Scientific paper

Potentiometric Study of the Dissociation and the Metal Complex-formation Competence of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (Dacarbazine)

Hasan Atabey,[1] Faisal Naji Al-Obaidi[2,*] and Hayati Sari[3]

[1] *Mersin National Education Directorate, Department of Analytical Chemistry, Mersin, Turkey.*

[2] *Retired Associate Professor at the University of Al-Mustansiryia, Faculty of Science, Baghdad, Iraq.*

[3] *Faculty of Science and Arts, Department of Chemistry, Gaziosmanpasa University, 60250 Tokat, Turkey.*

* *Corresponding author: E-mail: faisalnaji@hotmail.com; fkhedher@hotmail.com*

Tel: 44 7982600368

Received: 08-20-2022

Abstract

A potentiometric investigation has been carried out to disclose the coordination properties of Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (abbreviated DTIC) with particular transition metal ions (Zn^{2+}, Cu^{2+}, Ni^{2+} and Co^{2+}). The coordination of DTIC with these metal ions results in several complexes emerging in solution. The aim of this work is to determine the protonation constants of the DTIC and to show the extent of its coordination with (Zn^{2+}, Cu^{2+}, Ni^{2+} and Co^{2+}), in other words, establish the stability of the complexes formed between the DTIC and these metal ions by the determination of their stability constants. Experimental environments were organized to attain the coordination and measurements in aqueous solutions at 25±0.1 °C and an ionic background of 0.1 mol dm^{-3} NaCl. The HYPERQUAD computer program was used to determine both the protonation and stability constants for the ligand and metal-ligand complexes respectively. DTIC has five protonation constants that can be obtained under experimental conditions used; 10.54, 20.15, 26.99, 32.02 and 36.01. The results are interpreted in terms of the basicity of the donor atoms and structural composition of the ligand. All the complexes produced in the solution are exhibited in speciation diagrams.

Keywords: DTIC; Stability constants; Protonation constants; Potentiometric titration; distribution diagram; HYPERQUAD.

1. Introduction

DTIC is renowned for its antitumor activity [1–5] and as such is a drug utilised in chemotherapy for treating, specifically, malignant melanoma.[6–8] This is the most devastating form of skin cancer and its rate is increasing globally, particularly among the white population who are highly exposed to sunlight.[9,10] Malignant melanoma can also be located in other parts of the body, such as in the eye, the digestive tract and mucosal surfaces of lymph nodes.[10] But it is plausibly treatable through surgical removal after diagnosis at initial phases.[11] DTIC can also be used to treat numerous types of cancer, namely Hodgkin lymphoma, Sarcoma, and Islet Cell Carcinoma of the pancreas.[12] DTIC is presumed to attack and eliminate cancer cells by adding alkyl groups to their DNA.[10,13]

DTIC can be used in combination with various chemotherapy drugs for more effective treatment of adenocarcinoma and soft tissue sarcoma.[14–16] The anticancer properties of DTIC are boosted when introduced as a complex with certain metals such as copper (II), zinc (II), nickel(II) and Cobalt (II).[6,12, 16–19] Therefore the coordination of DTIC with metal ions is an immediately relevant topic in medicine as these types of interactions have gained traction in the medical field. The antitumor properties of DTIC is manifested in its triazene group is responsible for the chemical and physical properties of the molecule.[20,21]

The intention behind this investigation is to evaluate the coordination potential of the ligand DTIC by determining its dissociation constants and the stability of its complexes with some divalent ions, namely; Zn^{2+}, Cu^{2+}, Ni^{2+}, and Co^{2+}. DTIC has seven donor atoms so it is assumed to possess a variety of coordination sites.

2. Experimental

2. 1. Reagents

All the reagents used in this investigation were of analytical grade. The transition metals and NaCl were purchased from (Merck), potassium hydrogen phthalate (KHF) and Borax ($Na_2B_4O_7$) from (Fluka). DTIC and 0.1 mol dm^{-3} NaOH and 0.1 mol dm^{-3} HCl as standard from Aldrich. CO_2 free double distilled deionized water was utilized in all experiments and prepared by means of an aqua MAX™ – Ultra water purification system (Young Linst); its resistivity was 18.2 M Ω cm^{-1}. Potentiometric titration was operated by using the Molspin pH meter™ with an Orion 8102BNUWP ultra combination pH electrodes. The temperature in the double-walled glass titration vessel was continuously controlled using a thermostat (DIGITERM 100, SELECTA) and kept at 25.0 ± 0.1 °C. The cell contents were stirred at a constant rate.

Solutions of metal (2×10^{-3}) mol.dm^{-3} were prepared from $ZnCl_2$, $CuCl_2$, $NiCl_2$, and $CoCl_2$, and the exact concentration was determined analytically by means of ethylene-diamine-tetra acetic acid (EDTA).[22] Less diluted solution can be attained by volumetric dilution.

