

# Calculation of Solubility of Oxyquinolates

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## Abstract

The solubilities ( $s$ , mol/L) of different oxyquinolates (oxinates,  $\text{MeL}_2$ ) are calculated using the formulae obtained according to elementary algebra, with the use of Excel spreadsheets. The calculations are involved with solution of algebraic equation of the third degree, obtained on the basis of concentration balances. The root of this equation,  $x = [\text{L}^{-1}] = x(\text{pH})$ , is then inserted into the charge balance, and resolved according to zeroing procedure. In principle, the calculations are related to aqueous media. Nonetheless, the extension on liquid-liquid extraction systems is also proposed.

## Keywords

Solubility, Oxyquinolates

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## 1. Introduction

8-hydroxyquinoline (HL, **Figure 1**), known also as oxine, is a bidentate chelating agent. It forms three species:  $\text{H}_2\text{L}^{+1}$ , HL and  $\text{L}^{-1}$  [1]. The anionic ligands,  $\text{L}^{-1}$ , form the precipitates  $\text{MeL}_2$  with some divalent metal ions ( $\text{Me}^{+2}$ ), or  $\text{MeL}_3$  with some trivalent metal ions ( $\text{Me}^{+3}$ ). The related precipitates are known as 8-oxyquinolates (oxyquinolates), or briefly as oxinates.

The oxine and its complexes, functioning as a transcription inhibitor [2], exhibit antiseptic, disinfectant, and pesticide properties [3] [4]. Its 1% solution in alcohol is used in liquid bandages [5], to prevent infections (for external use only). The oxine derivatives were of interest as anti-cancer drugs [6] [7].

Oxidative damage is frequently found in many diseases such as aging, atherosclerosis, cancer, diabetes [8] and neurodegenerative diseases [9]. Free radicals are continuously produced in cells through a wide range of biological processes [10]. For example, the changing oxidation stage of Cu, which is a cofactor of superoxide

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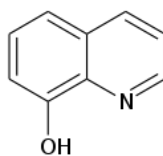


Figure 1. 8-hydroxyquinoline (oxine).

dismutases (SOD), results in the generation of reactive oxygen species (ROS) [11]. Therefore, antioxidant defenses, such as those afforded by tocopherol, ascorbic acid, SOD enzyme, and catalases, are necessary in the maintenance of homeostasis [12]. In this context, the oxine derivatives have been reported as potent antioxidants [13]-[16], which arise from their chelating ability. It is widely known that mixed ligand metal complexes can commonly occur in biological fluids from various bioactive ligands with metal ions [17]. Ability to chelate and lipophilicity have been regarded as essential to the action of oxine. The most widely held hypothesis on the mechanism of action of oxine holds that oxine is only active when it can form saturated chelates with metals in the medium which enters the cell and dissociate. Oxine possesses potent coordinating ability and good metal recognition properties [18]. Chelation of oxine with metals in the medium was found not to be a requirement for oxine fungitoxicity [19]. Potentiation of the action of oxine by metals is explained by the formation of more fungitoxic and soluble metal oxinates and antagonism by the formation of less soluble or less active metal oxinates.

In conclusion, metal ions play a very important role in biological processes, and metal homeostasis is required for the maintenance of metal balance [20] [21]. Many diseases arise from the loss of homeostasis including metal overload and deficiency, which are caused by abnormal metal metabolism or metal absorption. Of all the hydroxyquinoline derivatives, oxine is the most interesting one to be explored, owing to its multifunctional properties, such as diverse bioactivities and therapeutic potentials [22].

It is also worth noting that aluminum oxinate,  $\text{AlL}_3$ , is a common component of organic light-emitting diodes (OLED's) [23]. Variations in the substituents on the quinoline rings affect its luminescence properties [24]. Oxine is also widely used for analytical and separation purposes [25]-[27].

In this context, we are interested in the manner of calculation of (1) the solubility  $s$  [mol/L] and (2) pH of the solution obtained after introducing pure oxinate  $\text{MeL}_2$  into pure water. The calculations will be made with use of Excel spreadsheets applied to an algorithm based on some balances and full physicochemical knowledge on the systems in question, involved in the related equilibrium constants.

