pH as a Variable in Free Zinc Ion Concentration from Zinc-Containing Lozenges

In their letters, Eby and Godfrey claim that Zn^{2+} will be tightly bound to citrate in saliva upon administration of lozenges containing the two ingredients (G. A. Eby, Letter, Antimicrob. Agents Chemother. **32**:606–607, 1988; J. C. Godfrey, Letter, Antimicrob. Agents Chemother. **32**:605–606, 1988). The lozenges contained citric acid (6), however, and unless several equivalents of base per mole of citric acid are added, citrate will not be produced and tight citrate complexes cannot form. The limited buffer capacity of saliva (1) is insufficient to raise the pH to promote formation of tight complexes. Therefore, much of the zinc added with citric acid in a lozenge is likely to appear as free, unbound Zn^{2+} in saliva.

If a 4.5-g lozenge containing 2% citric acid (6) generates 20 ml of saliva (Godfrey, Letter), the citric acid concentration becomes 23 mM and produces a pH of 2.3. For citric acid (molecular weight, 192) the successive acidity constant pK_a values are 3.0, 4.4, and 5.8 (8). Addition of one equivalent or nearly 0.5 mmol of base raises the pH only to 3.7, and even addition of two equivalents of base or almost 1 mmol yields only a pH of 5.1. Thus, due to the acidity of citric acid and the low buffer capacity of saliva, much of the added Zn^{2+} is likely to remain as the free metal ion. Although ligands present in saliva will bind some Zn^{2+}, the acidity created by adding citric acid reduces their chelating ability.

Figure 1 shows the distribution of zinc-citrate species as mole fraction on a zinc basis versus pH for a citric acid-to-total-zinc mole ratio of 1.3, identical to that in the lozenges (6). Stability constants for the Zn^{2+} and citric acid system have been fairly well elaborated, and the values used are taken from a standard critical compilation (7). As indicated by the curve descending from the left in Fig. 1, the percentage of free, unbound Zn^{2+} begins to decrease at pH 3, passing through 50% at pH 3.7, 10% at pH 4.4, and remaining at 1.5% at pH 5.1. The neutral species $ZnLH^0$, likely to pass through membranes, exhibits a maximum mole fraction of 0.33 at pH 3.9, with significant concentrations from pH 3 to 5. At pH > 4, the 1:1 ZnL^- and 2:1 complexes dominate with the relative amounts, depending on the citrate-to-total-zinc mole ratio. Ternary hydroxo complexes appear to be of little importance at pH < 8.

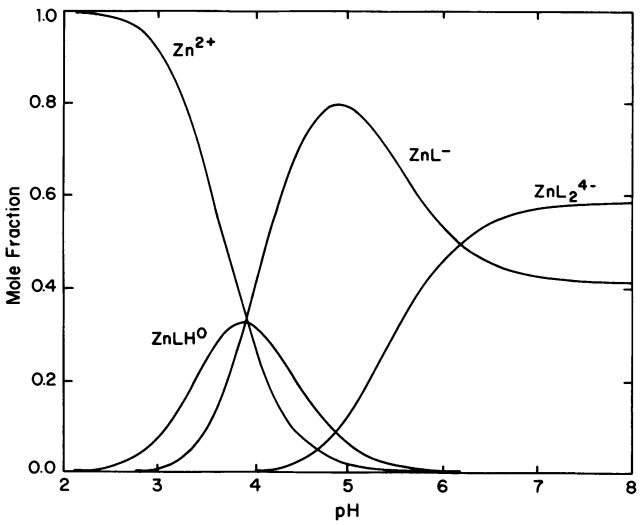

FIG. 1. Mole fraction Zn^{2+} species versus pH for solution with Zn^{2+} and excess citric acid (H_3L). At any pH, the curves sum to unity. Curves constructed from the stability-constant logarithms (7) in parentheses after each reaction: $Zn^{2+} + HL^{2-} \rightarrow ZnLH$ (3.0), $Zn^{2+} + L^{3-} \rightarrow ZnL^-$ (4.8), and $ZnL^- + L^{3-} \rightarrow ZnL_2^{4-}$ (1.7). Except for the ratio of the last two complexes, the general shape of the curves is independent of the specific concentrations of 18 mM Zn^{2+} and 23 mM citric acid. The successive pK_a values for citric acid deprotonations are $pK_1 = 3.0$, $pK_2 = 4.4$, and $pK_3 = 5.8$ (8). Not included in the analysis is a small amount of $ZnLH_2^+$ of low stability likely to form near pH 3.

Tartaric acid contained in the tablets in another study (4) had an acidifying effect similar to that of citric acid. However, since tartrate binds Zn^{2+} about 100 times less strongly than citrate (7), it is much less effective in reducing the free Zn^{2+} concentration. Thus, it is likely that in both studies (4, 6) significant fractions of total zinc appear as the free metal ion and the concentrations compare with those of the original study with zinc gluconate (5). Gluconate binds Zn^{2+} about 10 times less strongly than tartrate (3). In acidic solutions, and especially in the presence of chelating ligands, insoluble ZnO, $Zn(OH)_2$, $Zn_5(OH)_6(CO_3)_2$, and $ZnCO_3$ are unlikely to be significant factors (2, 10).

First-stability-constant logarithms for Zn^{2+} binding to ligands are as follows: citrate, 4.8; aspartate, 5.8 (7); tartrate, 2.7 (3, 7); and gluconate, 1.7 (3). Although determined at 25°C, these values are little affected by temperature. The value of 5.8 for aspartate needs to be reduced to allow for the protonated ammonium group ($pK_a = 9.7$), and the conditional (9) first-stability constant applicable to pH 6.8 is given by $\log K_c = 5.8 - 9.7 + 6.8 = 2.9$.

Eby (Letter) quotes a variety of irrelevant equilibrium (not first-stability) constants which for tartrate, aspartate, and citrate are from 5,000 to more than 1,000,000 times too high. For example, the value quoted for citrate refers to formation of a ternary hydroxo complex, and even this doubtful value indicates that the reaction does not become important until pH > 7.

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