2. 2 Potentiometric Measurements

The glass electrode was calibrated by means of two buffer solutions with pH of 4.005 (KHP) and pH = 9.018 (Borax) at 25.0 ± 0.1 °C following the guidelines of the Molspin manual [23] NaOH was standardized with primary standard (KHP) solution by pH metric titration. HCl solution was prepared from concentrated HCl and its concentration was determined with standardized NaOH. All potentiometric titrations were undertaken in 100 mL double-walled glass vessel using combination electrode and the temperature was controlled as it mentioned in section **2.1** above. Atmospheric CO_2 was excluded from the titration vessel by pumping nitrogen gas (99.9%) through the titration vessel and to keep an inert atmosphere. The vessel was equipped with a small magnetic stirrer, and a securely fitting cap containing three holes to accommodate the combined electrode, combined nitrogen gas inlet and outlet ports and an automatic burette to deliver the alkali solution. The system was maintained at a fixed ionic strength of 0.1 mol.dm^{-3} by means of NaCl as background electrolyte. All potentiometric titrations took place in solution, in a 100 mL double – walled glass vessel using the Molspin automatic titration system as mentioned previously.

Approximately 0.01 mmol of DTIC was placed in the reaction cell to which the needed quantity of the supporting electrolyte 0.1 mol.dm^{-3} NaCl and 0.1 mol dm^{-3} HCl were added, followed by doubly distilled deionized water to bring the total volume to 50 mL pH measurements of the solution were taken after the addition of 0.03 cm^3 of the standardized NaOH. Other solutions include the same quantities as above in addition to about 0.01 mmol of transition metal ions of Zn^{2+}, Cu^{2+}, Ni^{2+} and Co^{2+} in each iteration, followed by adding doubly distilled deionized water to make up the total volume 50 mL as before.

The potentiometric titrations were arranged so that the ratio ligand to metal ion is 1:1 throughout the whole investigation, with each titration repeated three times. The pK_w value used in the calculations is 13.41. The data obtained from potentiometric titration were used to calculate the protonation constants of the ligand and stability constants of the metal complexes using the HYPERQUAD computer program.[24]

3. Results and Discussion

3. 1. Dissociation Constants of DTIC

The protonation and deprotonation properties of the ligand DTIC Figure 1 are studied potentiometrically in this investigation. Figure 2 and Figure 3 demonstrate the titration curve and the species distribution diagram of DTIC ligand respectively. Both protonation and deprotonation (dissociation) constants of this ligand are determined through a sequence of numerous separated potentiometric measurements. The distribution diagram Figure 3 displays various ligand species concentration depending on pH. Six species have been observed during the potentiometric titration course; L, HL, H_2L, H_3L, H_4L and H_5L, which are governed by five dissociation constants. The five

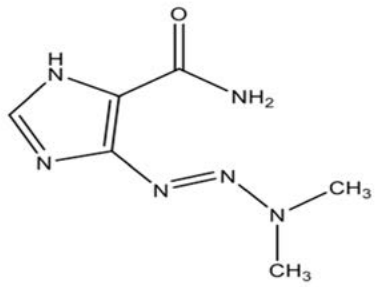

Figure 1. Chemical structure of DTIC

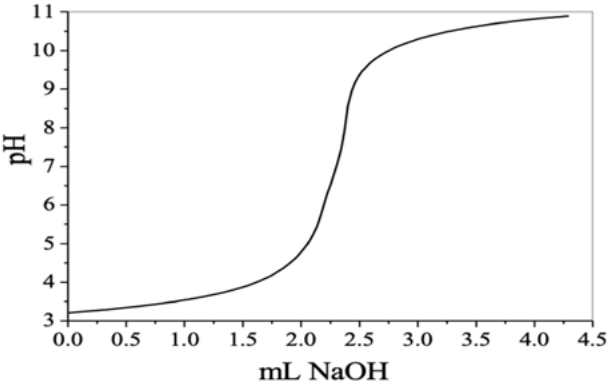

Figure 2. Titration curve of DTIC

values of the protonation and dissociation constants of the DTIC ligand are listed in Table 1. Figure 4 shows the fully protonated ligand, where the three nitrogen atoms in the Triazenyl group and oxygen atom of carbonyl group are protonated. DTIC can also exist in two tautomeric forms; a and b Figure 5. Tautomer b has a higher stability than tautomer a due to the formation of two intramolecular hydrogen bonds.[25,26]

