# Prediction of distribution of microspecies as function of the pH and its application for modeling of gallium complexing behaviour

Jozsef Szegezdi[+*], Alexander Fedin[**], Ferenc Csizmadia[*]

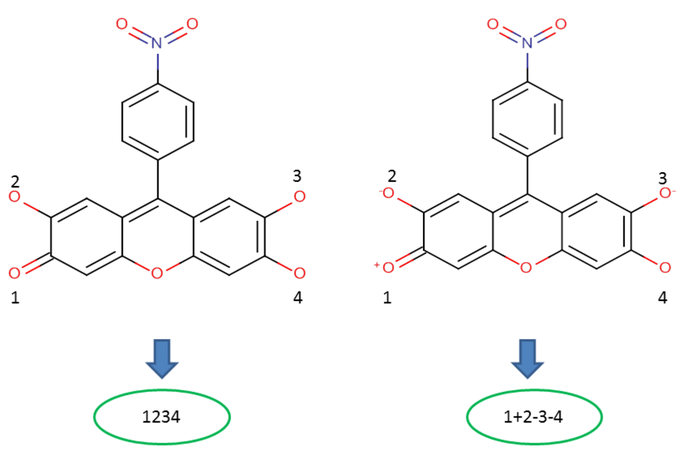
[+] corresponding author: jszegezdi@chemaxon.com, Discovery Group
[*] Chemaxon Ltd., 1031. Budapest, Záhony u. 7, Hungary
[**] 49005 Ukraine Dnepropetrovsk Pisargevsky str., 5, ISIC WESTA, Laboratory of clean water, prof. Fedin A.V.

**Abstract**
Polyprotic acids are ionized in aqueous solution in a wide pH range. The distribution of the ionized species is a multimodal function of the solution pH. Most of the physical-chemical model of a solution requires information about the p$K_a$ values of the molecules. In the present calculation a "trihydroxyfluorone" derivative, TOF, investigated in a complex formation reaction with Gallium ions. The metal elements in the XIII. group of the periodic system has significant rule both in medical applications and in pharmaceutical chemistry as well. For example Gallium has a wide range of usage in isotope medicine.

The distribution of the ionized species in aqueous solution governed by the p$K_a$ value of the parent species. Building of a physical-chemical model which is extensively based on ionized structures can be done more effectively in that case the constituent ionic structures are known as function of the pH. Accurate calculation of the ionic forms involves such structural effect as symmetry or even tautomerization of the query molecule. The Chemaxon's p$K_a$calculator is right for the later purposes because it contains a resonance and a tautomer filter option.

**Fig.1. The structure of the "TOF"**

Numbering of the ionization centers and their symbolic representation with 2 example species




The "TOF" is a polyprotic acid which has 4 p$K_a$ values. It used as a complex forming agent with metal ions. The structure of the TOF and the relevant microspecies p$K_a$ values were calculated with Marvin shown on the **Fig.1.** and on the **Fig.2**. Altogether 16 microspecies would be expected due to the 4 ionizable atoms of the TOF. After filtering out the symmetric resonance forms only 9 species will remain.

**Fig.2. Calculated micro species and micro p$K_a$ values of the "TOF"**

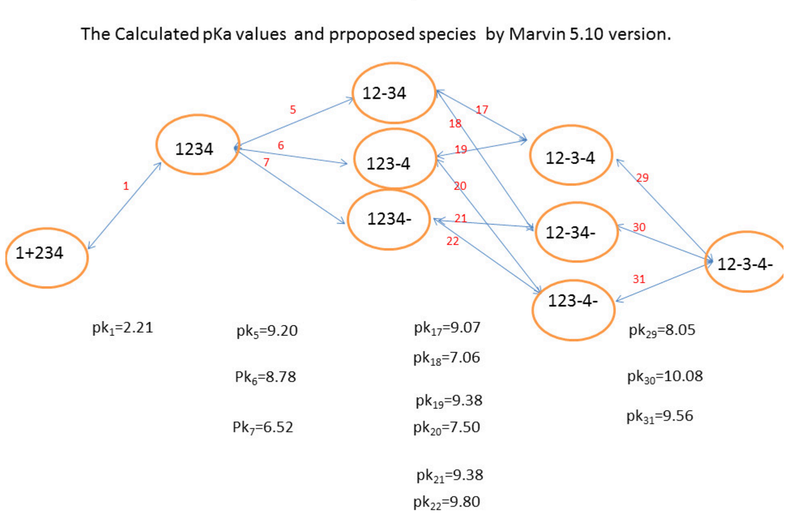
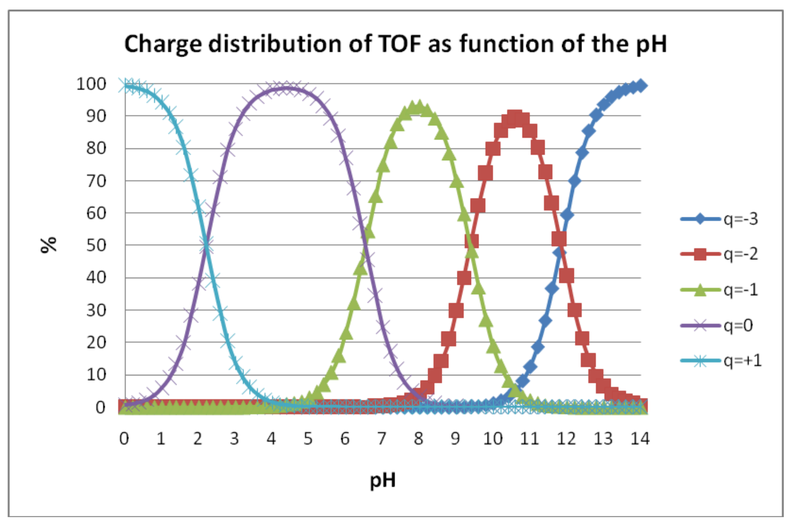