## 2. Equilibrium Constants

The precipitates of oxinates are characterized by the solubility product ( $K_{so}$ ) values. For the oxinate of  $\text{MeL}_2$  type we have:

$$[\text{Me}^{+2}][\text{L}^{-1}]^2 = K_{so} \quad (pK_{so} = -\log K_{so}) \quad (1)$$

The soluble complex species  $\text{MeL}_i^{+2-i}$  are characterized by stability constants ( $K_{iL}$ ):

$$[\text{MeL}_i^{+2-i}] = K_{iL} \cdot [\text{Me}^{+2}][\text{L}^{-1}]^i \quad (2)$$

The stability constants  $K_j^{\text{OH}}$  of the related hydroxo-complexes are defined as follows:

$$[\text{Me}(\text{OH})_j^{+2-j}] = K_j^{\text{OH}} \cdot [\text{Me}^{+2}][\text{OH}^{-1}]^j \quad (3)$$

The  $pK_{so}$ ,  $\log K_{iL}$  and  $\log K_j^{\text{OH}}$  values are collected in Table 1 for selected Me-ions. Dissociation constants ( $K_1, K_2$ ) of oxine [1] are formulated as follows:

$$[\text{H}^{+1}][\text{HL}] = K_1 \cdot [\text{H}_2\text{L}^{+1}] \quad (pK_1 = 5.13) \quad (4)$$

$$[\text{H}^{+1}][\text{L}^{-1}] = K_2 \cdot [\text{HL}] \quad (pK_2 = 9.89) \quad (5)$$

and ionic product of water:

$$[\text{H}^{+1}][\text{OH}^{-1}] = K_w \quad (pK_w = 14.0) \quad (6)$$

**Table 1.** Selected equilibrium constants [28]-[31] for some  $\text{Me}^{+2}$  ions.

$\text{Me}^{+2}$	Solubility products	Stability constants of $\text{MeL}_i^{+2-i}$ complexes		Stability constants of $\text{Me}(\text{OH})_j^{+2-j}$ complexes			
	$pK_{so}$	$\log K_{1L}$	$\log K_{2L}$	$\log K_1^{\text{OH}}$	$\log K_2^{\text{OH}}$	$\log K_3^{\text{OH}}$	$\log K_4^{\text{OH}}$
$\text{Cd}^{+2}$	22.0	7.2	13.4	4.3	7.7	10.3	12.0
$\text{Co}^{+2}$	24.2	9.1	17.2	4.3	8.5	9.7	10.2
$\text{Cu}^{+2}$	29.1	12.2	23.4	7.0	13.66	17.0	18.5
$\text{Ni}^{+2}$	25.5	9.9	18.7	4.97	8.55	11.33	-

On the basis of (4) and (5) we get:

$$[\text{HL}] = K_1^{\text{H}} [\text{H}^{+1}] [\text{L}^{-1}] \quad (\log K_1^{\text{H}} = pK_2 = 9.89) \quad (7)$$

$$[\text{H}_2\text{L}^{+1}] = K_2^{\text{H}} [\text{H}^{+1}]^2 [\text{L}^{-1}] \quad (\log K_2^{\text{H}} = pK_1 + pK_2 = 15.02) \quad (8)$$

### 3. Formulation of the Basic Functions

If pure  $\text{MeL}_2$  is introduced into pure water, then the following relationships (concentration and charge balances) are valid:

$$C_{\text{Me}} = c^o + [\text{Me}^{+2}] + \sum_{j=1}^m [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] + [\text{MeL}_2] = c^o + s \quad (9)$$

$$C_{\text{L}} = 2c^o + [\text{H}_2\text{L}^{+1}] + [\text{HL}] + [\text{L}^{-1}] + [\text{MeL}^{+1}] + 2[\text{MeL}_2] \quad (10)$$

$$[\text{H}^{+1}] - [\text{OH}^{-1}] + 2[\text{Me}^{+2}] + \sum_{j=1}^m (2-j) [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] + [\text{H}_2\text{L}^{+1}] - [\text{L}^{-1}] = 0 \quad (11)$$

where  $c^o$  concentration [mol/L] of the precipitate  $\text{MeL}_2$ ,  $m = \max(j)$ , and

$$s = [\text{Me}^{+2}] + \sum_{j=1}^m [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] + [\text{MeL}_2] \quad (12)$$

is the solubility of  $\text{MeL}_2$ . Assuming  $C_{\text{L}} = 2C_{\text{Me}}$  and applying the relationships (1) - (8), from (9) - (11) after cancellation of similar terms we obtain, by turns,

