Simple Derivation of the pH at Which the Rate of Nitrosation of a Secondary Amine Is Maximized

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Abstract: The rate of nitrosation of a simple secondary amine in aqueous solution is greatest at the pH that maximizes the total solution content of nitrous acid and free-base (unprotonated) secondary amine. The value of this pH, designated as pH_{max}, can be easily derived through consideration of the equilibria involved. The derivation of pH_{max} as given demonstrates that it is possible to predict from first principles some significant aspects of nitrosation kinetics. The importance of understanding pH_{max} with respect to promoting or avoiding nitrosamine formation is discussed.

Introduction

The carcinogenic nature of nitrosamines is well known, and the formation of nitrosamines in aqueous solution by the reaction of secondary amines with active nitrosating agents has been thoroughly described [1]. A simple representation of nitrosamine formation is given by eq 1.

$$\mathrm{Y{-}N{=}O + RR'NH \rightarrow RR'NNO + HY}$$

$$(\mathrm{Y = Cl^-, Br^-, SCN^-, NO_2^-, NO_3^-}, \text{etc.}) \qquad (1)$$

The most important process for the generation of active nitrosating agents involves the reaction of protonated nitrous acid with a dissolved anion to yield a nitrosyl species.

$$\mathrm{NO_2^- + H^+ \rightleftharpoons HNO_2} \qquad (2)$$

$$\mathrm{HNO_2 + H^+ \rightleftharpoons H_2O^+{-}N{=}O} \qquad (3)$$

$$\mathrm{H_2O^+{-}N{=}O + Y^- \rightarrow Y{-}N{=}O + H_2O} \qquad (4)$$

When Y^- is chloride, the active nitrosating agent is nitrosyl chloride (ClNO). When Y^- is bromide, the active nitrosating agent is nitrosyl bromide (BrNO). A special case occurs when only nitrite is involved in the equilibria.

$$\mathrm{NO_2^- + H^+ \rightleftharpoons HNO_2} \qquad (5)$$

$$\mathrm{HNO_2 + H^+ \rightleftharpoons H_2O^+{-}N{=}O} \qquad (6)$$

$$\mathrm{H_2O^+{-}N{=}O + NO_2^- \rightarrow NO_2{-}N{=}O + H_2O} \qquad (7)$$

In this case, the active nitrosating agent is nitrosyl nitrite, which is also known as N_2O_3, dinitrogen trioxide and nitrous anhydride. In order to produce nitrosamines it is apparent that a secondary amine and nitrite must be present, but it can also be seen that the pH of the aqueous solution has a substantial impact on the rate of nitrosamine formation. An understanding of how the pH of an aqueous solution influences the rate of nitrosamine formation is important for students in a variety of fields including organic chemistry, quantitative analysis, and toxicology. It is the purpose of this paper to demonstrate that a predicted value for pH_{max} (pH at which the rate of nitrosation of a secondary amine is maximized) can be easily derived from the pK_a of the amine under consideration coupled with the pK_a of nitrous acid (designated pK_{an} in this paper). For simplicity we will restrict our consideration to solutions containing only nitrite and no other anions. This is an unnatural situation in that nitrosamines are normally produced by the acidification of aqueous solutions of metal nitrite with mineral acids, and the anion associated with the mineral acid is of necessity present in the solution; however, in the absence of catalytic anions, such as thiocyanate and iodide, it is known that the rate of nitrosation of a secondary amine can be well approximated without consideration of peripheral anions [2, 3].

Derivation of pH_{max}

If we ignore spectator anions, then it is the reaction of free-base secondary amine with dinitrogen trioxide (nitrous anhydride) which produces a nitrosamine:

$$\mathrm{RR'NH + N_2O_3 \rightarrow RR'NNO + HNO_2} \qquad (8)$$

The kinetics for this process can be described by the following simple rate equation [2, 3]:

$$\frac{d[\mathrm{RR'NNO}]}{dt} = k[\mathrm{RR'NH}][\mathrm{N_2O_3}] \qquad (9)$$

The concentration of nitrous anhydride cannot be specified without reference to the method by which it is generated. The generation of nitrous anhydride is typically carried out through the acidification of nitrites, and thus we must consider the pK_a of nitrous acid (the pK_a of nitrous acid will be designated as pK_{an} throughout the rest of this paper).

$$\mathrm{HNO_2 \rightleftharpoons NO_2^- + H^+} \quad pK_{an} = 3.34 \text{ (r.t., aqueous) [4]} \qquad (10)$$

