The Effect of Boric Acid on the Dehydration Step in the Formation of Oxime from Salicylaldehyde

Edesio L. Simionatto, Pablo R. Yunes and Rosendo A. Yunes*
Departamento de Química, Universidade Federal de Santa Catarina, 88040-970-Florianópolis, SC-Brasil

Boric acid accelerates notably the reaction rate of oxime formation from salicylaldehyde. The kinetic results and the UV spectroscopic analysis, which demonstrate no complex formation between salicylaldehyde and boric acid, suggest that the effect of boric acid is on the transition state of the dehydration step of the reaction *via* its complexation with the neutral addition intermediate formed by a rapid equilibrium between salicylaldehyde and hydroxylamine. The mechanism proposed is different from that previously suggested.

The mechanism of dehydration of the addition intermediate, formed from carbonyl compounds and nitrogen nucleophiles, has not been widely studied.[1] We have recently suggested that the dehydration of the addition intermediate formed from 2-furaldehydes and phenylhydroxylamine exhibits intramolecular catalysis.[2]

Okuyama *et al.*[9] observed that the dehydration step in hydrazone formation from α-hydroxybutyrophenone is accelerated by boric acid in the pH range 7–10. This effect is of great interest in view of its similarity to enzyme catalysis.[4] Most of the work carried out on the effect of boric acid was with the mechanism as hydrolysis, the reverse of dehydration. Thus, the hydrolysis of *N*-salicylideneaniline,[5] phenyl salicylate[6] and thioesters of α- and β-hydroxy carboxylic acids[7] was demonstrated to be accelerated by boric acid. Okuyama *et al.*[8] found that boric acid retards the hydrolysis of *N*-salicylidene-2-methoxyethylamine below pH 5.5, but it accelerates the hydrolysis above pH 5.5.

On the other hand, boric acid forms complexes with polyols,[9] α-hydroxy carboxylic acids,[10] salicylate ions[11] and salicylaldehyde oxime.[12] This last complex led us to study the effect of boric acid on the reaction of oxime formation from salicylaldehyde, considering that in this two-step reaction it should be related to the dehydration step and also that from this effect we could obtain new evidence for the comprehension of this mechanism.

Results and Discussion

Fig. 1 shows a plot of the rate constants k_{obs} (pseudo-first-order rate constant working with excess of hydroxylamine) for the reaction between salicylaldehyde and hydroxylamine, with and without boric acid present, as a function of the pH. Between pH 5.5 and approximately pH 10.0, boric acid (0.01 mol dm^{-3}) accelerates the rate of the reaction, with a maximum at pH 7.3.

The effect is surprising because the increase of the rate constant is very high, seven times faster than that of the spontaneous rate at pH 7.3, at low concentrations of boric acid (0.01 mol dm^{-3}). Other buffers such as acetate, phosphate monoanion, *etc.*, showed general acid catalysis but only at 0.1–0.5 mol dm^{-3}. Buffers with pK_a similar to that of borate, such as morpholine and trimethylamine, did not show catalysis at a concentration of 0.01 mol dm^{-3}.

The rate increases linearly with the boric acid buffer concentration. The third-order rate constants determined in the presence of boric acid buffers were plotted against molar fraction of free acid for several different concentrations of buffer, always with $[B]_T$ < 0.04 mol dm^{-3} to avoid the association of boric acid molecules that may diminish its activity.[13] The plot showed that only the acidic component of the buffer catalyses the reaction. In Fig. 2 is shown the Brønsted plot for general acid catalysis by acetic acid, succinate monoanion, phosphate monoanion and hydroxylammonium ion in the reaction of oxime formation from salicylaldehyde (α = 0.79, r = 0.992). Statistical corrections were not applied. It is observed that the value of the apparent catalytic rate constant for boric acid, considering the total concentration of salicylaldehyde (dissociated + non-dissociated species), is 7000 times larger than predicted by the Brønsted relationship. This indicates that the effect of boric acid is not caused by a simple proton transfer, as it is for the other catalyst, but is caused by another special mechanism.

