

STABILITY OF COCAINE IN AQUEOUS SOLUTION

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SUMMARY

The effect of pH on the rate of hydrolysis of cocaine was investigated. Ionic strength had a negligible effect while the concentrations of the various buffers had a significant effect on the rate of hydrolysis. The pH rate profile in buffer showed a minimum at 1.95. The energies of activation were determined to be 95.9, 107.3 and 97.9 kJ mol⁻¹ respectively at pH 6.8, 5.0 and 2.2. The stability on storage of sterilized solutions of cocaine prepared by various methods and formulae was compared with the stability predicted from the results of the accelerated tests.

Cocaine is a naturally occurring alkaloid obtained from the dried leaves of *Erythroxylum coca* or *E. truxillense*. In addition, the leaves contain benzoylecgonine, ecgonine and a variety of other alkaloids (Fig. 1).

A number of studies on the degradation of cocaine have been reported since the late 19th century, but none of these authors isolated cocaine from benzoylecgonine and ecgonine before measuring the amount present and the degradation products were included in and responded to the assay.

It is used as a local anaesthetic in eye, nose and throat surgery and in euphoriant elixirs which are given to patients with terminal carcinoma.

MATERIALS

Cocaine hydrochloride was obtained from Macarthys Ltd., Edinburgh, and Macfarlan Smith Ltd., Edinburgh. Ecgonine was donated by May and Baker Co. Ltd, Dagenham, England. Water was prepared from an all-glass still. All other chemicals were reagent grade and those used as buffers were Analar.

ASSAY PROCEDURE

A sample (0.25 ml containing 2.5 mg of cocaine hydrochloride) was mixed with 10 ml of 5% sodium bicarbonate and extracted with ether (10, 10 and 15 ml). The combined extract was dried over sodium sulphate anhydrous and then extracted with 0.01 N HCl (100 and 50 ml). The combined aqueous extracts were diluted to 250 ml with 0.01 N HCl and the

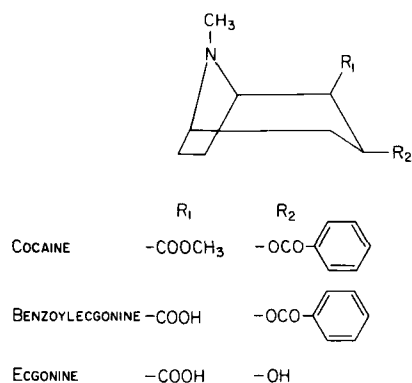


Fig. 1. Structure of main alkaloids of *Erythroxylum* spp.

extinction measured at 233 nm against 0.01 N HCl. Mean absorbance of ten experiments 0.381. Standard deviation (s.d.) 0.0022 and coefficient of variation (C.V.) 0.56%.

To ascertain that benzoylecgonine and ecgonine did not interfere with the assay of cocaine, cocaine 1% was measured in presence of 0.5% benzoylecgonine and 0.5% ecgonine. The mean absorbance = 0.382, s.d. = 0.003, and C.V. = 0.79%. Beer's Law was found to be obeyed.

KINETIC PROCEDURE

To determine the effects of pH on the rate of degradation of cocaine a solution of 1% cocaine hydrochloride in the appropriate buffer solution was prepared and immediately distributed into 5-ml glass ampoules and then immersed in a water bath at constant temperature. Two minutes were permitted for the temperature to equilibrate and then a sample was taken and cooled in ice and two 2-ml portions were assayed by the procedure quoted previously. Further samples of the solutions were taken at six appropriate times and assayed.

RESULTS AND DISCUSSION

Under the above conditions cocaine degraded to benzoylecgonine, no ecgonine was found on the basis of thin-layer chromatography evidence.

Order of reaction and observed rate constant

At constant pH and temperature the degradation of cocaine was found to observe pseudo first-order kinetics. Fig. 2 shows the results of several experimental runs at 80°C and at various pHs. The observed rate constants k_{obs} between pH 1 and pH 8.8 are shown (Table 1). A minimum rate was observed at pH 1.95. The observed rate was actually a summation of a series of catalytic reaction rates induced by the buffer species, hydrogen and hydroxide ions and water molecules.

General acid-base catalysis was observed and the rates of degradation of cocaine in citric acid-potassium citrate buffer solutions (Table 2) increased with increased concentration of buffer between pH 2.2 and 4.8.

Both acidic and alkaline hydrolysis is possible for cocaine. In solution it can exist as the

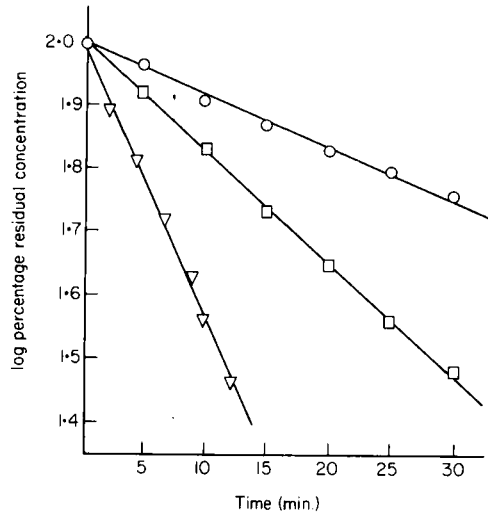


Fig. 2. Plot of log percentage residual concentration against time for solutions of cocaine hydrochloride at 80°C and pH 7.65 (Δ), pH 7.00 (□) and pH 6.48 (○).

