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Biological activity and Equilibrium studies of the solution of some divalent bio-metal ions (Ca(II), Cd(II)) with CTP & NA.

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***Abstract*:** Biological activity and Equilibrium studies of solution have been taken at constant ionic strength I= 0.1 mol/l $NaNO_3$ and temperature $37+0.1^0$C and the interaction of Ca (II) & Cd (II) divalent ions with Cytidine 5ˈ-triphosphate & NA. The deep formation of 1:1:1 ternary and 1:1:1:1 quaternary complex was inferred from the potentiometric titration curve. It was deduced that Cytidine 5ˈ-triphosphate acts as a primary ligand in the ternary complexes involving the NA. The complexation model for systems of Cytidine 5ˈ-triphosphate (CTP) and the NA with the transition metal ions have been established by the SCOGS Computer software from the potential metric data. The value of Δ log K show that the ternary complexes are less stable than the quaternary ones, suggesting that less interaction occur between the ligands in the ternary complexes. The order of the value of the stability constant of ternary complexes was M(II)CTP(NA) is less than M(II) M′(II)CTP (NA).

Key word: Divalent bio-metal ions, Cytidine 5ˈ-triphosphate (CTP), Nicotinic acid (NA), Potentiometer (pH - meter), ORIGIN 6.1 Software, SCOGS Computer programme.

Introduction:

Mulberries have rich calcium sources, as 100 gm of it contains 39mg of calcium. Kiwi fruits come with more than 34mg of calcium every 100 gm. Other fruits high in calcium include blackberries these offer about 29mg per 100 gm & milk cheese and other dairy foods, Green leafy vegetables such as curly kale, okra but not spinach (spinach does contain high level Calcium but the body cannot digest).

Human body needs calcium for building strong bone and teeth clotting blood, sending and receiving nerve signals and for muscles to move and for nerves to carry messages between your brain and every part of your body. Calcium also helps blood vessels move blood throughout your body and helps release hormones that affect many functions in your body.

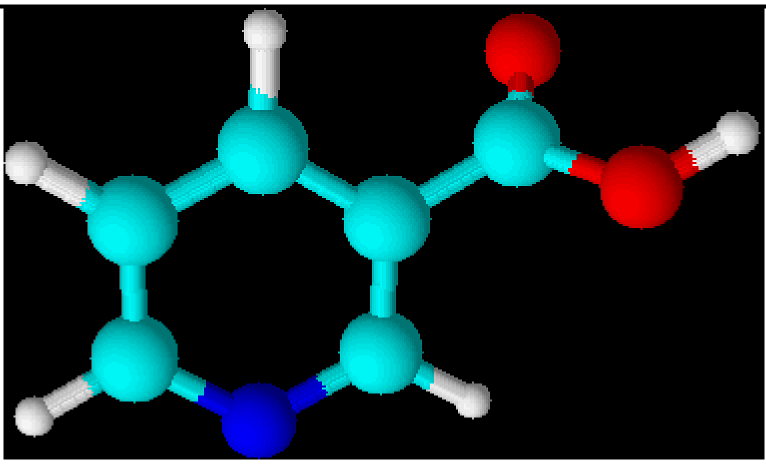
The food groups that contribute most of the dietary cadmium exposure are cereals and cereals products, vegetables, nut and pulses. Starchy roots are potatoes, meat and meat products. Due to their high consumption of cereals, nuts, oil seeds and pulses, vegetarian have a higher dietary exposure. Acute inhalation exposure to cadmium can result in flu like symptoms like fever, muscle pain, etc. and can damage the lungs. Chronic exposure can result in kidney, bone and wing disease there is no clinical or experimental evidences that background environmental exposures to cadmium causes cancer. Cadmium toxicity primarily affects the lungs and kidney with secondary effects on the skeletal systems. There is no known disease associated with cadmium deficiency however since cadmium and zinc are closely related, Zinc deficiency can lead to cadmium toxicity. Women are more prone to cadmium toxicity than men.

Workers in industries producing or using cadmium have the greatest potential for cadmium exposure. Hobbyists such as jewellery makers and artists may also be at increased risk cigarette smoke can add to the body cadmium burden.

Cadmium has no known beneficial function in the human body. Cadmium is cumulative toxin. Cadmium is transported in the blood bound to metallothionein. The greatest cadmium concentration is found in the kidney and liver. Cadmium can enter the body from smoking tobacco, eating and drinking food and water containing cadmium and inhaling heat from the air. The skin does not easily absorb cadmium. The best screening and diagnostic test for chronic cadmium exposure is a 24-hour urinary cadmium label normalised to creatinine excretion. Globally, cadmium in white rice varied from less than 4.9 to 3712 microgram per kg with a global median of 19 microgram per kg.