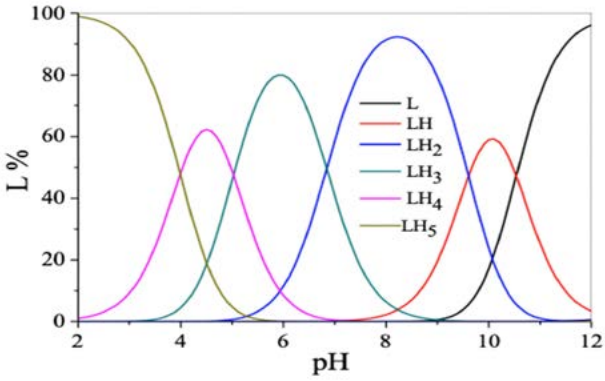

Figure 3. The species distribution diagram of DTIC

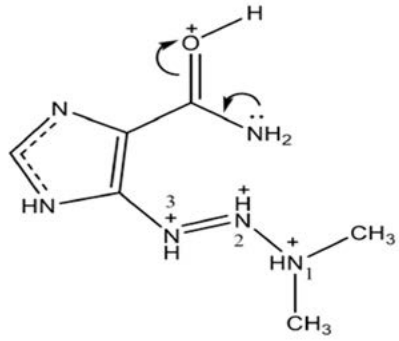

Figure 4. fully protonated DTIC

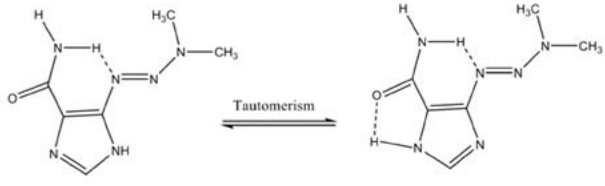

Figure 5. Tautomeric forms (a and b) of DTIC

The following equation represents the deprotonation equilibrium (charges are omitted for simplicity):

$$LH_n \rightleftharpoons LH_{n-1} + H$$

and the dissociation constants (K_n) are given as:

$$K_n = [LH_{n-1}][H] / [LH_n]$$

The species distribution diagram Figure 3 shows the pH range where all species of the ligand are formed and its concentration at any specific pH, represented as a percentage. The distribution diagram provides the requirements for the experimental conditions needed for the coordination between any species of the ligand with metal ions.

Table 1. Dissociation constants of the ligand (25.0 ± 0.1) °C, I = 0.1 mol dm^{-3} NaCl in aqueous solution)

Ligand	Species	$Log_{10}\beta$	pK_a values
DTIC	H_5L	10.54	3.99
	H_4L	20.15	5.03
	H_3L	26.99	6.84
	H_2L	32.02	9.61
	HL	36.01	10.54

Theoretical calculations were used to determine the protonation order of the three nitrogen atoms in DTIC. The proton affinity (PA) of each donor atom engaged in the protonation process, can be calculated from the following equation: [27]

$$PA(B) = 367.2 + \Delta H_f(B) - \Delta H_f(HB^+)$$

PA (B) is the proton affinity of molecule B, $\Delta H_f(B)$ and $\Delta H_f(HB^+)$ are the heat of formation of molecule B and protonated BH^+ respectively, and 367.2 is the heat formation of H^+.

Table 2. The calculated $\Delta_f H$ of TE and PA values for DTIC ligand and its mono-protonated forms using the PM3 method.

	PM3		
Species	**T.E. (kcal/mol)**	**Hf (kcal/mol)**	**PA**
DTIC	–49127,38	42.68	–
1 N-H$^+$	–49318,84	194.28	205.09
2 N-H$^+$	–49309,58	155.27	195.82
3 N-H$^+$	–49319,66	142.21	205.95

The protonation order in Table 2 displays the extent of the basicity of the donor atoms in the ligand. This is significant in demonstrating the coordination between the ligand and the proton or metal ion as well as the expectation of the coordination positions. The protonation constant of a ligand is essential to measuring its basicity.[28,29]

N#3 in Figure 4 is more basic than the other nitrogen donor atoms in the triazenyl group, and a probable intra-hydrogen bonding is presumed to develop with the hydrogen of the amide group. Intra-hydrogen bonding is also possible between the oxygen of the carbonyl group and the proton of the nitrogen in the imino group of the imidazole

moiety Figure 5.[25] This bonding will not be expected to preclude the coordination process between the ligand and metal ion; this is due to the tenuous construction of this bonding.[30,31] The existence of a C=O dipole and, to a smaller degree, an N-C dipole in the DTIC, allows it to operate as a hydrogen bond acceptor. The C=O dipole consists of a π-bonding structure and its oxygen atom has higher electronegativity than nitrogen in the N-C group, giving the carbonyl group greater electronegativity. DTIC can engage in hydrogen bonding with water molecules thus increasing the water solubility of the ligand in aqueous solutions. The high electron withdrawing environment of the carbonyl group through resonance is due to the delocalization of the loan pair of electrons on the nitrogen of amide moiety, thereby decreasing the basicity of the nitrogen atom. In other words, the electron withdrawal environment produced by this conjugated system will constrain the capability of the loan pair of electrons in the amide group to coordinate with electrophiles.

The ligand distribution diagram Figure 3 identifies the initial experimental conditions of the coordination between the ligand and metal ion.[31,32] Six species exist in solution within the pH range between above 2 to just lower than 12, the above mentioned diagram Figure 3 shows clearly the pH range and the amount of each species exists in the solution. Five protonation and five deprotonation (dissociation) constants are obtained in this study. pK_a of value 3.99 Table 1 is associated with the nitrogen N#2, where values are reported in literature 2.33 and 2.30 for monocyclic and bicyclic diazine respectively.[33,34] The pK_a value of 5.03 is related to the oxygen in carbonyl group, while pK_a of 6.84 is associated with pyridine like nitrogen atom in the imidazole moiety.[35] The other two pK_a values 10.54 and 9.61 are associated with N#3 and N#1 respectively.