We must also consider the condensation of nitrous acid with itself (nitrous acid dehydration):

$$2\,\mathrm{HNO_2} \rightleftharpoons \mathrm{N_2O_3} + \mathrm{H_2O} \qquad K_{\mathrm{eq}} = \frac{[\mathrm{N_2O_3}][\mathrm{H_2O}]}{[\mathrm{HNO_2}]^2} \tag{11}$$

Rearranging terms we obtain

$$[\mathrm{N_2O_3}] = \frac{[\mathrm{HNO_2}]^2 K_{\mathrm{eq}}}{[\mathrm{H_2O}]} \tag{12}$$

In eq 12, we can take $K_{\mathrm{eq}}/[\mathrm{H_2O}]$ to be a constant for dilute aqueous solutions.

Taking into account the actual mechanism for the generation of nitrous anhydride in aqueous solution, the rate of nitrosamine formation becomes

$$\frac{d[\mathrm{RR'NNO}]}{dt} = k'[\mathrm{RR'NH}][\mathrm{HNO_2}]^2 \tag{13}$$

The term $k' = kK_{\mathrm{eq}}/[\mathrm{H_2O}]$ has been inserted into eq 13. Now we need to express the nitrous acid concentration in terms of the total amount of nitrite present in the solution. This can be done by recognizing that the nitrite concentration in the dissociation equilibria for nitrous acid (K_{an}) can be replaced by the term $[\mathrm{NO_2^-}]_{\mathrm{tot}} - [\mathrm{HNO_2}]$ where $[\mathrm{NO_2^-}]_{\mathrm{tot}}$ is equal to the formal concentration of nitrite (total amount of nitrite in either the protonated or unprotonated form).

$$[\mathrm{HNO_2}] = \frac{[\mathrm{NO_2^-}]_{\mathrm{tot}}[\mathrm{H^+}]}{K_{\mathrm{an}} + [\mathrm{H^+}]} \tag{14}$$

$$\frac{d[\mathrm{RR'NNO}]}{dt} = k'[\mathrm{RR'NH}][\mathrm{HNO_2}]^2 = k'\frac{[\mathrm{RR'NH}]([\mathrm{NO_2^-}]_{\mathrm{tot}}[\mathrm{H^+}])^2}{(K_{\mathrm{an}}+[\mathrm{H^+}])^2} \tag{15}$$

We also need to take into account the effect of pH on protonation of the amine, as it is only the free-base form of the amine which can take part in the nitrosation reaction. We will use the p*K*a for protonated diethylamine as representative of simple dialkylamines.

$$\mathrm{Et_2NH_2^+} \rightleftharpoons \mathrm{Et_2NH} + \mathrm{H^+} \tag{16}$$

$\mathrm{p}K_{\mathrm{a}} = 10.84$ (r.t., aqueous) [4]

Again we use $([\mathrm{RR'NH}]_{\mathrm{tot}} - [\mathrm{RR'NH}])$ to replace $[\mathrm{RR'NH_2^+}]$ in the equilibrium equation, which with rearrangement leads to eq 17.

$$[\mathrm{RR'NH}] = \frac{K_{\mathrm{a}}[\mathrm{RR'NH}]_{\mathrm{tot}}}{K_{\mathrm{a}} + [\mathrm{H^+}]} \tag{17}$$

Combining eq 15 with eq 17 we get eq 18:

$$\frac{d[\mathrm{RR'NNO}]}{dt} = k'K_{\mathrm{a}}\frac{[\mathrm{RR'NH}]_{\mathrm{tot}}([\mathrm{NO_2^-}]_{\mathrm{tot}}[\mathrm{H^+}])^2}{(K_{\mathrm{a}} + [\mathrm{H^+}])(K_{\mathrm{an}} + [\mathrm{H^+}])^2} \tag{18}$$

We set $k'' = k'K_{\mathrm{a}}$ and we expand the denominator to yield eq 19:

$$\frac{d[\mathrm{RR'NNO}]}{dt} = \frac{k''[\mathrm{RR'NH}]_{\mathrm{tot}}([\mathrm{NO_2^-}]_{\mathrm{tot}}[\mathrm{H^+}])^2}{[\mathrm{H^+}]^3 + 2K_{\mathrm{an}}[\mathrm{H^+}]^2 + (K_{\mathrm{an}})^2[\mathrm{H^+}] + K_{\mathrm{a}}[\mathrm{H^+}]^2 + 2K_{\mathrm{a}}K_{\mathrm{an}}[\mathrm{H^+}] + K_{\mathrm{an}}{}^2K_{\mathrm{a}}} \tag{19}$$

Now we can look at the effect of pH on the denominator of eq 19.