$$2[\text{Me}^{+2}] + 2 \cdot \sum_{j=1}^m [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] = [\text{H}_2\text{L}^{+1}] + [\text{HL}] + [\text{L}^{-1}] \quad (13)$$

$$[\text{L}^{-1}]^3 \cdot \sum_{i=0}^2 K_i^{\text{H}} [\text{H}^{+1}]^i - K_{1L} K_{so} \cdot [\text{L}^{-1}] - 2K_{so} \cdot \left( 1 + \sum_{j=1}^m K_j^{\text{OH}} K_W^j / [\text{H}^{+1}]^j \right) = 0 \quad (14)$$

where  $K_0^{\text{H}} = 1$ . From (14) we have the equation of the type:

$$x^3 + c \cdot x + d = 0 \quad (15)$$

where  $x = [\text{L}^{-1}]$ , and:

$$c = c(\text{pH}) = -\frac{10^{\log K_{1L} - pK_{so}}}{10^{15.02-2\text{pH}} + 10^{9.89-\text{pH}} + 1} \quad (16)$$

$$d = d(\text{pH}) = -2 \cdot 10^{-pK_{so}} \cdot \frac{1 + \sum_{j=1}^m 10^{\log K_j^{\text{OH}} - j(14-\text{pH})}}{10^{15.02-2\text{pH}} + 10^{9.89-\text{pH}} + 1} \quad (17)$$

The Equation (15) is named as depressed cubic equation [32], when perceived in context with the general cu-

bic equation  $ax^3 + bx^2 + cx + d = 0$ . In contrast to the usual equation of the 3rd degree, where the coefficients  $c$  and  $d$  are specific numbers—in our case the coefficients  $c$  and  $d$  in Equation (15) are functions of another variable—here: pH. The coefficients are real numbers, and  $-c = |c| > 0$ ,  $-d = |d| > 0$ , at any pH value.

In general, Equation (15) can have real and complex roots for  $x$ . To distinguish between them, we calculate the sign of the discriminant (see Appendix):

$$\Delta = \Delta(\text{pH}) = \left(-\frac{d}{2}\right)^2 - \left(-\frac{c}{3}\right)^3 = q^2 - p^3 \quad (18)$$

where

$$p = -\frac{c}{3} \quad \text{and} \quad q = -\frac{d}{2} \quad (19)$$

If  $\Delta > 0$ , one root is real, and two ones are complex conjugates. The real root is as follows (see Appendix):

$$x = [\text{L}^{-1}] = \left(q + \sqrt{\Delta}\right)^{1/3} + \left(q - \sqrt{\Delta}\right)^{1/3} \quad (20)$$

If  $\Delta = 0$ , all roots are real and at least two are equal. If  $\Delta < 0$ , we define:

$$\theta = \arccos\left(\frac{q}{\sqrt{p^3}}\right) \quad (21)$$

where  $\arccos \gamma \equiv \cos^{-1} \gamma \equiv \arccos \gamma$ . Then the real positive ( $x > 0$ ) solution of Equation (15) has the form:

$$x = [\text{L}^{-1}] = 2 \cdot \sqrt{p} \cdot \cos\left(\frac{\theta}{3}\right) \quad (22)$$

and from Equation (1) we have  $[\text{Me}^{+2}] = 10^{-pK_{so}} / x^2$ .

The sign of  $\Delta$  (Equation (18)) can vary with change of the pH value; it also depends on the values of physicochemical constants involved in it. Three possible cases are exemplified by physicochemical systems considered in this paper, namely:

- 1)  $\Delta > 0$  within the pH-range in the vicinity of a  $\text{pH}_0$  value;
- 2)  $\Delta < 0$  within the vicinity of the  $\text{pH}_0$  value;
- 3)  $\Delta$  changes its sign in the vicinity of the  $\text{pH}_0$  value.

The  $\text{pH}_0$  value results from the following calculation procedure. The  $x$  values (Equation (20) or Equation (22)) obtained at different pH are inserted into the transformed charge balance (11):

$$z = z(\text{pH}) = 10^{-\text{pH}} - 10^{\text{pH}-14} + \frac{10^{-pK_{so}}}{x^2} \cdot \left(2 + \sum_{j=1}^m (2-j) \cdot 10^{\log K_j^{\text{OH}} - j(14-\text{pH})} + 10^{\log K_{1\text{L}}} \cdot x\right) + (10^{15.02-2\text{pH}} - 1) \cdot x \quad (23)$$

Zeroing the function (23), gives  $z(\text{pH}) = 0$  at  $\text{pH} = \text{pH}_0$ . For this  $\text{pH}_0$  value, considered as pH of the solution obtained after introducing the precipitate  $\text{MeL}_2$  into pure water, one can calculate concentrations of different species, e.g., the species involved in expression for solubility  $s$ , Equation (12).

