °C 323 K		40 °C 313 K		28 °C 301 K	
	mean %	mean log%	mean %	mean log%	mean %	mean log%	mean %	mean log%	mean %	mean log%
0	100.0	2.0000	100.0	2.0000	100.0	2.0000	100.0	2.0000	100.0	2.0000
5	85.3	1.9309	95.1	1.9781	–	–	–	–	–	–
10	77.6	1.8898	90.8	1.9581	95.8	1.9813	–	–	–	–
15	65.6	1.8169	78.4	1.8943	–	–	96.4	1.9841	–	–
20	56.2	1.7497	71.1	1.8518	88.70	1.9479	–	–	–	–
25	47.3	1.6748	63.3	1.8014	–	–	–	–	–	–
30	41.1	1.6138	56.3	1.7505	84.3	1.9258	92.0	1.9638	96.8	1.9859
40	32.4	1.5105	48.3	1.6839	79.1	1.8981	–	–	–	–
45	–	–	–	–	–	–	88.1	1.9449	–	–
50	24.6	1.3909	39.7	1.5987	75.3	1.8767	–	–	–	–
60	–	–	–	–	70.3	1.8469	83.6	1.9222	94.1	1.9735
70	–	–	–	–	65.7	1.8175	–	–	–	–
75	–	–	–	–	–	–	80.6	1.9063		
80	–	–	–	–	63.8	1.8048	–	–	–	–
90	–	–	–	–	–	–	75.8	1.8796	90.1	1.9547
105	–	–	–	–	–	–	71.3	1.8530	–	–
120	–	–	–	–	–	–	68.9	1.8382	87.9	1.9439
150	–	–	–	–	–	–	–	–	84.2	1.9253
180	–	–	–	–	–	–	–	–	78.5	1.8948
210	–	–	–	–	–	–	–	–	75.7	1.8790
240	–	–	–	–	–	–	–	–	71.6	1.8549
Code	a	b	c	d	e	f	g	h	i	j

Residual quantities of procaine HCl

Values are means of 3 assays. E_{act} is obtained by calculating linear regression of log k against $1/T$ absolute gradient = $-E_{act}/2.303\ R$ (R = gas constant). $E_{act} = 51.21$ kJ/mol.

Regression coefficients and reaction rate constants:

a = −0.9747; b = −0.9982, k = (0.283); c = −0.9876; d = −0.9968, k = (0.0142); e = −0.9955; f = −0.9969, k = (0.0058); g = −0.9990; h = −0.9957, k = (0.0032); i = −0.9960; j = −0.9929, k = (0.00139).

shows that the range of values for each data point is very much larger in the sonicated system. This may be a function of the localised temperature rises resulting from cavitation in which implosions of microbubbles liberate heat.

It will be noted that the activation energy is less in the case of the sonicated system falling from 51.12 kJ/mol to 24.14 kJ/mol. However, activation energy is related to $\Delta H^{\#}$ (enthalpy of activation) which corresponds to the energy necessary to effect the stretching and breaking of bonds. In both the sonicated and non-sonicated systems the activation energy (E_{act}) and $\Delta H^{\#}$ are positive. Consequently for part of the reaction pathway for the hydrolysis of procaine hydrochloride the free energy of activation will be positive, the two being related: $-\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$, where $\Delta G^{\#}$ = the free energy of activation, $\Delta H^{\#}$ = the enthalpy of activation, T = absolute temperature, $\Delta S^{\#}$ = the entropy of activation.

However, the Gibbs free energy of the whole reaction must be negative. Thus it would appear that sonication facilitates an alternative reaction pathway which may be due to free radical action. This suggestion was supported by the evidence accrued from the experiments with free radical scavengers (D-glucose and *n*-propyl gallate) (Tables 4 and 5).

