EFFECT OF BORATES ON THE STABILITY OF CHEMICAL AND PHARMACEUTICAL COMPOUNDS

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ABSTRACT:
Borate ions are found to have an important role in analytical and kinetic studies both for the purpose of maintaining pH and as a catalyst in the chemical degradation of a number of drugs such as atropine, benzylpenicillin, carbenicillin, cefotaxime, cephradine, hydrocortisone, indomethacin, oxytetracycline, phenylbutazone, minocycline, 5-fluorouracil, methacoline, octastatin etc. They have also been reported to exert a stabilizing effect on certain drugs including chloramphenicol, epinephrine, riboflavin, α-methyldopa, ethyl glucuronide, ribose and glucose. Borate buffer is widely used in ophthalmic formulations for the maintenance of pH and adjustment. Boric acid is involved in the catalysis of a number of reactions of biological importance including the L-arabinose isomerase catalyzed isomerization of D-galactose to D-tagatose in the presence of boric acid.

Keywords: Borates, Stability.

INTRODUCTION
Borate buffers are extensively used in chemical and pharmaceutical studies. They have been found to interact with many organic and medicinal compounds and to catalyze their degradation reactions. In certain cases these buffers exert a stabilizing effect on drug substances. The stabilization of compounds containing polyhydroxy groups including drugs is due to the complexation of these compounds with boric acid. Borate complexation has been used for the separation, identification and determination of polyhydroxy compounds using spectrometric, chromatographic and electrochemical techniques. The borate effects on drug stability and stabilization are presented in the following sections.

1. Effect on Drug Stability

1.1 Catalytic Effect
Borate buffers have been used to maintain pH in the study of the stability of drug substances. Alterations in pH may affect the kinetics and mode of a chemical reaction1-3. Borate buffers act as catalyst in the degradation of a number of drugs in the alkaline borax-boric acid medium, a 0.5% atropine solution degraded to the extent of 44% in one month4. Borate ions have a catalytic effect on the benzylpenicillinate ion in the degradation of benzylpenicillin5. Carbenicillin undergoes general-base catalyzed hydrolysis in the presence of borate ions6. Borate buffer increases the rate of degradation of cefotaxime in alkaline solution7. The dependence of the observed rate constants for cephradine hydrolysis on total buffer concentration in borate buffer has been shown8. Enhanced oxidative degradation of hydrocortisone in borate and phosphate buffers appears to be due to trace metals since the catalytic effects can be greatly reduced by the addition of disodium edetate9. The apparent activation energy for the degradation of hydrocortisone in 0.2 M borate buffer (pH 9.1) is 14.3 kcal mol\(^{-1}\) compared to that of 23.3 kcal mol\(^{-1}\) in 1.0 M HCl solution10. The catalytic effect of borate buffer on the alkaline hydrolysis of indomethacin (pH 8.5) is about two fold compared to that of the phosphate buffer11. In aqueous methotrexate solutions, borate buffer may catalyze the hydrolysis of the drug in a concentration-dependent manner12. The hydrolysis of oxytetracycline is subject to general-base catalysis by borate ions at pH 8.5-9.913. First-order rate constants for borate catalyzed hydrolysis of phenylbutazone at pH 9.1 have been determined.
The rate of hydrolysis is slightly greater than that of the hydrolysis product, N-(2-carboxycaproyl)-hydrazobenzene\textsuperscript{14}. The degradation of minocycline both under aerobic and anaerobic conditions is catalyzed by borate buffer\textsuperscript{15}. The advantage of using borate or phosphate buffer in high-temperature sterilization of procaine solutions is much less because of the rapid change in hydroxyl ion concentration with temperature in these buffers\textsuperscript{16}. The activation energies for the alkaline hydrolysis of 5-fluorouracil in borate buffer are higher than those in the unbuffered solutions\textsuperscript{17}. The methanolic chloride solutions prepared in borate buffer (pH 9.0) and stored at 27°C are degraded up to 60% after one week\textsuperscript{18}. Methanolic solutions of danazol in aqueous borate buffer undergo base-catalysis degradation by proton abstraction and follow pseudo-first order kinetics\textsuperscript{19}. The degradation of Octastatin, a cyclic octapeptide, is influenced by borate buffer\textsuperscript{20}.