3. 2. Stability Constants

The stability constants of mono-binary complexes of Dacarbazine with some divalent metal ions in aqueous solution were determined with the HYPERQUAD [24] computer program. The overall stability (β_{pqr}) constants for the complex formed from the metal ion (M), ligand (L) and acid (H):

$$pM + qL + rH = M_pL_qH_r$$

can be represented by:

$$\beta_{pqr} = [M_pL_qH_r]/[M]_p[L]_q[H]_r$$

where p, q and r are the respective stoichiometric coefficients. Various probable species form in the solution depending on pH; with only mono-binary complexes are formed for all the metal ions and possible existence of hydroxyl complexes at a high pH. The hydrolysis process which leads to the formation of the hydroxyl species in our system involves the water molecules bound to the metal ion and pH.[36,37] This happens as a result of the increase in acidity of the attached water molecules due to the formation of the coordinated bond. [36] The formation of coordinated bonds will induce the whole electronic charge distribution and increase the charge withdrawal environment towards the metal ion.[36,37] There is no indication of the chloro-complexes existing in the solution. Data in Table 3 represent values of stability constants for all species formed in the solution at the experimental conditions set.

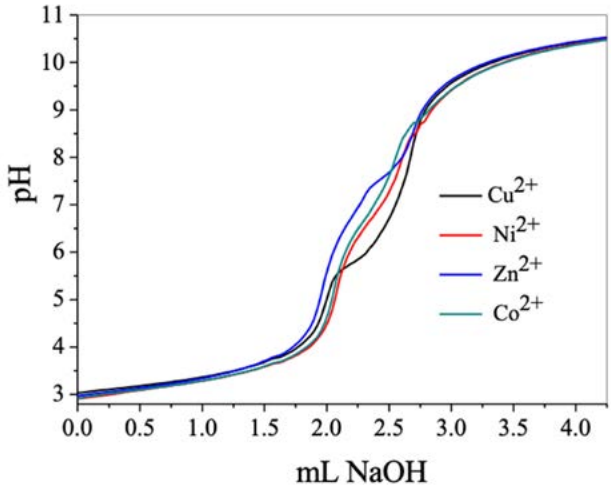

Figure 6. Titration curves of DTIC with Zn(II), Cu(II), Ni(II) and Co(II) at (298 K, I =0.1 mol dm^{-3} NaCl in aqueous solution.

Table 3. Stability constants of DTIC complexes with some divalent metal ions (25.0 ± 0.1) °C, *I*=0.1 mol dm^{-3} NaCl in aqueous solution.

Species	Cu^{2+}	Ni^{2+}	Zn^{2+}	Co^{2+}
mhl		$log_{10}\beta$		
101	19.61 (1)	18.30 (2)	19.10(6)	18.57 (1)
111	26.74 (3)	25.81 (6)	26.66 (4)	26.36 (6)
121	32.04 (4)	32.45 (9)	33.73 (6)	33.09 (7)
131	38.49 (5)	38.53 (9)	39.77 (8)	39.25 (8)
1–11	10.23 (4)	9.31 (9)	11.25 (6)	9.14 (8)
1–21	0.16 (3)	0.09 (5)	1.66 (7)	0.35 (1)
σ (sigma)	0.79	1.51	1.40	1.28

Conditions were organised as a 1:1 ligand to metal ratio throughout all experiments. Owing to substantial basicity and the bi-dentate mode of the DTIC ligand, mono-binary complexes were formed in solution at this ratio. All complexes of the ligand with all metal ions were present in the solution at early stages of coordination. This is additional evidence of DTIC's basicity strength.

The chemical, physical and anti-tumour properties are due to the existence of triazenyl group in the DTIC li-

gand.[20] The more basic nitrogen atom in this group is N#3 (see Table 2), so it can be assumed that the coordination of the DTIC ligand will take place through this nitrogen atom. Since the DTIC is of bi-dentate nature, the most appropriate donor atoms to coordinate with the metal ions are the nitrogen N#3 in the triazenyl group and the nitrogen atom of the amido group, where the six membered ring is formed. Possible intra-hydrogen bonding is expected to formulate between the oxygen of the carbonyl group and hydrogen of the imine group in the imidazole moiety.[25]

The size and structure of the ligand might develop the possibility of steric hindrance when coordinating with a metal ion to form a complex. But the reasonably high stability constants of the complexes in all metal ions used in this study (Table 3) reveal that steric hindrance has less impact than would be expected. This might be justified on the basis that the DTIC ligand is efficient in modifying its shape when the coordination process takes place, keeping steric hindrance at its minimum.[38]

Comparing titration curves of the free ligand Figure 2 with that of the metal-ligand complexes Figure 6 reveal that the latter half of the curves (of the metal ligand complexes) will shift downwards towards a lower pH. This is due to the liberation of protons during the formation of hydroxyl complexes. This complies with the species distribution curves Figure 7 a-d as they indicate the formation hydroxyl complexes at a high pH. The quantity of protons liberated varies with the strength of the metal-bond.