Clearly, the formation of hydroxyl radicals due to sonication of water used as a solvent facilitates

TABLE 2

Hydrolysis of procaine hydrochloride in Clark Lubs borate buffer pH 9.15, sonicated

Time (min)	80 °C 353 K		65 °C 338 K		50 °C 323 K		40 °C 313 K		28 °C 301 K	
	mean %	mean log%	mean %	mean log%	mean %	mean log%	mean %	mean log%	mean %	mean log%
0	100.0	2.0000	100.0	2.0000	100.0	2.0000	100.0	2.0000	100.0	2.0000
5	89.3	1.9507	95.1	1.9782	–	–	–	–	–	–
10	77.1	1.8868	90.8	1.9578	94.6	1.9756	90.1	1.9544	93.8	1.9721
15	65.6	1.8165	78.4	1.8947	–	–	–	–	–	–
20	56.7	1.7847	71.1	1.8521	86.3	1.9360	86.2	1.9355	88.5	1.9469
25	52.8	1.7226	63.3	1.8014	–	–	–	–	–	–
30	45.1	1.6541	56.3	1.7505	72.4	1.8597	76.9	1.8859	83.7	1.9227
40	37.6	1.5751	48.3	1.6839	64.9	1.8122	70.9	1.8506	75.2	1.8762
50	30.6	1.4857	39.7	1.5987	57.7	1.7611	66.2	1.8208	73.3	1.8651
60	–	–	–	–	52.3	1.7185	59.8	1.7767	68.7	1.8360
70	–	–	–	–	47.8	1.6794	53.9	1.7316	64.0	1.8062
80	–	–	–	–	43.4	1.6374	51.8	1.7143	54.1	1.7331
Code	a	b	c	d	e	f	g	h	i	j

Residual quantities of procaine HCl. Valves are means of 3 assays.

E_{act} is obtained by calculating the linear regression of log k against $1/T$ (absolute).

Gradient $= -E_{act}/2.303$ R (R = gas constant).

$E_{act} = 24.14$ kJ mol^{-1}.

Regression coefficients and reaction rate constants: a $= -0.9673$; b $= -0.9970$, $k = 0.0240$; c $= -0.9875$; d $= -0.9961$, $k = 0.0194$; e $= -0.9872$; f $= -0.9962$, $k = 0.01097$; g $= -0.9931$; h $= -0.9975$, $k = 0.00845$; i $= -0.9939$; j $= -0.9870$, $k = 0.00707$.

the hydrolysis of procaine hydrochloride. Thus any factor which affects cavitation will have some bearing on the rate of hydrolysis of the test drug. Suslick et al. (1983) have suggested that the maximal temperature generated during the implosion of a microbubble is related to the vapour pressure of the solvent:

$$T_{max} = T_0 \times p_a \times (\gamma - 1)/Q$$

T_{max} = maximum temperature generated, T_0 =

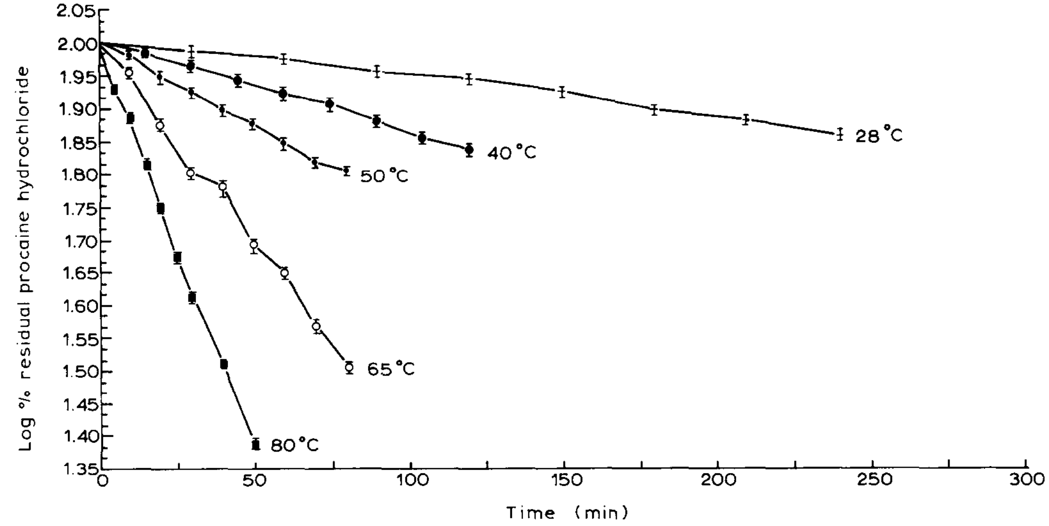

Fig. 1. Hydrolysis of procaine hydrochloride in Clark Lubs borate buffer pH 9.15 without sonic energy.