#### 4. Solubility of Oxinates in Aqueous Media

In the calculations, the pH interval 6.0 - 8.5 was taken as the basis for calculation of  $\text{pH}_0$  value for the systems presented in Table 1. In this interval, the sign for  $\Delta$  was taken first for considerations. For  $\Delta > 0$ ,  $[\text{L}^{-1}]$  was calculated from Equation (20), whereas for  $\Delta < 0$ , the formula (22) was applied. The  $\text{pH} = \text{pH}_0$  values were calculated with accuracy  $< 0.01$  pH units, see Figure 2. At the  $\text{pH} = \text{pH}_0$  values, concentrations of individual species and then solubilities  $s$  (Equation (12)) were calculated, see Table 2.

Note that in all instances, where  $\text{MeL}_2$  is the equilibrium solid phase, we have:

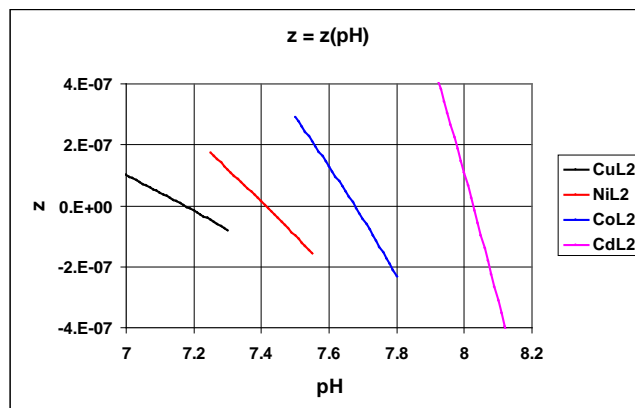
$$[\text{MeL}_2] = K_{2\text{L}} \cdot K_{so} \quad (24)$$

i.e., it is a constant component in Equation (12), independent on pH values. For comparison, when applying the formula [31]:

$$4 \cdot (s^*)^3 = K_{so} \quad (25)$$

**Table 2.** Results of calculations.

Me <sup>+2</sup>	pH <sub>0</sub>	$[X_i^{z_i}]$ for indicated species $X_i^{z_i}$ at $z(\text{pH}_0) = 0$ in Equation (21)							s
		Me <sup>+2</sup>	MeOH <sup>+1</sup>	Me(OH) <sub>2</sub>	Me(OH) <sub>3</sub> <sup>-1</sup>	Me(OH) <sub>4</sub> <sup>-2</sup>	MeL <sup>+1</sup>	MeL <sub>2</sub>	
Cd <sup>+2</sup>	8.03	4.71E-07	1.01E-08	2.71E-11	1.16E-14	6.21E-19	1.09E-07	2.51E-09	5.93E-07
Co <sup>+2</sup>	7.68	8.56E-08	7.80E-10	5.65E-12	4.09E-17	5.92E-23	2.93E-07	1E-07	4.79E-07
Cu <sup>+2</sup>	7.17	3.26E-10	4.82E-10	3.26E-10	1.05E-13	4.93E-19	8.06E-08	2.00E-6	2.08E-06
Ni <sup>+2</sup>	7.41	1.72E-08	4.13E-10	4.04E-13	5.84E-18	-	1.85E-07	1.58E-07	3.61E-07

**Figure 2.** Fragments of the  $z$  vs.  $\text{pH}$  relationships (Equation (10)) for indicated precipitates **MeL<sub>2</sub>** in the vicinity of  $z = 0$ .

obtained on the basis of simplified assumptions:  $[\text{Me}^{+2}] = s^*$ ,  $[\text{L}^{-1}] = 2s^*$ , we obtain  $s^* = (K_{so}/4)^{1/3}$  (see **Table 3**); note that  $s^* \ll s$ , see Equation (12). Thus, the uselessness of formula (25) for calculation of the solubility  $s$  of **MeL<sub>2</sub>** is demonstrated. All known species involved with this system and the related equilibrium constants (1) - (6) are included in the balances (9) - (11). It is an example of the two-phase system where minimal solubility of a precipitate is limited by the concentration of soluble species of the same formula (here: **MeL<sub>2</sub>** and **MeL<sub>2</sub>**).