All species of Zn-DTIC are higher in stability than the corresponding Cu^{2+}, Ni^{2+} and Co^{2+} (except Cu-HL and Cu-L species) Table 3. This might indicate that the Zn-DTIC complex is susceptible in modifying its structure from octahedral $[Zn(H_2O)_6]^{2+}$ to a tetrahedral $[Zn(DTIC)(H_2O)_2]^{2+}$ when the complex is formed.[36] The extra stability is due to an increase in entropy as a result of the alteration in structure.[37] Zn-DTIC species forms in solution throughout a broad range of pH 4 – 11 Figure 7-a. At pH range 4.5–5.5 the only species that exist in solution are Zn-H_3L and Zn-H_2L, with a maximum percentage of Zn-H_3L over 90% of the total concentration of the metal ions at pH 4, while the species Zn-H_2L forms just above pH 5 and reaches its maximum percentage of 65% of the metal ions at pH 6.5. Zn-HL forms initially at pH just above 6 and attains a maximum percentage of 40% of the metal ion at pH 7.25. Zn-L starts to form in an appreciable amount at pH just above 7 and reaches maximum percentage of 35% at pH 7.75. At higher pH values, between 8 and 11, the main constituents in the solution are Zn-$H_{-1}L$ and $ZnH_{-2}L$. The Zn-$H_{-1}L$ species reaches a peak of 75% at pH 9 while $ZnH_{-2}L$ starts to form at pH just after 9 and achieves a peak at 95% with pH 11.

The mono-binary Zn-DTIC system (and also other systems of other metal ions) subsists with numerous species mentioned earlier, with each species initiated from its predecessor as a consequence of proton release. The deprotonation process, which is ongoing during the coordination progression, occurs as a consequence of the coordinated bond formation, which yields electron withdrawal in the direction of the metal ion. This leads to an increase to the dissociation of water molecules attached to the metal ions to produce hydroxyl groups. For this reason, the coordination between the metal ion and ligand will increase the dissociation of these water molecules, and any another acidic hydrogen in the complex, as a result of electron density shifted from the ligand towards the metal ion.

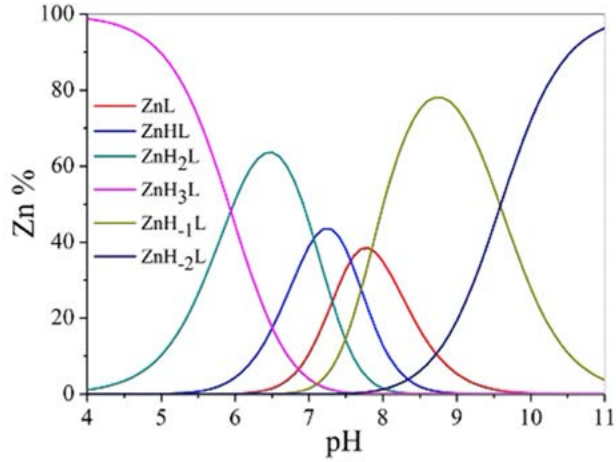

Figure 7-a. Species distribution diagram for Zn-DTIC system.

Figure 7-b displays all the probable species from the coordination of Cu^{2+} with the DTIC; six species of Cu-DTIC complex can be traced by means of our computer program when produced in detectable quantities. The complexes formed at pH levels between 4 and 6 are Cu-H_3L, Cu-H_2L and Cu-HL. The dominant species under pH 5 is Cu-H_3L, and at pH 5.75, the species Cu-H_2L, which comprises 10% of all of the metal ions at its peak. The species Cu-HL forms at just above pH 5, and at pH 6.5 reaches its maximum proportion of 70% of all of metal ions. The

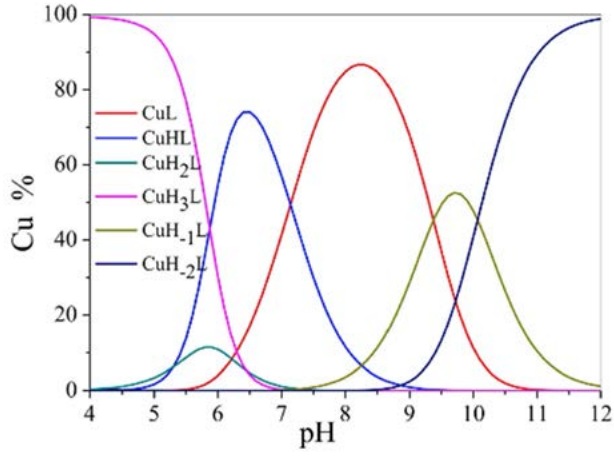

Figure 7-b. Species distribution diagram for Cu- DTIC system.