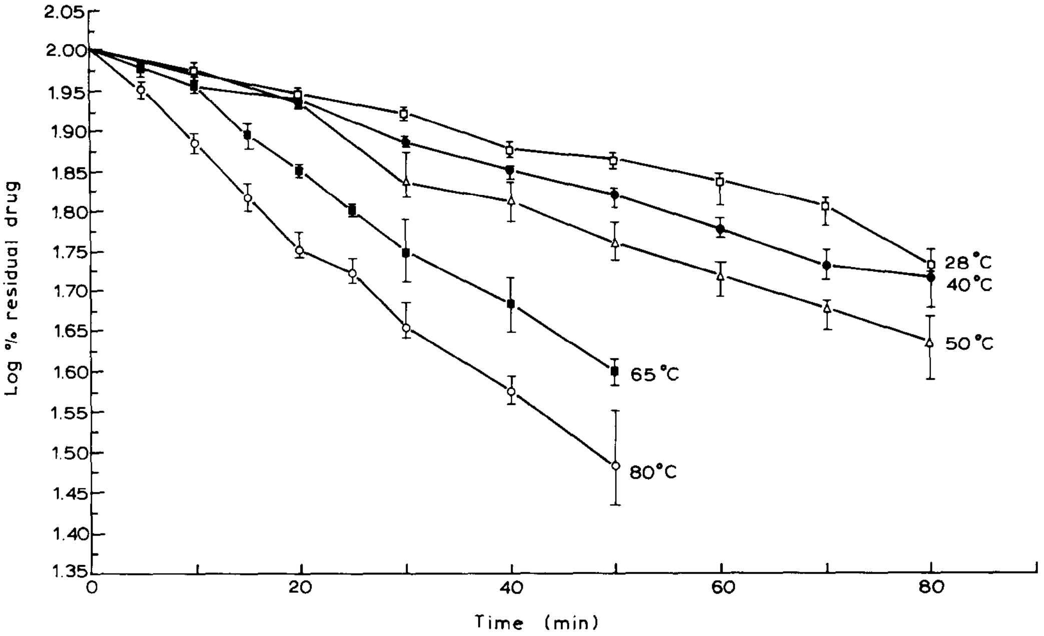

Fig. 2. Hydrolysis of procaine hydrochloride in Clark Lubs borate buffer pH 9.15 with sonic energy.

TABLE 3

The influence of sonic energy on the amount of procaine hydrochloride hydrolysed after 30 minutes

Temp. (°C)	Percentage hydrolysed without sonic energy	Percentage hydrolysed with sonic energy	Increase (%)
28	3.2	16.3	13.1
40	8.0	23.1	15.1
50	15.7	27.6	11.9
65	43.7	43.7	0.0
80	58.9	54.9	−4.0

TABLE 4

The influence of the addition of D-glucose (5% w/v) on the hydrolysis of procaine hydrochloride in Clark Lubs borate buffer at pH 9.15 at 28°C with and without sonic energy

Time (min)	With sonic energy		Without sonic energy	
	With glucose	Without glucose	With glucose	Without glucose
0	100.0	100.0	100.0	100.0
30	97.8	83.7	98.8	96.8
60	96.0	68.7	97.0	94.1

Procaine HCl remaining.
Each figure represents the mean % of 3 assays.