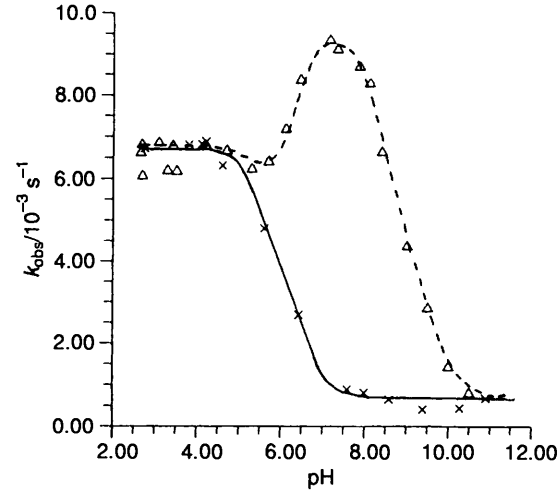


Fig. 1 Pseudo-first-order constant k_{obs}(s^{-1}) for oxime formation from hydroxylamine (0.01 mol dm^{-3}) and salicylaldehyde (10^{-4} mol dm^{-3}) as a function of pH at 25 °C, ionic strength 1.0 mol dm^{-3} (KCl): (△) with boric acid present (0.01 mol dm^{-3}); (×) without boric acid present. The lines (—) and (- - -) were calculated using eqn. (3) corresponding to the dehydration step.

To analyse the mechanism of the effect of the boric acid we must consider the following points: (i) The UV spectra of salicylaldehyde (10^{-4} mol dm^{-3}) at pH 5.70 and 9.30 do not change with the addition of boric acid (0.01–0.04 mol dm^{-3}), suggesting that these compounds do not interact. (ii) It is not known that there is any interaction between hydroxylamine and boric acid. (iii) Ripan *et al.*[12] showed that salicylaldehyde oxime and boric acid (0.01 mol dm^{-3}) form a stable complex in the pH range 7.10–11.47. (iv) We have found that the rate of the reaction

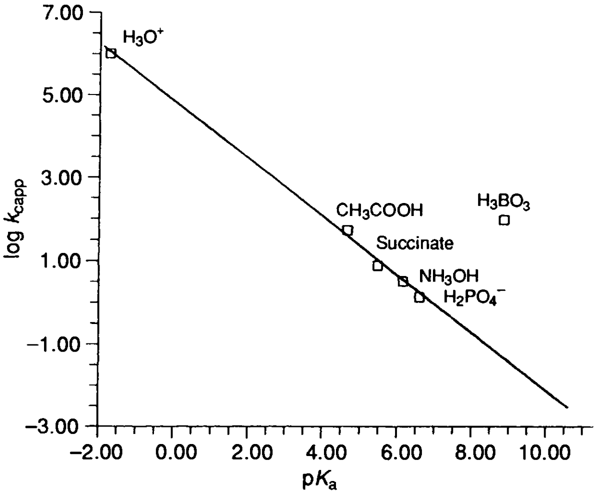
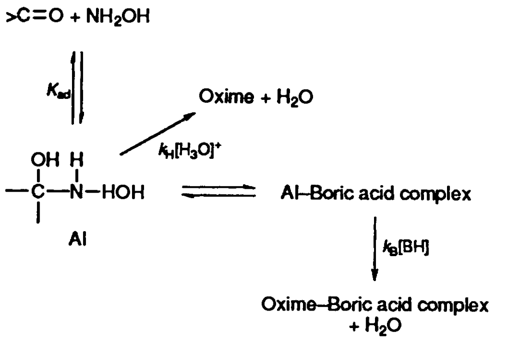


Fig. 2 Brønsted plot for general acid catalysis of the dehydration step of the reaction between salicylaldehyde and hydroxylamine in water, at 25 °C and ionic strength 1.0 mol dm^{-3} (KCl)

of salicylaldehyde oxime with boric acid (0.01 mol dm^{-3}) at pH 5.5–10.0, to give the salicylaldehyde oxime–boric acid complex, is very large compared with the rate of the reaction of salicylaldehyde and hydroxylamine in the presence of boric acid (0.01 mol dm^{-3}). The rate of the same reaction, without the presence of boric acid, is the slowest. (v) It is known that above pH 5.5 the rate-determining step of the reaction of benzaldehydes with hydroxylamine is the dehydration of an addition intermediate formed by a rapid equilibrium between the reagents.[14,15] All of these points suggest that the effect of the boric acid to accelerate the reaction is on the transition state of the dehydration step of the reaction, probably *via* the complexation of the addition intermediate formed between salicylaldehyde and hydroxylamine according to Scheme 1.