**Fig3. Calculated charge distribution of TOF**




Our purpose is to calculate the metal-complex formation of the "TOF" with Ga ions. This is why we need to know the distribution of the charged species as function of the pH. The five peak maximum of the charged species on the **Fig.3.**is a characteristic of the multi-ionizable acids like the "TOF". The neutral carbonyl group and the negatively charged hydroxyl groups are strong complex forming sites against the cationic gallium ions.

The pH - distribution of the hydrolyzed gallium ions are depicted on the **Fig.4**. The experimental p$K_a$ values of the consecutive deprotonation steps of the gallium ions are taken form the **ref.2.** Their values are summarized in **Table1**.

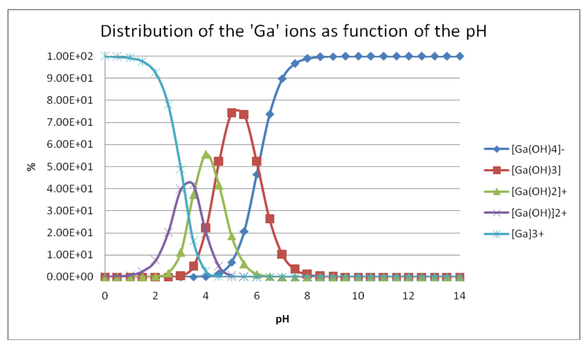
**Table 1. Sequential hydrolysis p$K_a$ values of the gallium ions.**

| | |
|---|---|
| $pK_{a1}$ | 3.09 |
| $pK_{a2}$ | 3.55 |
| $pK_{a3}$ | 4.40 |
| $pK_{a4}$ | 6.05 |

The p$K_a$values of the gallium ions are defined according to the consecutive deprotonation steps of the aqua complexes.

$[Ga(H_2O)_n]^{3+} + H_2O \rightleftharpoons [Ga(H_2O)_{n-1}(OH)]^{2+} + H_3O^+$

$$K_{ai} = \frac{\left[Ga(OH)_i\right]^{+3-i}}{\left[Ga(OH)_{i-1}\right]^{+4-i}}$$




The experimental concentration of the gallium as function of the pH was determined in two pH ranges. The numerical values of the observations are collected in the **Table 3**. And sketched on the **Fig.5.**The complex ratio of the metal and ligand is a function of the pH range according to the experimental results. They are given in the **Table 2**.

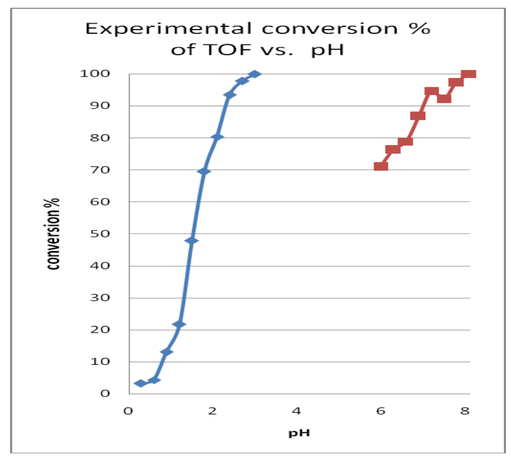
**Table 2.Experimental conditions**

| pH range | Concentration ($10^{-5}$[mol/l]) | | Ga:TOF ratio |
|---|---|---|---|
| | Ga | TOF | |
| 0<pH<3 | 1.1 | 1.1 | 1:1 |
| 6.0<pH<8.0 | 1.1 | 2.1 | 1:2 |

**Table 3. Experimental data points**

| pH | % conversion |
|---|---|
| | |
| 0.29 | 3.2 |
| 0.59 | 4.3 |
| 0.89 | 13.0 |
| 1.19 | 21.7 |
| 1.49 | 47.8 |
| 1.79 | 69.5 |
| 2.09 | 80.4 |
| 2.39 | 93.4 |
| 2.69 | 97.8 |
| 2.99 | 99.9 |
| | |
| 5.98 | 71.0 |
| 6.28 | 76.3 |
| 6.58 | 78.9 |
| 6.88 | 86.8 |
| 7.18 | 94.7 |
| 7.48 | 92.1 |
| 7.78 | 97.3 |
| 8.08 | 100.0 |