1.2 Stabilizing Effect
Borate buffer has been found to exert a stabilizing effect on chloramphenicol solutions whereas phosphate and citrate buffers catalyze the hydrolysis of the drug\textsuperscript{21}. Boric acid is useful in ophthalmic formulations because of its physiological compatibility, its utility for adjustment of isotonicity and its stabilizing action on epinephrine\textsuperscript{22}. The oxidation of \(\alpha\)-methyldopa solutions is inhibited by the addition of borate ions\textsuperscript{23}. Cocaine hydrochloride is incompatible with sodium borate, which liberates the free-base cocaine in alkaline solution\textsuperscript{2}.

Under acidic conditions boric acid increases the thermostability of ribose and under basic conditions that of glucose\textsuperscript{24}. It is a useful preservative for the stabilization of ethyl glucuronide in urine samples that is employed as a specific and sensitive marker of ethanol consumption\textsuperscript{25}.

Borate buffer is known to complex with the ribityl side chain of riboflavin (vitamin B\textsubscript{2}) in a reversible 1:1 association and the negatively charged complex is more resistant to hydroxyl ion attack on the isoalloxazine ring\textsuperscript{36}. The boric acid component of the buffer is involved in the formation of the riboflavin-borate complex\textsuperscript{27-30}, which could influence the rate of its photolysis reactions\textsuperscript{31-32}. Recently a detailed study of the photolysis of riboflavin at 8.0-10.5 in the presence of borate buffer has been conducted and the rate constants for the reaction have been determined\textsuperscript{33}. The values of the rate constants have been found to decrease with an increase in buffer concentration suggesting that the borate species inhibit the rate of photolysis of riboflavin as a result of the formation of riboflavin borate complex. The rate constants for the photolysis of riboflavin are about two times slower than those obtained in the absence of borate buffer indicating a significant buffer effect on the reaction.

2. Borate Catalyzed Reactions
Boric acid catalyzes the selective esterification of alpha-hydroxycarboxylic acids. The procedure is high-yielding and applicable to alpha-hydroxycarboxylic acids in the presence of other carboxylic acids including beta-hydroxy acids within the same molecule\textsuperscript{34}. N-methyl-4-boronopyridinium iodide is a more effective catalyst than boric acid for the esterification of alpha-hydroxycarboxylic acids\textsuperscript{35}. The kinetics of the oxidation of substituted phenyl methyl sulfides by hydrogen peroxide in borate/boric acid buffers has been studied as a function of pH, total peroxide and total boron concentrations. Second-order rate constants at 25°C for the reaction of methyl-4-nitrophenyl sulfoxide and hydrogen peroxide, monoperoxoborate, or diperoxyborate are 8.29 x 10\textsuperscript{-5}, 1.51 x 10\textsuperscript{-2} and 1.06 x 10\textsuperscript{2} M\textsuperscript{-1}s\textsuperscript{-1}, respectively\textsuperscript{36}. An L-arabinose isomerase mutant enzyme has been used to catalyze the isomerization of D-galactose to D-tagatose with boric acid. Maximum production (74%) of D-tagatose occurs at pH 8.5-9.0, 60°C, and 0.4 molar ratio of boric acid to D-galactose\textsuperscript{37}.

The photodecomposition of hydrogen peroxide in borate/boric acid buffer is inhibited at higher pH. The quantum yield of the reaction is 0.8±0.1\textsuperscript{38}. Boric acid inhibits the acid-catalyzed depolymerization of cellulose in sulpholane at high temperature. Formation of dehydration products such as levoglucosenone, furfural and 5-hydroxymethyl furfural is also effectively inhibited\textsuperscript{39}. The inhibition of protease activity in rat liver chromatin by certain boronic acids has been reported\textsuperscript{40}. The 2-phenylethaneboronic acid has been found to inhibit cell replication and this effect may be higher in rapidly proliferating cancer cells than in the normal tissues\textsuperscript{41}. 

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CONCLUSION
Boric acid / borates have found wide analytical applications in the form of buffers and catalyzing / stabilizing agents for drug substances. Their presence may alter the rate of a chemical reaction especially of drug degradation. Boric acid has been involved in enzyme catalyzed biological reactions such as the isomerization of D-galactose to D-tagatose. A study of the catalytic reactions produced by borates / boric acid may enable a better understanding of the mode of stabilization of certain drug substances. This is based on the complexation of these drugs with boric acid.

REFERENCES