## 5. Solubility of Oxinates in Liquid-Liquid Extraction Systems

Let us consider a two-phase liquid-liquid extraction system, composed of two practically immiscible solvents, e.g.  $\text{H}_2\text{O} + \text{CHCl}_3$ . The  $\text{CHCl}_3$  is not soluble in water (mutual solubility is less than 0.01%) [33]; then the presence of the organic phase does not affect the values of equilibrium constants in aqueous phases; the balances involve the division of neutral (uncharged) organic components, **HL** and **MeL<sub>2</sub>**, between the two phases. Interfacial distribution of these components is ruled by the partition constants:  $K_{\text{HL}}$  and  $K_{\text{MeL}_2}$ , expressed by the formulas:

$$[\text{HL}_{(o)}] = K_{\text{HL}} \cdot [\text{HL}] \quad \text{and} \quad [\text{MeL}_{2(o)}] = K_{\text{MeL}_2} \cdot [\text{MeL}_2] \quad (26)$$

where subscript  $(o)$  denotes organic phase, and notation with lack of subscript (in parentheses) refers to aqueous phase.

Let  $V_{(o)}$  and  $V$  denote volumes [mL] of organic and aqueous phases, and  $V_{(o)}/V = r$ . The numbers of millimoles of **Me** and **L** are as follows:

$$n_{\text{Me}} = \left( c^o + [\text{Me}^{+2}] + \sum_{j=1}^m [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] + [\text{MeL}_2] \right) \cdot V + [\text{MeL}_{2(o)}] \cdot V_{(o)} \quad (27)$$

$$n_{\text{L}} = \left( 2c^o + [\text{H}_2\text{L}^{+1}] + [\text{HL}] + [\text{L}^{-1}] + [\text{MeL}^{+1}] + 2[\text{MeL}_2] \right) \cdot V + \left( [\text{HL}_{(o)}] + 2[\text{MeL}_{2(o)}] \right) \cdot V_{(o)} \quad (28)$$

**Table 3.** Comparison of  $s$  (Equation (12)) and  $s^*$  (Equation (25)) values.

MeL <sub>2</sub>	CdL <sub>2</sub>	CoL <sub>2</sub>	CuL <sub>2</sub>	NiL <sub>2</sub>
$s$	5.93E-07	4.79E-07	2.08E-06	3.61E-07
$s^*$	2.92E-08	5.40E-09	1.26E-10	1.99E-09

At  $n_L = 2n_{Me}$ , from (27) and (28), after cancellations, we obtain by turns,

$$\begin{aligned} & \left( 2 \cdot [\text{Me}^{+2}] + 2 \cdot \sum_{j=1}^m [\text{Me}(\text{OH})_j^{+2-j}] + [\text{MeL}^{+1}] \right) \cdot V = ([\text{H}_2\text{L}^{+1}] + [\text{HL}] + [\text{L}^{-1}]) \cdot V + [\text{HL}_{(o)}] \cdot V_{(o)} \\ & [\text{Me}^{+2}] \left( 2 + 2 \cdot \sum_{j=0}^m K_j^{\text{OH}} [\text{OH}^{-1}]^j + K_{\text{IL}} [\text{L}^{-1}] \right) = [\text{L}^{-1}] \cdot (K_2^{\text{H}} [\text{H}^{+1}]^2 + K_1^{\text{H}} [\text{H}^{+1}] (1 + K_{\text{HL}} \cdot r) + 1) \\ & \frac{K_{so}}{[\text{L}^{-1}]^2} \cdot \left( 2 + 2 \cdot \sum_{j=0}^m K_j^{\text{OH}} [\text{OH}^{-1}]^j + K_{\text{IL}} [\text{L}^{-1}] \right) = [\text{L}^{-1}] \cdot (K_2^{\text{H}} [\text{H}^{+1}]^2 + K_1^{\text{H}} [\text{H}^{+1}] (1 + K_{\text{HL}} \cdot r) + 1) \\ & [\text{L}^{-1}]^3 \cdot (K_2^{\text{H}} [\text{H}^{+1}]^2 + K_1^{\text{H}} [\text{H}^{+1}] (1 + r \cdot K_{\text{HL}}) + 1) - K_{so} K_{\text{IL}} [\text{L}^{-1}] - 2 \cdot K_{so} \cdot \left( 1 + \sum_j K_j^{\text{OH}} [\text{OH}^{-1}]^j \right) = 0 \end{aligned}$$