species Cu-L starts to form at pH just above 6 and at pH 8.5 reaches its maximum of 85% of all of the metal ions. At a high pH, there is a possibility that the hydrated Cu(II) ion would hydrolyse, forming hydrolysed species.[35] When the pH value exceeds 8, Cu-$H_{-1}L$ (hydrolysis species) starts to form and reaches its maximum of about 50% of all metal ions at pH approximately 9.75, followed by the formation of the second hydrolysed species $CuH_{-2}L$ at just about pH 9 and reaches its maximum at pH above 11 (Figure 7-b). The formation of the hydrolysed species in the solution also depends on the presence of water molecules on the solvated metal ion and type of metal ion.[36]

Figure 7-c displays the distribution diagram for a Ni-DTIC system which shows resemblance to the cases of both Cu-DTIC system and Zn-DTIC system. All the species of the Ni-DTIC system formed almost in the same pH range as that of Cu (II)-DTIC system. This indicates that the species of both Ni-DTIC and Cu-DTIC are similar in strength (Table 3). Ni-H_3L, Ni-H_2L and Ni-HL formed in perceptible amounts in the pH range of 4 to 6.5, which is almost the same range as that of the Cu(II) species. The maximum percentage of Ni-H_3L occurs in the solution at pH 4, while the maximum percentage of Ni-H_2L is at 45%, formed at pH around 6.5. The Ni-HL species starts to form at pH just above pH 6 and reaches its maximum of 55% at pH 7.25. The maximum percentage composition of Ni-L is 75% of the total metal ions at pH 8.25. At pH just above 8 the hydrolysed species Ni-$H_{-1}L$ started to form and reached its maximum at 35% of the total metal ions at pH 9.25, Ni-$H_{-2}L$ starts at pH just above 8.5 and rises to above 10.5.

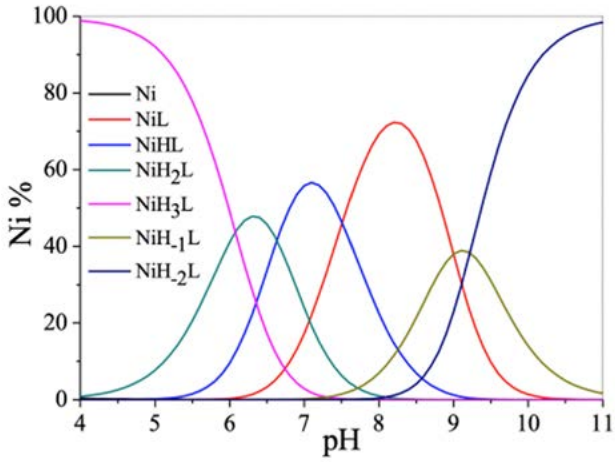

Figure 7-c. Species distribution diagram for Ni- DTIC system

Similarly, Co(II) also forms 6 species as a result of coordination between the metal ion and DTIC Figure 7d. The coordination starts at a low pH to form the Co-H_3L species followed by the species Co-H_2L as it starts to form just above pH 5 and reaches maximum of 50% at pH 6.5. Another species presents in the solution is Co-HL which reaches a maximum of about 60% at pH 7.25. Co-L species forms at pH just over pH 7 and exists and attains a maximum percentage of 70% at about pH 8.5 and fades away at approximately pH 10.

Hydrolysed species start to occur in significant amounts at pH exceeding 8 as a result of the dissociation of water molecules attached to the partially complexed metal ion in the basic medium as mentioned above. Only two hydrolysed species occur in the experimental conditions used, Co-$H_{-1}L$ and the Co-$H_{-2}L$, with the first species existing at a maximum of about 15% at pH 9 whilst the latter becomes the dominant species at pH above 10 Fig 7-d.

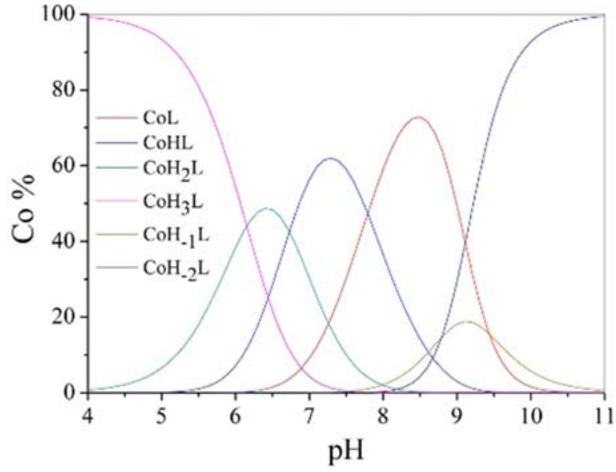

Figure 7-d. Species distribution diagram for Co- DTIC system.