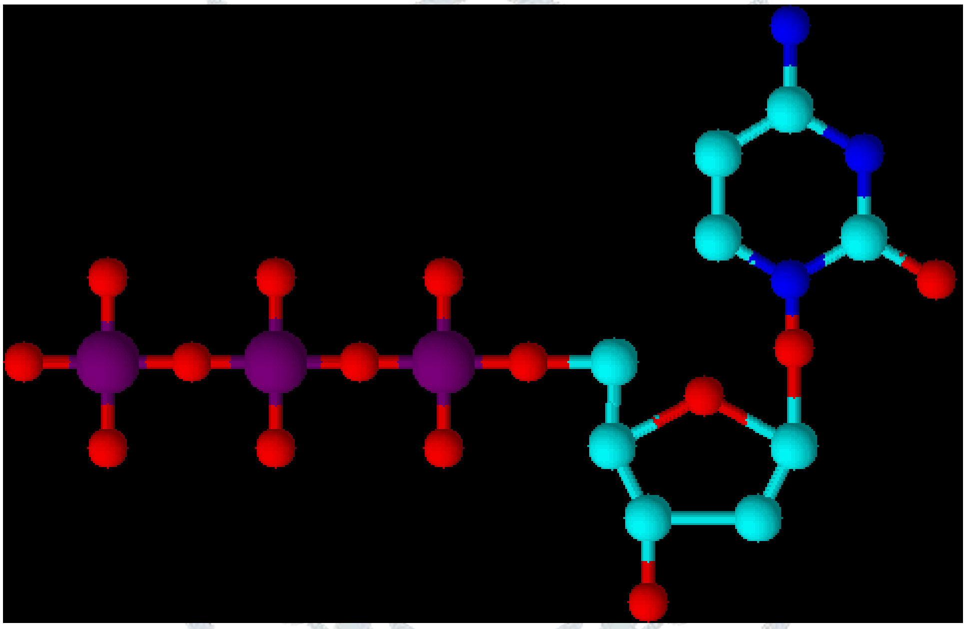
Cadmium (Cd) is a toxic heavy metal without known biological function in humans. It can be easily found in house dust and tobacco smoke (1) (Hogervorst et al., 2007)

As recently demonstrated in a human airway tissue model (2) (Xiong et al., 2019), Cd impairs cilia functions and enters the lung, where it can induce apoptosis by reactive oxygen species (ROS) production and by altering the reduced



3D-Structure of Nicotinic Acid

Nicotinic acid (niacin) is a water-soluble vitamin (B-3), which is used for the treatment of schizophrenia, hypercholesterolemia, diabetes, osteoarthritis, autoimmune diseases and pellagra (3). Natural and synthetic derivatives of Nicotinic Acid are used in medicinal chemistry because of their physiological behaviour (4-6).



3D-Structure of Cytidine 5′-triphosphate

The effective centres of coordination with metal ions {Ca(II), Cd(II)} are the donor nitrogen atoms N(3) from pyrimidine bases and the oxygen atoms from the phosphate groups of the cytidine 5'-triphosphate (nucleotide). These centres are also the sites of non- covalent interactions with the other bio-ligands present in living organisms, such as small organic, polyamines, polycations or amino acids (7, 8).

Material and Methods

Stock solutions of Nicotinic Acid and cytidine 5'- triphosphate were used as such Carbonate free sodium hydroxide solution which is prepared by standard method (9). Metal nitrate solutions were prepared and standardized by EDTA titration. Solution of NaOH and HNO_3 were prepared in double distilled water and standardized against standard oxalic acid as usual.

The ionic strength of all mixture solutions was kept 0.01M $NaNO_3$.The free acid concentration was kept 0.02M in each case. The following sets of solutions were prepared keeping the total volume 50 ml in each case. The molar ratio of binary ternary and quaternary system was taken in 1:1, 1:1:1 and 1:1:1:1ratio respectively (10).

