*J. Pharm. Pharmac.*, 1970, **22**, 612–614 *Received January* 20, 1970

# A borax-chloramphenicol complex in aqueous solution

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A 1,2-complex between borax and chloramphenicol occurs in aqueous solution. The relative stabilities of simple aqueous solutions of chloramphenicol and the B.P.C. eye-drops are explained by the existence of this complex.

The kinetics of the hydrolysis of chloramphenicol in aqueous solution have been investigated by Higuchi, Marcus & Bias (1954) who showed that the reaction was general acid-base catalysed, and was slowest and substantially independent of pH between 2 and 7. It is therefore necessary to buffer aqueous chloramphenicol solutions within this range, and borax and boric acid are used for this purpose in the B.P.C. eye-drops. These substances appear to have a more specific effect on chloramphenicol than most buffers, thus Fenton (1955) showed that chloramphenicol is more soluble in 0·6% borax solution than in either water or 0·6% sodium carbonate, and Broadhurst & Wright (1959) found that chloramphenicol was nearly 5 times more stable in borax buffer than in phosphate buffer, even though both had the same pH.

Boric acid is known to complex with hydroxy compounds (Sciarra & Elliott, 1960). An investigation was therefore undertaken to determine if the influence of the borax-boric acid buffer of the B.P.C. eyedrops on chloramphenicol could be due to the existence of a similar complex.

## EXPERIMENTAL

*Thin-layer chromatography.* The procedure has been described (James & Leach 1970).

*Solubility determinations.* Excess chloramphenicol was shaken at the required temperature with solutions of borax or boric acid of the required strengths until saturated. Preliminary experiments showed that 4 h were sufficient. Samples of saturated solution were withdrawn and assayed spectrophotometrically at 274 nm. The degree of hydrolysis during the 4 h equilibrium period was less than 1% and was therefore disregarded.

*pH determinations.* pH values of solutions of chloramphenicol with boric acid and of chloramphenicol with borax were measured using a Pye-Unicam 290 pH meter. Concentrations of borax and boric acid were kept constant throughout, and precautions were taken to exclude carbon dioxide.

*Determination of decomposition rates.* Samples of a 0·05% solution of chloramphenicol in water were packed in 5 ml ampoules and immersed in a constant temperature bath for 6 h. Samples were withdrawn at hourly intervals, and assayed by the amine method, described previously (James & Leach, 1970).

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## DISCUSSION

Thin layer chromatography of fresh aqueous solutions of chloramphenicol gave one spot, but freshly prepared solutions in the borax-boric acid buffer gave two, the upper spot corresponding to that of the aqueous solution, indicating that chloramphenicol exists in the borax-boric acid buffer in a form not encountered in simple aqueous solutions.

pH determinations revealed no evidence for complexation of chloramphenicol with either borax or boric acid. Solubilities were not influenced by the presence of boric acid, but increased with borax concentration. These results were not directly due to the effect of borax on pH since there is no correlation between solubilities and pH values (Table 1). Confirmation was obtained by determining solubilities in a range of glycine buffers between pH 6·9 and 9·1 and observing that the solubility was constant.

Table 1. *Solubility of chloramphenicol in borax solutions*

| Molar borax concentration | Solubility % | pH of solution |
|---|---|---|
| 0 | 0·375 | 4·70 |
| 0·0001 | 0·391 | 7·15 |
| 0·001 | 0·438 | 8·65 |
| 0·005 | 0·614 | 8·65 |
| 0·01 | 0·732 | 8·65 |
| 0·02 | 1·23 | 8·65 |
| 0·05 | 2·14 | 8·70 |
| 0·11 | 3·46 | 8·90 |
| 0·125 | 3·67 | 8·90 |
| 0·15 | 3·87 | 9·00 |

