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Communication

Effect of Inhibitors on the Catalyzed Dehydration of HCO_3^- by Copper(II) Complexes Re-Evaluated

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In a recent paper by Cheng and co-workers (Sun, Y.-J.; Zang, L. Z.; Cheng, P.; Lin, H.-K.; Yan, S.-P.; Sun, W.; Liao, D.-Z.; Jiang, Z.-H.; Shen, P.-W. *Inorg. Chem.* **2003**, *42*, 508–515), kinetic evidence for inhibitor effects of specific ligands on the catalyzed dehydration of HCO_3^- by copper(II) complexes of the type [Tp^{Ph}]CuX ($X^- = OH^-$, N_3^-, and NCS^-) was reported. The analysis of the kinetic data is not correct, and a re-evaluation shows that the claimed catalytic activity of the studied complexes on the dehydration reaction of bicarbonate is indeed questionable. Furthermore, the apparent inhibitor effect of specific selected ligands in the Cu(II) complexes does not seem to exist at all and is based on a wrong interpretation of the kinetic data.

Introduction

Cheng and co-workers recently reported in this journal[1] a kinetic study of the effect of inhibitors on the catalyzed dehydration of HCO_3^- by a series of Cu(II) complexes of the type [Tp^{Ph}]CuX, where [Tp^{Ph}] = hydrotris(3-phenylpyrazolyl)borate and X = OH^- (**1**), N_3^- (**2**), and NCS^- (**3**). The analysis of the kinetic data, on which basis the effect of the inhibitors X and the catalytic role of the Cu(II) complexes was interpreted, is unfortunately not correct and calls for a re-evaluation of the data in order to prevent further misinterpretation of this and related reports in the literature. Furthermore, the reported data is of fundamental importance to the understanding of the catalytic function of carbonic anhydrase,[2,3] and could be misleading to chemists not familiar with the kinetic details of such studies. Our experience in this area,[2,4−11] especially with the handling and interpretation of kinetic data for such reactions, has made us aware of the potential importance of the reported findings[1] and encouraged the composition of this Communication.

Cheng and co-workers[1] studied the dehydration rate of HCO_3^- as a function of the concentration of the selected Cu(II) complexes, and found that the observed first-order dehydration rate constant depends on the concentration and nature of the selected Cu(II) complex. From this concentration dependence, they estimated rate constants for the catalytic process. A careful inspection of their results (Figure 4 in ref 1) shows that the plots of k_{obs} versus [Cu(II)] not only exhibit the mentioned concentration dependence, but also shows a significant intercept at zero Cu(II) concentration. In fact, the observed acceleration (i.e., increase in k_{obs} with increasing [Cu(II)]) is indeed very small as compared to the large intercepts observed for the three studied complexes. Furthermore, the slopes of the plots are so similar that the three complexes exhibit virtually the same catalytic activity within the error limits of such kinetic measurements. It is only the intercepts of the plots, i.e., a contribution from a Cu(II) complex independent pathway, that show some dependence on the nature of the complex. The authors do not comment on the intercepts at all and conclude that the dehydration rate constant varies linearly with the total Cu(II) concentration, which is only true if one ignores the large intercepts in the plots. In order to demonstrate this point, the data as presented by the authors are plotted in Figure 1, and the same data are plotted in Figure 2 on a scale selected to show the importance of the ignored intercepts. It is quite clear from Figure 2 that the apparently observed catalytic effect is indeed very small within the experimental error limits of such measurements.

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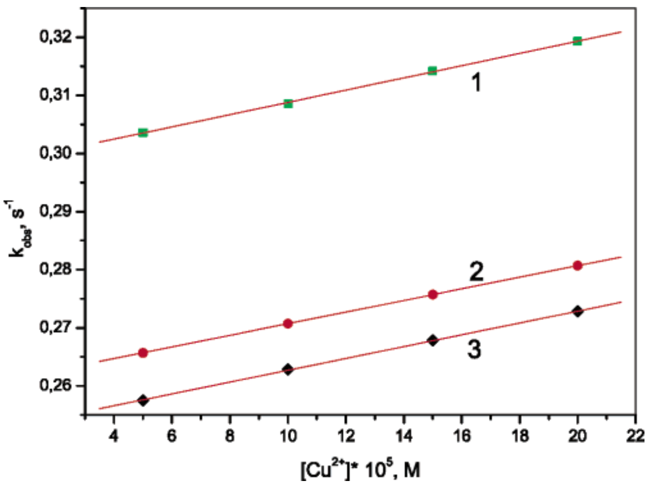

Figure 1. Data plotted as reported in Figure 4 of ref 1.