Then we get the equation  $x^3 + c' \cdot x + d' = 0$ , where  $x = [\text{L}^{-1}]$ , and:

$$c' = c'(\text{pH}) = - \frac{K_{so} K_{\text{IL}}}{K_2^{\text{H}} [\text{H}^{+1}]^2 + K_1^{\text{H}} [\text{H}^{+1}] (1 + K_{\text{HL}} \cdot r) + 1} \quad (29)$$

$$d' = d'(\text{pH}) = -2K_{so} \cdot \frac{1 + \sum_{j=1}^m K_j^{\text{OH}} [\text{OH}^{-1}]^j}{K_2^{\text{H}} [\text{H}^{+1}]^2 + K_1^{\text{H}} [\text{H}^{+1}] (1 + K_{\text{HL}} \cdot r) + 1} \quad (30)$$

## 6. Final Comments

For resolution of cubic equations, the Excel spreadsheets were used; the coefficients of these equations were the functions of pH; resolution of the related equation was the primary step for zeroing the transformed charge balance,  $z(\text{pH}_0) = 0$ . Two options applicable for resolution of these equations were distinguished. Other examples with cubic equations involved were presented in [34]-[36]. For more complex systems, e.g. ones involved with struvite,  $\text{MgNH}_4\text{PO}_4$  [37], or dolomite,  $\text{CaMg}(\text{CO}_3)_2$  [38], the iterative computer programs are required [39].

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## Appendix

Derivation of Equation (15) at  $\Delta > 0$  (Equation (18)).

Setting

$$x = u + v \quad (\text{A1})$$

in Equation (15), after further rearrangements we get

$$u^3 + v^3 + (u + v)(3uv + c) + d = 0 \quad (\text{A2})$$

At  $3uv + c = 0$ , i.e.,

$$v = -\frac{c}{3} \cdot \frac{1}{u}, \quad u = -\frac{c}{3} \cdot \frac{1}{v} \quad (\text{A3})$$

from (A2) and (A3) we have  $u^3 + v^3 + d = 0$  and then

$$u^6 + d \cdot u^3 - \left(\frac{c}{3}\right)^3 = 0 \quad \text{or} \quad v^6 + d \cdot v^3 - \left(\frac{c}{3}\right)^3 = 0 \quad (\text{A4})$$

Setting

$$u^3 = y \quad \text{or} \quad v^3 = z \quad (\text{A5})$$

in (A3) we have

$$y^2 + d \cdot y - \left(\frac{c}{3}\right)^3 = 0 \quad \text{or} \quad z^2 + d \cdot z - \left(\frac{c}{3}\right)^3 = 0 \quad (\text{A6})$$

$$y = -\frac{d}{2} \pm \sqrt{\Delta} \quad \text{or} \quad z = -\frac{d}{2} \pm \sqrt{\Delta} \quad (\text{A7})$$

where

$$\Delta = \left(\frac{d}{2}\right)^2 + \left(\frac{c}{3}\right)^3 \quad (\text{A8})$$

As we see (Equation (A7)), the formulae for  $u$  and  $v$  are identical. Note that

$$\left(-\frac{d}{2} - \sqrt{\Delta}\right)^{1/3} \cdot \left(-\frac{d}{2} + \sqrt{\Delta}\right)^{1/3} = -\frac{c}{3} \quad (\text{A9})$$

Then, on the basis of Equations (A7) and (A9),

$$u = \left(-\frac{d}{2} - \sqrt{\Delta}\right)^{1/3} \rightarrow v = \left(-\frac{d}{2} + \sqrt{\Delta}\right)^{1/3} \quad \text{or} \quad u = \left(-\frac{d}{2} + \sqrt{\Delta}\right)^{1/3} \rightarrow v = \left(-\frac{d}{2} - \sqrt{\Delta}\right)^{1/3}$$

i.e.,  $u$  and  $v$  are interchangeable in Equation (A1). Then from Equation (A1) we have Equation (20). Note that  $q = -d/2 > 0$  and  $p = -c/3 > 0$ , at any pH-value, see Equation (19) and comments for Equations (16) and (17).

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