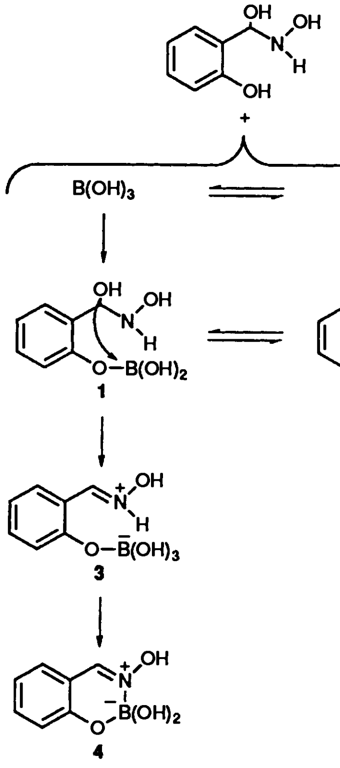


Scheme 1

Scheme 1 enables us to explain Fig. 1. Below a pH value of approximately 2.5, the rate-determining step of the reaction is the attack of the nucleophile on the carbonyl compounds[15] ($v = k_1[>C{=}O][RNH_2]$), between pH 2.5 and 5.5 the rate-determining step is the hydronium ion-catalysed dehydration of the addition intermediate ($v = k_H[AI][H_3O^+]$), and finally at pH higher than 5.5 the boric acid-catalysed dehydration of the addition intermediate becomes the rate-determining step. In this last case the term ($k_B[AI][BH]$) should become greater than the term ($k_H[AI][H_3O^+]$) at pH 5.5 and, as the concentration of boric acid is practically constant in the pH range 5.5–7.3, it is clear that the increase of the reaction rate is caused by the increase of the addition intermediate concentration (pK_a of NH_2OH = 6.15).

The pK_a for dissociation of the hydroxy group of the salicylaldehyde is 8.07,[16] (μ = 0.7), the pK_a of boric acid 8.85[17] and the pK_a for the phenolic hydroxy group of the addition intermediate can be calculated as 9.83 from the pK_a of phenol, applying the equation pK_a = 9.92–2.23σ_0[18] and the value of σ_0 for $-CH_2OH$ = 0.04[19] (the group –NHOH should not introduce a significant change in the pK_a value). Consequently, the decrease in the rate constant above pH 7.3 should be related to the decrease in the concentration of boric acid, because the basic form is not a catalyst of the reaction. It should be noted that the equilibrium constant for the formation of the addition intermediate from the non-dissociated salicylaldehyde and hydroxylamine was determined as K_{ad} = 0.217 and that corresponding to the dissociated salicylaldehyde and hydroxylamine as K_{ad} = 0.205; in this way, it is possible to consider the total concentration of salicylaldehyde as the reacting species.

Okuyama *et al.*[7] have suggested that the mechanism of the dehydration of the addition intermediate is the microscopic reverse of the mechanism of hydrolysis in the case of the Schiff's base derived from α-hydroxyisobutyrophenone and 2-methoxyethylamine. This mechanism applied to the reaction studied in this work is indicated in Scheme 2.



Scheme 2

The product **4** is reasonable, considering that Kliegel *et al.*[20] have demonstrated that salicylaldehyde oxime reacts with diphenylborinic acid anhydride to give a chelate that contains a six-membered heterocyclic ring with intramolecular N–B coordination. However, this mechanism has questionable points. The equilibrium for formation, in water, of the intermediate **1** must lie far to the left, because it is readily hydrolysed, and fundamentally the intermediate **3** should be very unstable, owing to its pK_a. From the pK_a of the protonated oxime of *p*-chlorobenzaldehyde[21] which is −1.25, the pK_a of intermediate **3** can be estimated to be one or two pK_a units higher owing to the lack of the chlorine atom and the presence of the negatively charged boron atom.