ambient temperature, p_a = acoustic pressure at the point of bubble implosion; γ = ratio of specific heats; Q = gas pressure in the bubble at the point of implosion. If Q is equal to the vapour pressure of the solvent (p_v) and since the hydrolysis of procaine hydrochloride in Clark Lubs borate buffer at pH 9.15 follows Arrhenius behaviour then:

$$\ln k = \frac{\ln A - E_{act} \times p_v}{R \times T_0 \times p_a(\gamma - 1)}$$

TABLE 5

The influence of the addition of n-propyl gallate (0.05%) on the hydrolysis of procaine hydrochloride in Clark Lubs borate buffer at pH 9.15 at 28°C with and without sonic energy

Time (min)	With sonic energy		Without sonic energy	
	With *n*-propyl gallate	Without *n*-propyl gallate	With *n*-propyl gallate	Without *n*-propyl gallate
0	100.0	100.0	100.0	100.0
30	92.6	83.7	97.9	96.8
60	82.4	68.7	94.0	94.1

Procaine HCl remaining.
Each figure represents the mean % of 3 assays.

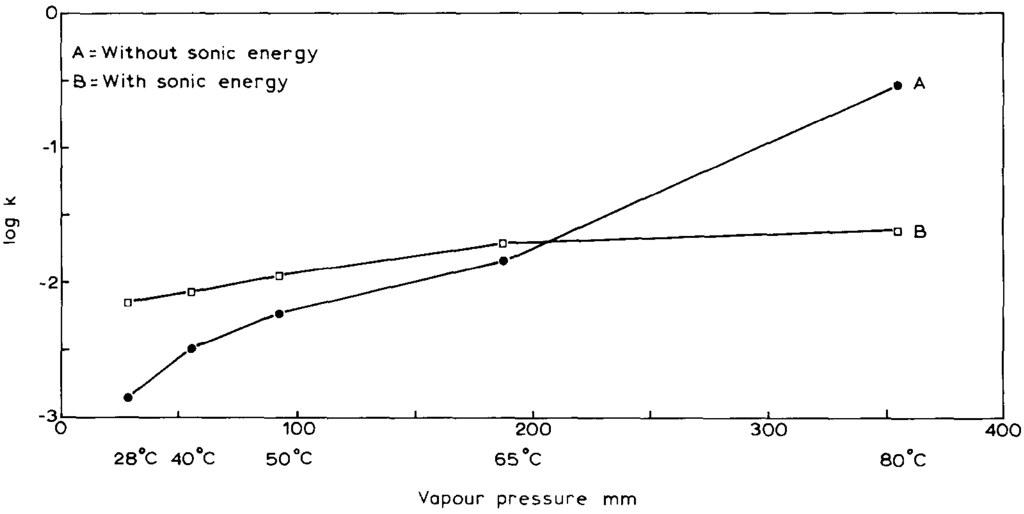

Fig. 3. Plot of log of reaction rate against vapour pressure of water at various temperatures.

where A = the reaction constant (Sykes, 1980), R = gas constant (8.32 J mol^{-1} K^{-1}).

Plotting log k against vapour pressure (Fig. 3) shows in the case of the sonicated system a change in direction of the line at a vapour pressure of 187.54 mmHg which corresponds to 65 °C. This may imply that the hydroxyl radical plays an important role in the hydrolysis of procaine hydrochloride below this temperature under the test conditions. This may offer some explanation for the regression coefficients of the log of the mean residual percentages of the drug plotted against time being similar to those of the mean residual percentages plotted against time at temperatures of 65 °C and below (Tables 1 and 2). This suggests that there may be a change in reaction order when hydroxyl radicals are exerting their effect.

Conclusions

The rate constants for the reaction with sonic energy are greater than those for the reaction carried out without sonic energy. This effect was attributed to the action of hydroxyl radicals generated by the action of sonic energy on water. The formation of hydroxyl radicals is facilitated by reduction in vapour pressure and thus temperature. Although sonic energy facilitates dissolution of the drug in an aqueous medium it does promote decomposition and so it should be used with extreme caution with solutions of procaine hydrochloride.

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