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml L_1 (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5MLHNO$_3$ (0.02M) + 5ml L_2 (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml M (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5mlM (0.01M) + 5ml L_1 (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml M (0.01M) + 5ml L_2 (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml M (0.01M) + 5ml L_1 (0.01M) + 5ml L_2 (0.01M) + H_2O

5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml M_1 (0.01M) +5ml M_2 (0.01M) + 5ml L_1 (0.01M) + 5ml L_2 (0.01M) + H_2O

Result and Discussion

Cd-CTP-NA System: Formation curve for Cd-CTP- NA system shown in fig. 1. The ternary complex species shows its remarkable presence at higher pH range. Protonated ligand species; HCTP, HNA both decreases with increasing pH, which is exist in higher concentration at different pH. The binary complex of Cd-CTP complex is the major binary complex species whose concentration 80% which is greater than Cd-NA at the same pH 3.8. It is clear from the speciation diagram that the Cd-NA complex is the minor binary complex species whose concentration is 60% at pH ~3.8. With further increase in pH, its concentration gradually decreases and the ternary species shows increase in concentration with further rise in pH ~ ≥ 2.80. Therefore, a step wise formation of the binary and then ternary species is seen in the present systems (11). The maximum concentration ternary complex is found to be ≈73.02% at pH ~6.7.

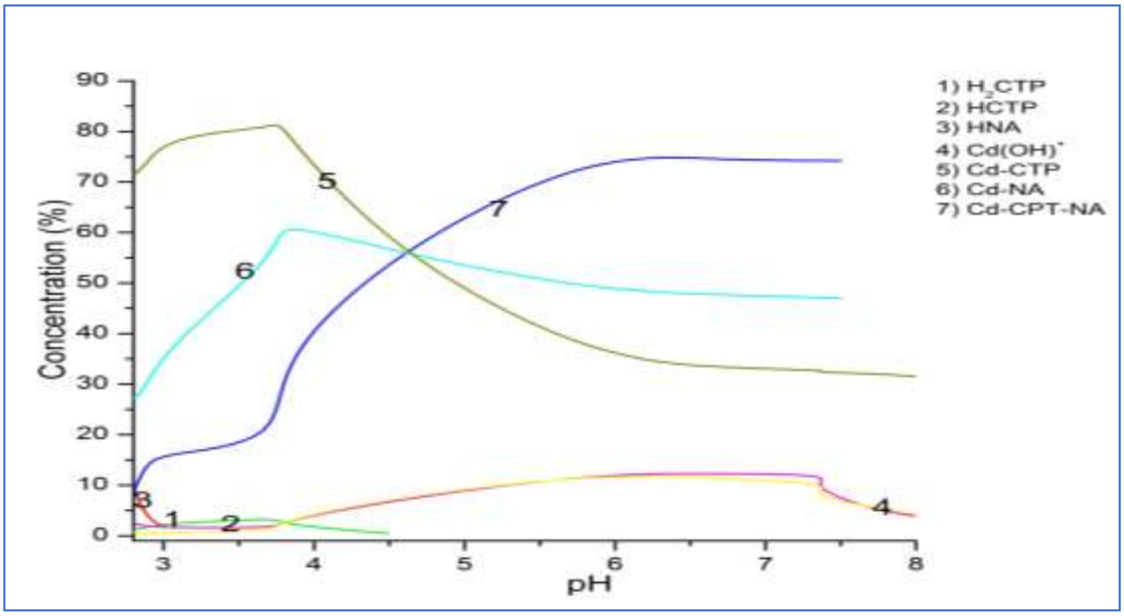


Fig. 1: Species formation curves of ternary (1:1:1) Cd-CTP-NA system.

***Ca-CTP-NA System*:** Speciation curve for Ca-CTP-NA system is represented by fig.2. Following species are assumed in the ternary system; Protonated ligand species viz. H_2CTP, HCTP, HNA, binary species Ca-CTP and Ca -NA and ternary species Ca-CTP-NA. The tendency of complex formation in binary and ternary system of metal and ligand has represented their coordination behaviour in terms of stability (12). This study, describes the relative stability constants and possible species concentration of metal complexes in binary and ternary system. The highest species percent concentration of binary complexes of Ca-CTP and Ca-NA systems was found to be ~45%, ~60% at different pH range from ~2.9, ~4.2 respectively, while (1:1:1) ternary system Ca-CTP-NA was found ~81% at (~3.5) pH (13,14).