In this mechanism of dehydration two facts should be considered; the first is that the inversion of trigonal boric acid giving tetrahedrally coordinated borate ion is very rapid,[10] the second is that interaction of ligands with boric acid, stabilizing a four-coordinate species, would be reflected in an increased rate;

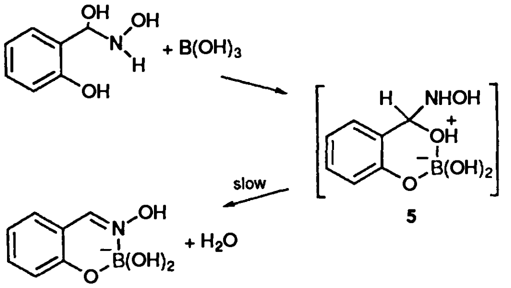
Table 1 General acid-catalysed rate constants for salicylaldehyde oxime formation[a]

Catalyst	k_{capp}/dm^3 mol^{-1} s^{-2}[b]	log k_{capp}	pK_a
Hydronium ion	9.531 × 10^5	5.979	−1.74
Acetic acid	54.4	1.735	4.65
Succinate	7.8	0.892	5.48
Hydroxylammonium	3.3	0.518	6.15
Phosphate monoanion	1.4	0.146	6.60
Boric acid	98.0	1.992	8.85

[a] In aqueous solution at μ = 1.0 mol dm^{-3} (KCl) and 25 °C. [b] $k_{capp} = kK_{ad}$.

thus salicylaldehyde oxime, where this kind of interaction is favoured by the position and nature of the ligands, reacts with boric acid faster than the addition intermediate of the reaction of salicylaldehyde with hydroxylamine. In this way another mechanism should be considered.

Reliable determination of the K_{ad} (equilibrium constant of dihydroxy addition-intermediate formation) permits us to determine the true dehydration constant for benzaldehyde oxime and salicylaldehyde oxime formation. The values are: K_{ad} = 17 dm^3 mol^{-1},[14] k_0 = 5.0 × 10^{-4} dm^3 mol^{-1} s^{-1} for benzaldehyde oxime and K_{ad} = 0.21 dm^3 mol^{-1}, k_0 = 0.21 dm^3 mol^{-1} s^{-1} for salicylaldehyde oxime. The dehydration rate constant for salicylaldehyde oxime formation is approximately 400 times greater than that of benzaldehyde oxime formation, showing that the *ortho* aromatic hydroxy group catalyses the dehydration of the addition intermediate stabilizing the departure of the hydroxide ion leaving group in the transition state. In this way, a probable mechanism that can explain the high increase of the rate constant by boric acid is, assumed by analogy with the intramolecular catalysis previously indicated, by the formation of a boron four-coordinate complex with the addition intermediate of the reaction giving a stable six-membered ring (Scheme 3, structure 5).



Scheme 3

The pK_a of the protonated oxygen of intermediate **5** could be estimated from the pK_a of a protonated ether (for diethyl ether pK_a = −2.39[22]). Using the values of σ^* 0.30[19] and 0.75[19] for -NHOH and -Ph groups respectively, and the equation $\Delta pK = 0.06 + 0.63\,\sigma^*$,[19] correction for these substituents gives pK_a = −4.31. However, the negative charge on the boron atom should increase this pK_a (by approximately 12 ± 2 units), considering its effects to be analogous to that of the negatively charged oxygen atom on the pK_a of the substituted ammonium ion in the intermediate $T^{\pm}$ of the reaction between *p*-chlorobenzaldehyde and 2-methyl-3-thiosemicarbazone[23] and of the reaction of *p*-chlorobenzaldehyde with methoxyamine.[24]

Intermediate **5** should be more stable than intermediate **3** (of Scheme 2) suggested by Okuyama.[7] The departure of the hydroxy group as hydroxide ion is stabilized by the effect of the boric acid, and the subsequent pathway to give oxime should be very fast as long as the rapid double bond formation leads to the ideal configuration for the bonding between the boron and the nitrogen atom.