4. Conclusion

The importance of DTIC is due to its anticancer properties, used on its own and combined with other drugs in chemotherapy treatments. These properties are enhanced when DTIC is present as a complex with certain metals. The coordination between the DTIC ligand and some selected di-valent transition metal ions are achieved potentiometrically, yielding numerous complexes including hydroxyl complexes in the solution depending on pH. This investigation was aimed to determine the dissociation constants of the ligand and the stability constants of the ligand-metal complexes. Experimental conditions were arranged for 1:1 ligand to metal ratio, so only mono-binary complexes were expected to form in the solution. Intra-hydrogen bonding is presumed to occur in both, the free ligand and complexed ligand *via* the oxygen of the carbonyl group and hydrogen in imidazole moiety. All metal-ligand species formed in the solution are exhibited in the speciation diagrams provided.

Acknowledgement

The authors would like to gratefully acknowledge the financial support of the Scientific Research Council of Gaziosmanpaşa University for our research.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

5. References

1. T. Kan, S. Takahagi, M. Kawal, D. Matsubara, A. Tanaka, M. Hide, *J. Dermatol.* **2020**, 47, 907–910. **DOI:**10.1111/1346-8138.15408
2. K. Maktia, H. Hara, E. Sano, Y. Okamoto, Y. Ochiai, T. Ueda, T. Nakayama, S. Aizawa, A. Yoshino, *Int. J. Oncol.* **2019**, *54*, 1864–1874. **DOI:**10.3892/ijo.2019.4743
3. S. Bhatia, S. S. Tykodi, J. A. Thompson, *Oncology* **2009**, *23*, 488–496.
4. M. Respondek, A. Beberok, Z. Rzepka, J. Rok, *Fundam. Clin. Pharmacol.* **2020**, *34*, 20–31. **DOI:**10.1111/fcp.12503
5. S. Kakumanu, J. B. Tagne, T. A. Wilson, R. J. Nicolosi, *Nanomedicine* 2011, *7*, 277–283. **DOI:**10.1016/j.nano.2010.12.002
6. C. G. Hartinger, M. G. Ferri-Mendoza, A. A. Nazarov, B. K. Keppler, *Polyhedron* **2006,** *25*, 1971–1978. **DOI:**10.1016/j.poly.2005.12.022
7. M. L. Benitz, C. B. Bender, T. L. Oliveria, K.M. Schachneider, T. Collares, F. K. Seixas, *Appl. Microbiol. Biotechol.* **2019**, *103*, 7903–7916. **DOI:**10.1007/s00253-019-10057-0
8. E. Eskin, D. Polat, A. Erdem, *Electroanalysis* **2019,** *31*, 2012–2019. **DOI:**10.1002/elan.201900284
9. C. Garbe, U. Leiter, *Clin. Dermatol.* **2009,** *27*, 3–9**.** **DOI:**10.1016/j.clindermatol.2008.09.001
10. H. Asiabi, Y. Yamini, M. Alipour, S. Shamasayei, S. Hosseinkhani, *J. Mater. Sci.* **2019,** *97*, 96–102. **DOI:**10.1016/j.msec.2018.12.017
11. A. Piotrowska, J. Wierzbicka, A. Rybarczyk, R.C. Tuckey, A. T. Slominski, M. A. Zmuewski, *Int. J. Oncol.* **2019**, *54*, 1481–1495. **DOI:**10/ 10.3892/ijo.2019.4725
12. T. Kumari, J. Shukla, S. Joshi, *Int. J. chem. Sci.* **2011**, *9*, 1751–1762.
13. S. L. Safgren, J. M. Reid, R. Rios, M. M. Ames, *J. Chromatogr. B* **2001** *754*, 91–96. **DOI:**10.1016/S0378-4347(00)00586-7
14. D. C. Lev, A. Onn, V. O. Melinkova, C. Miller, V. Stone, M. Ruiz, E. C. McGary, H. N. Ananthaswamy, J. E. Price, M. Bar-Eli, *J. Clin. Oncol.* **2004**, *22*, 2092–2100**.** **DOI:**10.1200/JCO.2004.11.070
15. Y. M. Temerk, M. M. Kamal, M. S. Ibrahim, H. S. M. Ibrahim, W. Schuhmann, *Electroanalysis* **2011**, *23*, 1638–1644**.** **DOI:**10.1002/elan.201100038
16. A. M. M. Eggermont, J. M. Kirkwood, *Eur. J. Cancer* **2004,** *40*, 1825–1836**.** **DOI:**10.1016/j.ejca.2004.04.030
17. Y. Temerk, H. Ibrahim, *J. pharm. Biomed. Anal.* **2014**, *95*, 26–33. **DOI:**10.1016/j.jpba.2014.02.010
18. G. Swiderski, R. Lazny, M. Sienkiewicz, M. Kalinowska, R. Swislocka, A. O. Acar, A. Golonko, M. Matejczy, W. Lewandowski, *Materials* 2021, *14*, 1–21. **DOI:**10.3390/ma14123274
19. T. Iwamoto, Y. Hiraku, M. Okuda, S. Kawanishi, *Pharm. Res.* **2008**, *25*, 598–604. **DOI:**10.1007/s11095-007-9413-2
20. G. Roman, E. N. Grau, A. D. Company, A. Juan, S. Simonetti, *A letters Journal Exploring the Frontiers of Physics* **2019**, *126,* P1–P6. **DOI:**10.1209/0295-5075/126/58002
21. F. Marchesi, M. Turriziani, G. Tortorelli, G. Avvisati, F. Torino, L. Vecchis, *Pharmacol. Res.* **2007,** *56* 275–287. **DOI:**10.1016/j.phrs.2007.08.003
22. G. H. Jeffery, J. Bassett, J. Mendham, R. C. Denney: Vogel's Textbook of Quantitative Chemical Analysis sixth edition. Longman, London **1999.**
23. L. D. Pettit, : Molspin Software for Molspin pH Meter; Sourby Farm: Timble. Otley, LS21 2PW U. K **1992**.
24. P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996,** *43*, 1739–1753. **DOI:**10.1016/0039-9140(96)01958-3
25. M. Amirmostofian, J. P. Jaktaji, Z. Soleimani, K. Tabib, F. Tanbakosazan, M. Omarani, F. Kobarfard, *Iran. J. of Pharm. Res.* **2013**, *12*, 255–265.
26. M. J. S. Dewar, K. M. Dieter, *J. Am. Chem. Soc.* **1986,** *108*, 8075–8086. **DOI:**10.1021/ja00285a033
27. H. Yu, R. Kuhne, R. Ebert, G. Schuurmann, *J. Chem. Inf. Model* **2010,** *50*, 1949–1960. **DOI:**10.1021/ci100306k
28. S. Spirtovic-Halilovic, D. Zavrsnik, *J. Serb.Chem. Soc.* **2010,** *75*, 243–248. **DOI:**10.2298/JSC1002243S
29. S. A. Shteingolts, V. V. Davydova, M. A. Mar'yasov, O. E. Nasakin, R. R. Fayzullin, O. A. Lodochnikova, *J. Struct. Chem.* **2020,** *61*, 928–937. **DOI:**10.1134/S002247662006013X
30. F. N. Al-Obaidi, H. Sari, M. Macit, *J. Chem. Eng. Data* **2010,** *55*, 5576–5580. **DOI:**10.1021/je1003803
31. H. Atabey, H. Sari, F. N. Al-Obaidi, *J. Solution Chem.* **2012,** *41*, 793–803. **DOI:**10.1007/s10953-012-9830-7
32. H. J. S. Machado, A. Hinchliffe, *J. Mol. Struct. (Theochem)* **1995**, *339*, 255–258. **DOI:**10.1016/0166-1280(94)04108-5
33. A. O. Eseola, N. O. Obi-Egbedi, *Spectrochim. Acta A* **2010,** *75*, 693–701. **DOI:**10.1016/j.saa.2009.11.041
34. H. Sari, A. K. Covington, *J. Chem. Eng. Data* **2005,** *50*, 1425–1429. **DOI:**10.1021/je050091l
35. J. Burgess, Metal ions in Solution. Jon, Ellis Horwood Limited, Division of John Wiley & sons, Chichester **1978**.
36. J. E. Huheey, E. Keiter, R. L. Keiter, Inorganic chemistry, Principles of Structure and Reactivity 4rd. edition. Harper Collins, New York **1993.**
37. H. Sari, F. N. Al-Obaidi, M. Macit, H. Atabey, *J. Solution Chem.* **2011,** *40*,1618–1628. **DOI:**10.1007/s10953-011-9733-z