At pH = 1, assuming that concentration can be used in place of activity for the proton, we obtain

$$\text{denominator eq 19} = 10^{-3} + 10^{-5.04} + 10^{-7.68} + 10^{-12.84} + 10^{-14.88} + 10^{-17.52} \tag{20}$$

At pH = 2, assuming that concentration can be used in place of activity for the proton, we have

$$\text{denominator eq 19} = 10^{-6} + 10^{-7.04} + 10^{-8.68} + 10^{-14.84} + 10^{-15.88} + 10^{-17.52} \tag{21}$$

It is apparent for pH ≤ 2 that the assumption that the denominator of eq 19 $\approx [\mathrm{H^+}]^3$ is valid.

At pH = 6, assuming that concentration can be used in place of activity for the proton, we obtain

$$\text{denominator eq 19} = 10^{-18} + 10^{-15.04} + 10^{-12.68} + 10^{-22.84} + 10^{-19.88} + 10^{-17.52} \tag{22}$$

At pH = 5, assuming that concentration can be used in place of activity for the proton, we get

$$\text{denominator eq 19} = 10^{-15} + 10^{-13.04} + 10^{-11.68} + 10^{-20.84} + 10^{-18.88} + 10^{-17.52} \tag{23}$$

It is apparent for pH ≥ 5 that the assumption that the denominator of eq 19 $\approx (K_{\mathrm{an}})^2[\mathrm{H^+}]$ is valid.

We now take

$$K = k''[\mathrm{RR'NH}]_{\mathrm{tot}}([\mathrm{NO_2^-}]_{\mathrm{tot}})^2$$

For pH ≥ 5, the rate of nitrosation increases with the addition of acid.

$$\frac{d[\mathrm{RR'NNO}]}{dt} = K\frac{[\mathrm{H^+}]}{(K_{\mathrm{an}})^2} \tag{24}$$

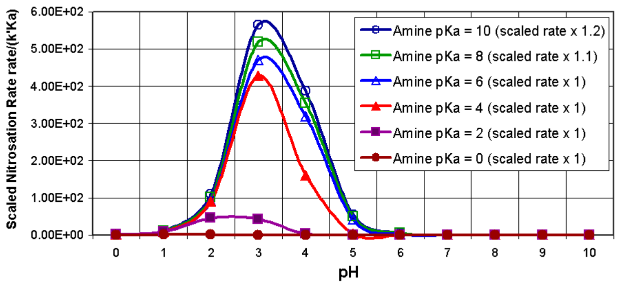

Figure 1. The scaled nitrosation rate according to eq 19 versus the pH for simple dialkyl amines with pK_a values between 0 and 10. To resolve the plots, the rate values for amines with pK_a = 10 and pK_a = 8 were multiplied by the arbitrary factors of 1.2 and 1.1, respectively. The formal concentrations of nitrite and secondary amine were both taken to be 1 M in order to simplify the formula. Symbols are employed in these plots so that the different curves can be resolved even in black and white. The use of symbols is not meant to imply that actual data is being displayed. The curves shown here are calculated from eq 19.

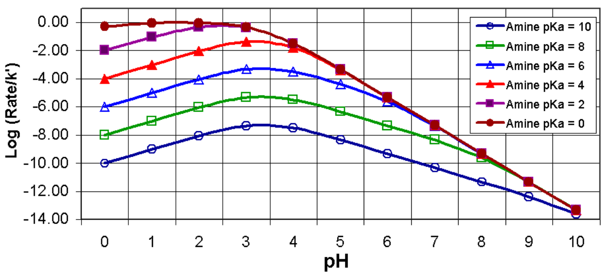

Figure 2. The log of the nitrosation rate normalized by k' plotted versus pH (according to eq 19) for simple dialkyl amines with pK_a values between 0 and 10. The formal concentrations of nitrite and secondary amine were both taken to be 1 M in order to simplify the formula. Symbols are employed in these plots so that the different curves can be resolved even in black and white. The use of symbols is not meant to imply that actual data is being displayed. The curves shown here are calculated from eq 19.