Table 1. Stability at 80°C of a 0.1% solution of cocaine hydrochloride from pH 8.8 to pH 1.0 in single strength buffer*

pH	Rate constant k (s^{-1})	Standard error of rate constant (s^{-1})
8.80	0.4604×10^{-2}	0.1679×10^{-3}
8.45	0.3985×10^{-2}	0.1494×10^{-3}
8.00	0.2480×10^{-2}	0.5804×10^{-4}
7.65	0.1691×10^{-2}	0.3257×10^{-4}
7.00	0.6747×10^{-3}	0.8506×10^{-5}
6.48	0.3160×10^{-3}	0.6148×10^{-5}
6.00	0.1294×10^{-3}	0.8426×10^{-6}
5.60	0.3854×10^{-4}	0.4000×10^{-6}
5.20	0.1662×10^{-4}	0.2333×10^{-7}
4.95	0.9675×10^{-5}	0.3634×10^{-6}
4.55	0.4898×10^{-5}	0.8716×10^{-7}
4.25	0.3180×10^{-5}	0.6227×10^{-7}
3.60	0.1695×10^{-5}	0.2843×10^{-7}
3.18	0.1035×10^{-5}	0.4558×10^{-7}
2.61	0.7274×10^{-6}	0.1122×10^{-7}
1.95	0.4757×10^{-6}	0.1285×10^{-7}
1.30	0.1798×10^{-5}	0.1452×10^{-6}
1.00	0.4475×10^{-5}	0.2636×10^{-7}

*pH 1-1.85 Clark and Lubs potassium chloride-hydrochloric acid buffer. pH 2.2-8.0 McIlwaine's citric acid-phosphate buffer. pH 8.0 Bates and Bower borax-hydrochloric acid buffer.

Table 2. Effects of the molar concentration of citric acid-potassium citrate buffer solution on the stability of a 1.0% solution of cocaine hydrochloride at 80°C and various pH values. Observed rate constant $\times 10^{-6} \text{ s}^{-1}$ \pm confidence limits at total buffer concentration mol/l

pH	Buffer concentration					K_o^*	$\log K_o^*$
	0.05	0.1	0.2	0.3	0.4		
2.2	0.494 \pm 0.02	0.569 \pm 0.01	0.729 \pm 0.01	0.918 \pm 0.02	1.05 \pm 0.01	0.45 \pm 0.02 -0.03	-6.346
3.2	0.971 \pm 0.05	0.881 \pm 0.03	1.25 \pm 0.03	1.59 \pm 0.06	1.84 \pm 0.06	0.81 \pm 0.04 -0.08	-6.125
4.2	2.27 \pm 0.04	2.58 \pm 0.1	3.21 \pm 0.05	3.93 \pm 0.1	4.17 \pm 0.09	2.05 \pm 0.21 -0.14	-5.688
4.8	5.94 \pm 0.13	6.63 \pm 0.25	7.94 \pm 0.32	9.46 \pm 0.21	10.60 \pm 0.63	5.27 \pm 0.001 -0.02	-5.278

*The rate at buffer-free condition was obtained by extrapolation.

free base and as the monoprotonated form, the concentration of these two species being dependent upon the pH of the solution and the ionization constant of cocaine.

The effect of ionic strength

The rate constants at pH 1.15, 5.0 and 6.0 were compared with rate constants at the same pHs obtained with 1.169% NaCl present and the differences were found to be negligible.

Apparent heat of activation

The temperature dependence of the hydrolytic rate constant of cocaine in aqueous solution was shown by the results obtained from pH 6.8, 5.0 and 2.2 at a range of temperatures; the Arrhenius type plots are shown in Fig. 3.

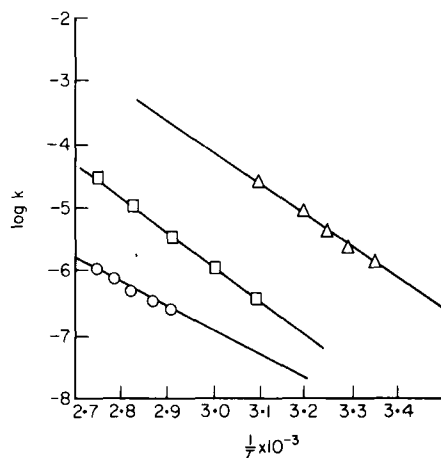


Fig. 3. Plot of the log rate constant $k(s^{-1})$ against $1/T$ (K^{-1}) for a 1.0% solution of cocaine hydrochloride at pH 6.8 (Δ), pH 5.0 (\square) and pH 2.2 (\circ).

The calculated energies of activation are 95.9 ± 3.7 kJ mol^{-1} at pH 6.8, 107.3 ± 6.0 kJ mol^{-1} at pH 5.00 and 97.9 ± 9.3 kJ mol^{-1} at pH 2.2. These values are in the same range as those quoted for other ester hydrolyses although direct comparisons are not possible unless the determinations are made at the same pH values.

PHARMACEUTICAL APPLICATIONS

The main application of the work has been the determination of the stability of Cocaine Eye Drops BPC and a comparison with buffered cocaine solutions. The results are shown in Tables 3 and 4.

Cocaine Eye Drops BPC are unbuffered sterile solutions, the stability of which after autoclaving or steaming in 5-ml glass ampoules is shown in Table 3.

At pH 6.8 in Table 4 and 25°C the predicted $t_{10\%}$ was $24.5 \text{ h} + 1.1, -1.06$ ($P = 0.95$) and the experimental $t_{10\%}$ was in the range 23.4-22.7 h. However, at 5°C the predicted and experimental $t_{10\%}$ were not in close agreement, the difference being possibly due to the difficulty in control of the storage temperature at 5°C . At pH 5.0 good agreement was

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