**Fig5. Experimental conversion of TOF vs. pH**




**The models of the metal complex formation**

The major ionic structures which are relevant in the Ga-ligand bonding process can be read from the species distribution-pH curves **Fig.3** and **Fig.4.**
The **model 1.**is acceptable in the acidic region : 0<pH<3. The "TOF" has two major microspecies forms in this pH range: the neutral and the protonated carbonyl structure. The gallium has two major forms in the acidic media: $Ga^{3+}$and $Ga^{2+}$. The mono cationic ($Ga^{1+}$) form is also present but it is not considered in our model as a major form.
The **model 2.**It is apparent that in the alkaline medium the reaction mechanism is more complicated than in the acidic region. Reaction scheme of the models sketched on the **Fig. 6**.A more deeper analysis will be necessary in the near future so that a more simple reaction model could be constructed for modeling the Ga-ligand formation process in the alkaline pH region.

**Fig.6.** Reaction schemes in the acidic and in the alkaline pH ranges

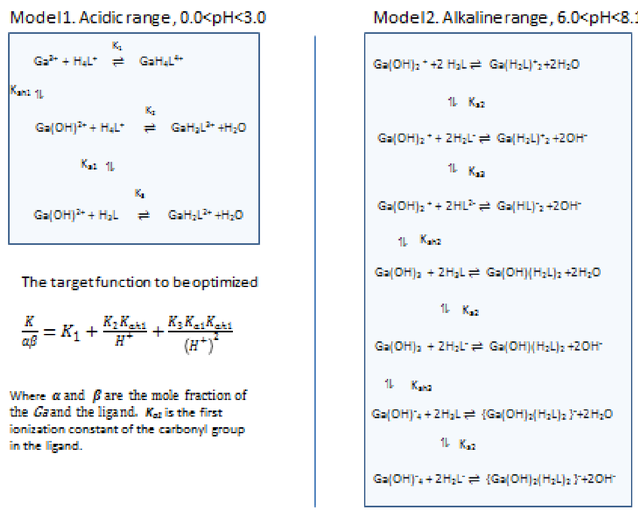



**Table 3.** The characteristic microspecies of the models

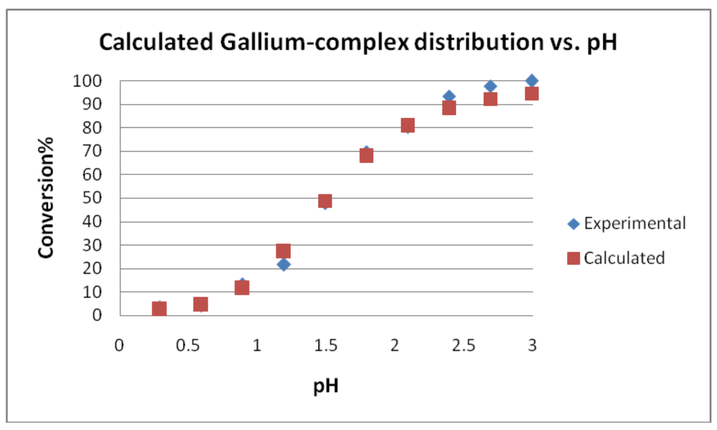
| pH range | Major Species | |
|---|---|---|
| 0<pH<3 | $Ga^{3+}$, $Ga^{2+}$,( $Ga^{1+}$) | $H_4L^+$,$H_3L$ |
| 6<pH<8 | ( $Ga^{1+}$),$Ga^0$, $Ga^{-1}$ | $H_3L$, $H_2L^-$, ($HL^{-2}$) |

In acidic medium the calculated formation constants which are specified in the **model 1.**are summarized in the **Table 4**.The numerical solution of the target equation was done with Genetic algorithm **ref.3.**

**Table 4.**Calculated formation constants of the model 1.

| $pK_1[M^{-1}]$ | $pK_2[M^{-1}]$ | $pK_3[M^{-1}]$ |
|---|---|---|
| 3.2 | 0.0 | 8.8 |

**Fig.5. Calculated and experimental conversion of Ga in acidic media according to the model 1.**




Chemaxon's p$K_a$ calculator is implemented in Java language. Wide range of API functions are available for program developers to implement their specific models. Our conclusion is that we are on a good way for supporting the modeling efforts of such kind of physical-chemical processes which are requiring intensive usage of multi ionized species of a parent structures. Relatively good accuracy of the generated parameters on the other hand make it possible to replace the lack of the experimental ionization constants which are available only for a few molecules.

**References:**

**1. Tarita Biver et al., J. Phys. Chem. B 2009, 113, 1598-1606**
**2. Wesley R. Harris et al., Coordination Chemistry Reviews, *228* (2002) 237-262**
**3. M. Gulsen et al., Int. J. Prod. Res., 1995, vol. 33, No. 7, 1911-1923**

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