For pH ≤ 2, the rate of nitrosation decreases with the addition of acid.

$$\frac{d[\mathrm{RR'NNO}]}{dt} = K\frac{1}{[\mathrm{H}^+]} \qquad (25)$$

Above pH = 5, the rate of nitrosation increases as we decrease the pH. Below pH = 2, the rate of nitrosation increases as we raise the pH. Thus, we know that the maximum rate of nitrosation is between pH = 2 and pH = 5.

For 2 ≤ pH ≤ 5, the denominator of eq 19 is approximately

$$[\mathrm{H}^+]^3 + 2K_{\mathrm{an}}[\mathrm{H}^+]^2 + (K_{\mathrm{an}})^2[\mathrm{H}^+] \qquad (26)$$

This yields the rate expression given by eq 27:

$$\frac{d[\mathrm{RR'NNO}]}{dt} = K\frac{[\mathrm{H}^+]}{([\mathrm{H}^+] + K_{\mathrm{an}})^2} \qquad (27)$$

Now we can take the derivative of the above rate expression with respect to $[\mathrm{H}^+]$ and set this derivative equal to zero to derive $\mathrm{pH}_{\mathrm{max}}$ (pH for maximum rate of nitrosamine formation).

$$d(\mathrm{rate})/d[\mathrm{H}^+] = 0 \text{ at the maxima} \qquad (28)$$

$$\begin{aligned}\frac{d(\mathrm{rate})}{d[\mathrm{H}^+]} &= K\frac{d\{[\mathrm{H}^+]/([\mathrm{H}^+] + K_{\mathrm{an}})^2\}}{d[\mathrm{H}^+]} \\ &= K\frac{([\mathrm{H}^+] + K_{\mathrm{an}})^2 - 2([\mathrm{H}^+] + \mathrm{K}_{\mathrm{an}})[\mathrm{H}^+]}{([\mathrm{H}^+] + K_{\mathrm{an}})^4} = 0\end{aligned} \qquad (29)$$

If K ≠ 0, then $([\mathrm{H}^+] + K_{\mathrm{an}})^2 - 2([\mathrm{H}^+] + K_{\mathrm{an}})[\mathrm{H}^+]$ must equal zero.

$$([\mathrm{H}^+] + K_{\mathrm{an}})^2 - 2([\mathrm{H}^+] + K_{\mathrm{an}})[\mathrm{H}^+] = 0 \qquad (30)$$

$$[\mathrm{H}^+] = K_{\mathrm{an}} \qquad \mathrm{pH}_{\mathrm{max}} = \mathrm{p}K_{\mathrm{an}} \qquad (31)$$

The above logical analysis is verified by a visual display of the function given in eq 19 (see Figure 1). The rate of nitrosation plotted in Figure 1 is scaled through division by the combined kinetic constant k' and, in order to keep all the plots on the same scale, by K_a. Also, in order to resolve the plots, the curves for dialkyl amines with pK_a = 10 and pK_a = 8 were arbitrarily adjusted by factors of 1.2 and 1.1, respectively. Without adjustment, eq 19 yields a nearly identical plot of scaled nitrosation rate versus pH for any amine with pK_a ≥ 6.

For simple dialkylamines with pK_a ≥ 6, the value of $\mathrm{pH}_{\mathrm{max}}$ is 3.34 (the pK_a of nitrous acid, referred to as pK_{an} in this paper). Note that when a pK_a value is quoted for an amine, unless stated otherwise, the value refers to the protonated form of the amine at room temperature in dilute aqueous solution containing an appropriate supporting electrolyte. For secondary amines with pK_a values less than 6, the simplified denominator used in eq 27 above is no longer valid and the value of $\mathrm{pH}_{\mathrm{max}}$ becomes a more complicated function of pH. Experimental measurements of the value of $\mathrm{pH}_{\mathrm{max}}$ have been given in the literature, and empirical observation of the approximate equivalence of $\mathrm{pH}_{\mathrm{max}}$ with pK_{an} (pK_a of nitrous acid) has been previously described [3, 5, 6]. Naturally, the result given by eq 31 is only as valid as the original rate expression, and actual values for $\mathrm{pH}_{\mathrm{max}}$ vary somewhat depending upon the experimental conditions and the structure of the amine. As far as the experimentalist is concerned, the value of $\mathrm{pH}_{\mathrm{max}}$ given here (i.e., approx. 3.34) is an approximation that can be used in the absence of actual kinetic data.