Povzetek

Izvedli smo potenciometrično raziskavo koordinacijskih lastnosti dakarbazina, 5-(3,3-dimetil-1-triazeno)-imidazol-4-karboksamida (DTIC), z ioni nekaterih prehodnih kovin (Zn^{2+}, Cu^{2+}, Ni^{2+} in Co^{2+}). Koordinacija DTIC z omenjenimi ioni povzroči nastanek večjega števila kompleksov v raztopinah. Namen dela je določiti konstante protonacije DTIC in pokazati obseg njegove koordinacije z ioni Zn^{2+}, Cu^{2+}, Ni^{2+} in Co^{2+} oziroma določiti stabilnosti kompleksov med DTIC in temi ioni z določitvijo njihovih konstant stabilnosti. Meritve smo izvedli v vodnih raztopinah pri 25±0.1 °C v 0.1 mol dm^{-3} NaCl. Za izračun konstant protonacije in stabilnosti za ligand in komplekse smo uporabili program HYPERQUAD. DTIC ima pet konstant protonacije, katerih vrednosti znašajo pod eksperimentalnimi pogoji 10.54, 20.15, 26.99, 32.02 in 36.01. Rezultate smo interpretirali glede na bazičnost donorskih atomov in strukture liganda. Vsi kompleksi, nastali v raztopinah, so prikazani na speciacijskih diagramih.