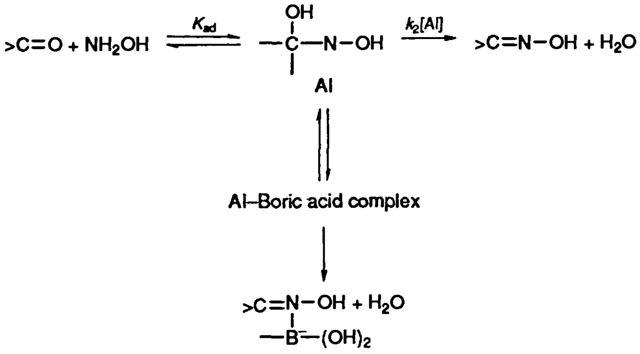
The formation of a four-coordinate complex between the boric acid and the aromatic hydroxy group and the nitrogen atom, forming a stable six-membered cyclic configuration, is not supported by the fact that reaction between salicylaldehyde and *N*-methylhydroxylamine to give the corresponding nitrone exhibits the same behaviour as the reaction between salicylaldehyde and hydroxylamine. In the case of the reaction between salicylaldehyde and *N*-methylhydroxylamine the formation of the last indicated complex between the boric acid and the addition intermediate of the reaction should inhibit the dehydration step.

Experimental

Materials.—All reagents were obtained commercially and, except for reagent grade inorganic salts, were either recrystallized or redistilled before use.

Kinetic Measurements and Treatment of Data:—The reactions were followed spectrophotometrically by monitoring the formation of salicylaldehyde oxime at 300 nm with initial concentration of the hydroxylamine 10^{-2} mol dm^{-3} and of the salicylaldehyde 10^{-4} mol dm^{-3} so that pseudo-first-order behaviour is observed. All kinetic experiments were carried out at 25 °C, in water at an ionic strength of 1.0 mol dm^{-3} (KCl), and rate constants were calculated with a computer.

The mechanism of the reaction is outlined in Scheme 4.



Scheme 4

The dehydration step exhibits general acid catalysis and the special effect of boric acid. When the dehydration is the rate-determining step, considering that both species of salicylaldehyde (dissociated and non-dissociated) give approximately the same value of their equilibrium constant with the addition intermediate formed with hydroxylamine, the rate law has the form indicated in eqn. (1).

$$\text{rate} = k_H K_{ad}[C{=}O]_T[N][H^+] + k_H K_{ad}[C{=}O]_T[N][AH] + k_B K_{ad}[C{=}O]_T[N][BH] \qquad (1)$$

As k_{obs} = rate/[C=O]$_T$, eqn. (2) holds, where $k_H K_{ad}$, $k_{AH} K_{ad}$

$$k_{2app} = k_{obs}/[N] = k_H K_{ad}[H^+] + k_{AH} K_{ad}[AH] + k_B K_{ad}[BH] \qquad (2)$$

and $k_B K_{ad}$ are the k_{capp} (apparent catalytic constants) given in Table 1.

The line in Fig. 1 was calculated using eqn. (3).

$$k_{obs} = k_H K_{ad}[N][H^+] + k_B K_{ad}[N][BH] \qquad (3)$$

The k_{capp} for the general acid catalysis was obtained from the plot of $k_{2\text{app}}$ *vs.* [AH] (concentration as free acid in the buffer), working with different concentrations of buffer corresponding to each acid (0.1 to 0.5 mol dm^{-3}) at constant pH, without boric acid present, and the k_{capp} for boric acid was obtained from the plot of k_{B} *vs.* [BH] (concentration as free boric acid in the buffer) working with different concentrations of boric acid (0.01–0.04 mol dm^{-3}) between pH 8.15 and 9.45, at constant pH.

Equilibrium Constant Determination.—The equilibrium constant of the neutral addition intermediate formation from hydroxylamine and the non-dissociated salicylaldehyde at pH = 5.2 (acetate buffer) and ionic strength 1.0 mol dm^{-3} (KCl) was determined spectrophotometrically following the method of Reimann and Jencks.[25] The value obtained was 0.217. The equilibrium constant for the dissociated salicylaldehyde at pH 9.30 (HCO_3^- buffer) was 0.205.

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