It is also interesting to examine the impact of the pK_a of the dialkylamine on the rate of nitrosation (i.e., the rate predicted by eq 19) as is shown in Figure 2. The value of $\mathrm{pH}_{\mathrm{max}}$ is not shown clearly in this plot, but the significant effect of the pK_a of the dialkylamine on the rate of nitrosation is very clearly seen. As the pK_a of the amine is reduced, the rate of nitrosation increases significantly at lower pH values. As the pH is raised, all of the nitrosation rates become equal. This makes sense in that eq 19 is based on the requirement that only the unprotonated form of the amine can be nitrosated. Dialkylamines with lower pK_a values remain unprotonated at lower pH values. At a high enough pH value all of the rates

Table 1. Expected Rate Decrease from pH Adjustment Using Equation 27

pH	Rate of Nitrosation	% of Maximum Rate
pH = pK_{an}	Maximum = 1K/4(K_{an})	100%
pH = pK_{an} ± 1	10K/121(K_{an})	33%
pH = pK_{an} ± 2	100K/10,201(K_{an})	3.9%

merge into one as all of the amines become completely unprotonated.

Modification of the pK_a cannot be used to change the rate of nitrosation of a simple dialkylamine as the pK_a of any given amine is a fixed property. If the dialkylamine under consideration cannot be changed, then only modification of the temperature, solvent, pH, nitrite concentration and/or amine concentration can be used to alter the rate of nitrosation. On the other hand, if the dialkylamine to be employed has not yet been chosen, then a consideration of pK_a values might be useful in optimizing performance.

It should be noted that the sole purpose of the above derivation was to demonstrate that a predicted value for pH_{max} could be obtained from a commonly employed rate expression for nitrosation. The straightforward derivation given represents an interesting exercise in extracting specific information from a more general statement (i.e., the rate equation). Readers interested in a more detailed discussion of real pH_{max} values should consult the original literature [1–3, 5, 6].

Reducing Unwanted Nitrosamine Formation

Commercial products are sometimes plagued by the formation of unwanted nitrosamines. Many nitrosamines are carcinogenic, and the occurrence of even traces of nitrosamine in a commercial product can lead to a total lack of customer acceptance. Indeed, the following legal regulations control the use of secondary amines and nitrite salts in many products:

- 40CFR747.115 (USA Code of Federal Regulations) requires product labeling to warn customers not to add nitrites to metalworking fluids containing amines.
- 21CFR184.1890 (USA Code of Federal Regulations) describes the addition of tocopherols (antioxidants) to bacon as a means of inhibiting nitrosamine formation.
- TRGS 611 (German Technical Regulation) disallows the use of secondary amines in cutting fluids because there is a chance of accidental mixing with nitrites.
- TRGS 552 (German Technical Regulation) sets limits for permissible levels of nonpolar nitrosamines in emulsion polymerization latex solutions.

One can obviously reduce the rate/extent of nitrosamine formation by lowering the concentration of secondary amine, lowering the concentration of nitrite, and/or by adjusting the pH away from pH_{max}. The extent of the expected rate decrease, assuming eq 27 is valid, as one adjusts the pH away from pH_{max} is given in Table 1.

Nitrous acid is unstable in aqueous solution at room temperature. An important reaction in the decomposition of nitrous acid is

$$3\ HNO_2 \rightarrow NO_3^- + H^+ + H_2O + 2\ NO(g)\uparrow \qquad (32)$$

Adjusting the pH of a nitrite containing solution away from pH_{max} is a very useful nitrosamine amelioration strategy in that slowing the rate of nitrosamine formation makes it more likely that any nitrous acid that does form will be decomposed (e.g., eq 32) before it can find free-base secondary amine.

Conclusions

The pH at which the rate of nitrosation of simple dialkylamines is maximized has been designated as pH_{max} (aqueous solution, r.t.). Under certain conditions, the value of pH_{max} is equal to the pK_a of nitrous acid (designated pK_{an} in this paper, pK_{an} = 3.34, aqueous solution, r.t.). The derivation of pH_{max} from the rate equation as shown herein demonstrates that important kinetic values can sometimes, with a little effort, be accurately estimated from general principles. The pK_a of the dialkylamine also has a significant effect on the rate of nitrosamine formation, and consideration of amine pK_a may be useful in optimizing a particular system. Understanding the influence of pH on the nitrosation of secondary amines is important both for optimizing the synthesis of nitrosamines and for preventing their inadvertent formation in commercial products.

References and Notes

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