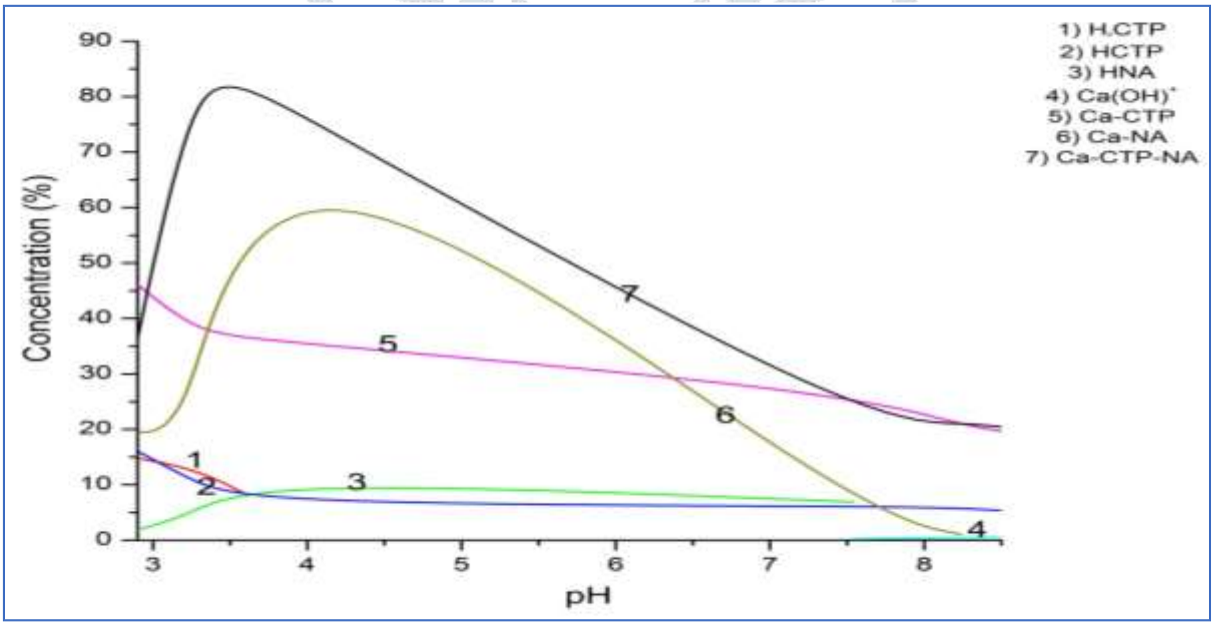


Fig. 2: Species formation curves of ternary (1:1:1) Ca-CTP-NA system.

***Cd-Ca-CTP-NA System*:** Fig. 3 of Cd-Ca-CTP-NA system shown the speciation curves of H_3CTP, H_2CTP, HNA, Ca-CTP, Ca-NA, Cd -CTP, Cd -NA, Ca-CTP-NA, Cd-CTP-NA, Cd-Ca-CTP-NA species The protonated ligand species H_3CTP, H_2CTP, HNA were found to be very low concentration. The concentration of Cd-CTP and Cd-NA species were found to have constant concentration up to pH~ 2.7-7 after that pH concentration increases with increasing pH and cover maximum concentration ~ 40% and ~ 8% at same pH~ 9 respectively.

The ternary Cd-CTP-NA and Ca-CTP-NA species firstly increases with increasing pH and obtained maximum concentration ~88.9% and 5.2% at same pH 2.8. The quaternary Cd-Ca-CTP-NA forms at the beginning of the titration and presents in the maximum concentration ~ 55.2% at lower pH ~ 3.47 and after that decreases with increasing pH.