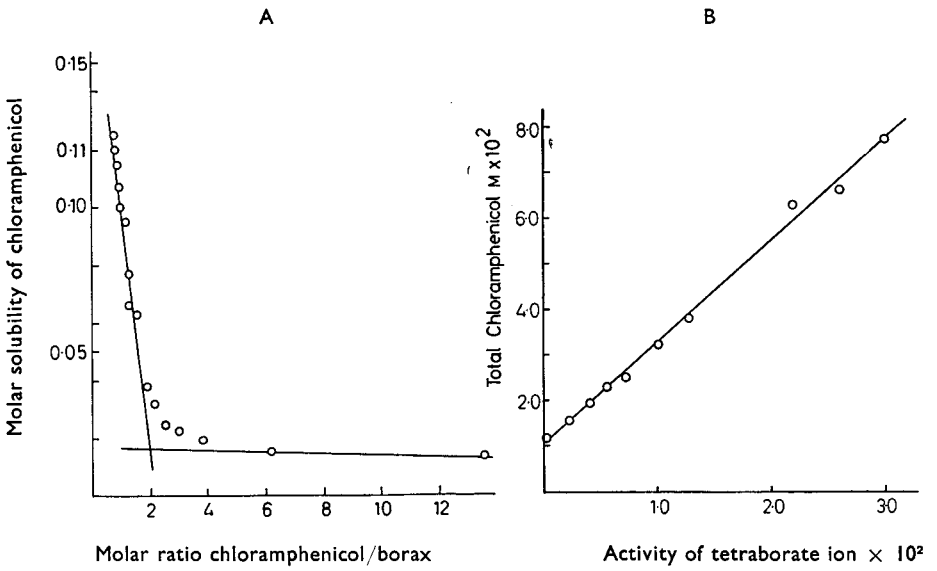


FIG. 1A. Determination of stoichiometric ratio of chloramphenicol to borax.
B. Solubility of chloramphenicol in aqueous borax solutions at 25°.

Solubilities at 25·5° are plotted against the molar ratio, chloramphenicol/borax, in Fig. 1A. The graph shows an inflection at a ratio of 2, suggesting the equilibrium,

$$2C + B \overset{K_1}{\rightleftharpoons} C_2B \tag{1}$$

where C represents chloramphenicol, and B borax.

A plot of total chloramphenicol in solution ($C_t$) against total borax ($B_t$) is linear for this type of equilibrium, with an intercept ($C_o$), representing the solubility of chloramphenicol in water. The actual graph was curved and presumed to be a consequence of non-ideal behaviour of borax. The mean activity coefficients (f) of electrolyte solutions of ionic strength ($\mu$) up to about 0·25, are given by Debye-Hückel theory as,

$$\log f = \frac{Az^+ z^- \sqrt{\mu}}{1 + \sqrt{\mu}} \tag{2}$$

where z represents the charges on the respective ions, and A is a temperature dependent constant, having a value of 0·51 at 25°. The graph of total chloramphenicol against tetraborate ion activity, calculated from equation (2) is in fact linear, as shown in Fig. 1B, confirming equilibrium (1). A similar plot was obtained with the 37° results.

The quantity of uncomplexed chloramphenicol ($C_o$) is limited by its aqueous solubility, and is constant, so that the equilibrium can be expressed as,

$$K = \frac{[C_2B]}{C_o^2\,[B]} \tag{3}$$

$[C_2B]$ can be placed equal to $\frac{1}{2}(C_t - C_o)$, and uncomplexed borax concentration [B] calculated as $[B_t - \frac{1}{2}(C_t - C_o)]f$. Substitution in equation (3) gave mean equilibrium constants of $2{\cdot}9 \times 10^4$ at 25° and $1{\cdot}1 \times 10^4$ at 37°. An approximate heat of complexation of 67 kJ $mol^{-1}$ was obtained from these results. If this is assumed to be independent of temperature, an equilibrium constant of about 100 would be anticipated at 100°. Chloramphenicol solutions for intrathecal injection or for irrigation of infected wounds are sometimes sterilized by autoclaving. Such solutions are not usually buffered, and were therefore expected to decompose more rapidly than the eye-drops. In contrast, rate determinations gave first order constants of $7{\cdot}74 \times 10^{-4} min^{-1}$ at 100° and $2{\cdot}01 \times 10^{-3} min^{-1}$ at 115°, compared with $1{\cdot}15 \times 10^{-3}$ and $3{\cdot}03 \times 10^{-3}$ respectively, for the eye-drops. Any stabilizing effect due to complexation will be reduced by general acid-base catalysis by the buffer ions. The poor stability of the eye-drops at elevated temperatures, compared with that of the simple aqueous solution, probably arises because the degree of complexation is so small in this region that the second effect predominates.

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