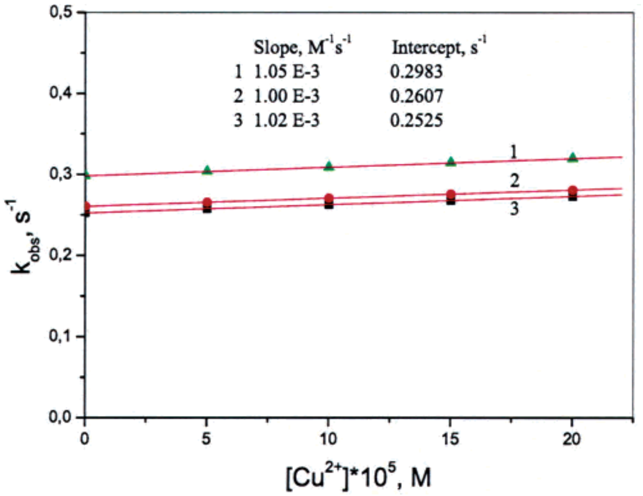

Figure 2. Data from Figure 1 plotted on a different scale to illustrate the large effect of the intercept and the minor influence of the studied catalysts (see ref 1 for more detail on the selected systems).

In the subsequent work described in their paper (viz. studies on the pH dependence, effect of free inhibitors, and temperature dependence),[1] the authors select a typical catalyst concentration of 1.5 × 10^{-4} M for all investigations. However, according to the data in Figure 2, the value of k_{obs} under such conditions includes at least a 90% contribution of the intercept, i.e., merely a 10% contribution of the reaction path that depends on the concentration of the Cu(II) complexes. From the value of k_{obs} at the selected Cu(II) concentration, the authors conclude that the catalytic activity of the model complexes decreases in the order **1** > **2** > **3**, which apparently shows (according to the authors) that the dehydration process is affected by the Cu(II) complexes containing certain inhibitors. However, on correcting the observed rate constant for the large contribution of the complex independent term (intercept), this statement is totally wrong since the slopes of the lines (which actually represents the catalytic activity of the Cu(II) complexes) are practically constant for all three selected systems, and the claimed observed inhibition is only due to the different intercepts observed. All the subsequent measurements performed under these selected conditions for the variables mentioned above must now be reinterpreted in terms of the combined contributions of the very large intercept (>90%) and the relatively small contribution caused by the Cu(II) complex (<10%).

The subsequent analysis of k_{obs} as a function of pH (keeping in mind that k_{obs} mainly consists of the unidentified intercept at zero Cu(II) concentration) results in an apparent first-order rate constant for the catalytic activity of the aqua complexes and their corresponding pK_a values (see Table 4 in ref 1). The practically constant values of k and K_a for the three studied systems (unfortunately no error limits are given by the authors) once again illustrates that the reported quantities cannot be mainly due to the contribution of the Cu(II) complexes. The same is true for the temperature dependence measured under the selected conditions, and again, the activation parameters reported in Table 5 of ref 1 are, within the usual experimental error limits for such data (not given in ref 1), practically the same for all three systems.

What the authors should have done is quite clear to experienced kineticists, viz. k_{obs} should have been measured as a function of the Cu(II) complex concentration in all subsequent experiments in which the pH, free inhibitor concentration, and temperature (their Figures 5−7)[1] were varied, in order to be able to differentiate between the contributions of the intercept and slope of the plots shown in Figure 1 under the selected conditions. Only in that way would it have been possible to draw valid conclusions about the catalytic activity of the studied complexes.

A fundamental question (not treated by the authors) concerns the nature and possible origin of the large intercepts in Figure 1. A logical explanation would be to assign the intercepts to the spontaneous dehydration of HCO_3^-, which will consist of contributions from "water" and "acid" catalyzed pathways, viz. $k_{obs} = k_{water} + k_H[H^+]$. These rate constants are known from the literature, viz. $k_{water} = 2 \times 10^{-4}$ s^{-1} and $k_H = 5.6 \times 10^4$ M^{-1} s^{-1} at 25 °C.[2] However, at pH 7.0, these rate constants cannot account for the observed intercepts that vary between 0.25 and 0.30 s^{-1}. Thus, another process must account for the occurrence of the intercepts. This could be due to a spontaneous dehydration reaction of intermediate bicarbonate complexes, since it is well-known that such complexes are unstable and easily decarboxylate to the corresponding hydroxo complexes, for which loss of CO_2 via O−C bond cleavage could be the rate-determining step. Typical rate constants for decarboxylation reactions of coordinated bicarbonate vary between 0.3 and 2 s^{-1} at 25 °C for a series of octahedral complexes.[2] Under such conditions, the formation of intermediate bicarbonate complexes and their subsequent decarboxylation reactions could account for the large intercepts and be considered as a parallel reaction path for the dehydration of bicarbonate. This, however, would require a very efficient complex-formation reaction between the studied Cu(II) complexes and bicarbonate.

In conclusion, the claimed catalytic activity of the investigated Cu(II) complexes on the dehydration reaction of bicarbonate is indeed questionable and calls for a more detailed, complete kinetic investigation as suggested above. In addition, the apparent inhibitor effect of particularly selected ligands in the Cu(II) complexes on the catalytic activity does not seem to exist at all and is based on a wrong interpretation of the kinetic data.

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