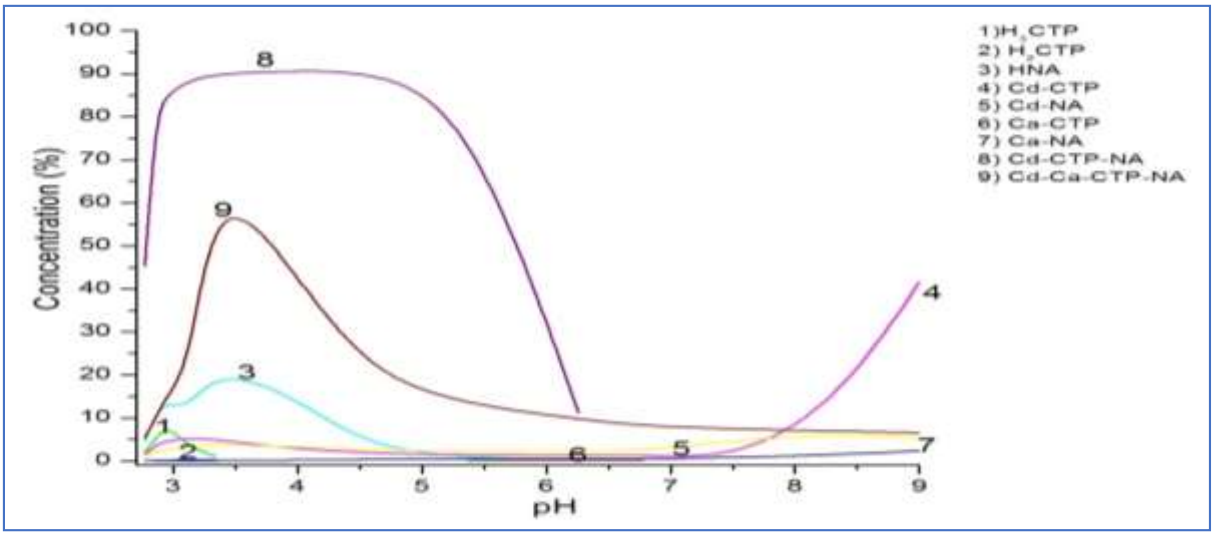


Fig.3: Species formation curves of quaternary (1:1:1:1) Cd-Ca-CTP-NA system.

Table 1

Mixed ligand (1:1:1) ternary complex potentiometric titration data of Cd-CTP-NA system.

Volume of alkali (mL)	pH of solution			
	A	B	C	D
0.00	3.15	2.48	2.65	2.66
0.20	3.24	2.54	2.67	2.69
0.40	3.43	2.61	2.75	2.75
0.60	3.69	2.68	2.78	2.80
0.80	7.88	2.76	2.80	2.86
1.00	10.31	3.86	2.86	2.92
1.20	10.61	4.1	2.91	3.02
1.40	10.75	4.34	2.94	3.12
1.60	10.88	4.96	3.10	3.28
1.80	10.98	6.2	3.22	3.45
2.00	11.04	9.32	3.33	3.78
2.20	11.11	9.48	3.59	4.24
2.40	11.16	11.52	3.98	4.69
2.60	11.20	11.98	6.06	5.14
2.80	11.25	12.48	7.06	5.72

Table 2

Mixed ligand (1:1:1) ternary complex potentiometric titration data of Ca-CTP-NA system.

Volume of alkali (mL)	pH of solution			
	A	B	C	D
0.00	2.42	2.48	2.75	2.67
0.20	2.5	2.54	2.8	2.75
0.40	2.56	2.61	2.88	2.87
0.60	3.6	2.68	3.04	3.01
0.80	3.72	2.76	3.23	3.8
1.00	3.81	3.86	3.78	3.73
1.20	4.02	4.1	5.48	4.49
1.40	4.3	4.34	6.59	5.83
1.60	4.32	4.96	8.01	6.7
1.80	4.48	6.2	10.02	7.68
2.00	6.36	9.32	10.49	10.13
2.20	9.35	9.48	10.77	10.6
2.40	11.56	11.52	10.93	10.83
2.60	12.42	11.98	11.02	10.95
2.80	……	12.48	11.11	11.02
3.00	……	……	11.17	11.10
3.32	……	……	11.30	11.16

Table 3

Mixed ligand (1:1:1:1) quaternary complex potentiometric titration data of Cd-Ca-CTP- NA system.

Volume of alkali (mL)	pH of solution				
	A	B	C	D	E
0.00	2.42	2.48	2.66	2.67	2.77
0.20	2.5	2.54	2.69	2.75	2.86
0.40	2.56	2.61	2.75	2.87	2.95
0.60	3.6	2.68	2.80	3.01	3.13
0.80	3.72	2.76	2.86	3.8	3.34
1.00	3.81	3.86	2.92	3.73	3.90
1.20	4.02	4.1	3.02	4.49	4.55
1.40	4.3	4.34	3.12	5.83	5.37
1.60	4.32	4.96	3.28	6.7	6.26
1.80	4.48	6.2	3.45	7.68	6.78
2.00	6.36	9.32	3.78	10.13	8.26
2.20	9.35	9.48	4.24	10.6	9.93
2.40	11.56	11.52	4.69	10.83	10.50
2.60	12.42	11.98	5.14	10.95	10.70
2.80		12.48	5.72	11.02	10.88
3.00				11.10	11.04
3.20				11.16	11.12

Conclusion:

CTP has more coordination positions available for binding a given bivalent metal ion as compared to the NA ligand, the stability constant for the formation of metal ligand bond in case of CTP is greater than that for NA, as also logβ values presented as follows Stability constants ($\log\beta_{1001t}$) of binary complexes Cd-CTP=5.05, Ca-CTP=3.81, Cd-NA=3.51, Ca-NA=2.65. Stability constants ($\log\beta_{1011t}$) for ternary complexes Cd-CTP-NA=10.92, Ca-CTP-NA=7.50 & Stability constants ($\log\beta_{1111t}$) for quaternary complexes Ca-Cd-CTP-NA=14.22.

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