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Speciation behaviour of multinuclear chelates involving biologically active transition metal ions with L-2-aminopropanoic acid and 6-methyl-2-thiouracil

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Abstract

The complexation properties of L-2-aminopropanoic acid [Alanine,(Ala)] to form multinuclear chelates with significant biologically effective transition metal ions (Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}) in presence of 6-methyl-2-thiouracil (MTU) have been determined pH-metrically in biotiically relevant conditions. Formation constants of chelates at 35 ± 1^0C and at constant ionic strength 0.1M $NaNO_3$ have been calculated using Stability Constants of Generalized Species (SCOGS) computer program. The graph and speciation equilibria were elucidated with the help of ORGIN 6.1. Solution of di positive transition metal ions copper, nickel, zinc, cobalt (0.01M) were processed and standardized by complexometric titration Pyrimidine base derivative (methyl thiouracil) 0.01M solution was prepared by dissolving the ligand into one equivalent of alkali sodium hydroxide (NaOH). Whereas solution of amino acid alanine (0.01M) were prepared in double distilled water only. The molar ratio of metal and ligand endeavoured was kept 1:1:1 for ternary mixture and 1:1:1:1 for quaternary mixtures. Multinuclear chelates understudy demonstrate the formation of multimetal-multiligand complexes of stoichiometry $M_1M_2L_1L_2$ in addition to ML_1L_2, ML_1 and ML_2 complexes for all metal ions. The pH titration curves, species distribution curves, hydroxo complex species and overall stability order found for heterobinuclear chelates are discussed in terms of Irving-Williams order. Solution structures of metal complexes with said ligands have been compared and discussed.

Keywords: Heterobinuclear Chelates/Amino acid (Alanine)/Pyrimidine base derivative (MTU)/ Species Distribution Curves/SCOGS.

Introduction

There is heightened attentiveness in analyzing the qualities of livingly active ligands like amino acids, peptides, pyrimidine bases and its by-products. The amino acids and peptides which are familiar in human foods, fascinated animal feeds and fooder plants are danger to animal and human health. They procure extensive cluster of chemical structures and frequently accommodate functional groups not often present in natural products[1,2] . Chelation is the proceeding of undoable binding of exceedingly active ligand to a metal ion. The speciation repercussion of pyrimidine derivatives emanate from their clinical points[3,4] biotic, agriculural[5] and transition metal coordination chelates of pyrimidines show an significant character in catalysis of drug cooperations[6].

The metal complexes of uracil and thiouracil has antiviral, antifungal, antimicrobial[7] and antitumor properties[8-12]. The formation of multi-metal, multi-ligand chelates by titration of two metal ions and two competing ligands has attracted attention concerning their structure and stability[13,14]. Ternary/ Quaternary chelates performance an important role in biological[15] processes as illustrated by numerous occasion in which enzymes[16,17] are familiar to be animated by metal ions[18,19]. In the speciation procedure utilizing chelating agents in vivo, it should be appropriated into description that there is an every occasion complete for the complexation situation between toxic and important metal ions such as Ca(II), Mg(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) are concerned in great number of redox processes compelling electron transfer[20].

Cobalt, Nickel, copper and zinc is a significant elements for plants and animals and is imbroiled in ternary and quaternary speciation. In prolongation of our studies on metal chelates[22-34], we communique here in the speciation equilibria of multi metal multi ligand chelates their overall formation constants and percentage distribution curves in consonance with pH alterations.

Materials and Methods

All chemicals used were analytical grade (Merck / BDH). Standard solutions of nitric acid, sodium nitrate and sodium hydroxide were processed by the usual manner in double distilled carbonate free water. The solutions of metal ions were inclined in the study of complexation and standardised by ethylene diamine tetra acetic acid complexometric titration[35-37].

A automated pH meter with glass electrode equipped with the instrument at 35±1^{0}C reading up to 0.01 units was accustomed for calculating the pH of adapted solutions. Previous to each set observations the potentiometer was calibrated with buffer solutions of 4.0 (acidic), 7.0 (neutral) and 9.2 (basic) correspondingly. The entire experiments were accomplished in an atmosphere of refined nitrogen by bubbling it over the solution in which the electrode was sinking. Irving and Rossotti pH titration technique was practiced for potentiometric resolution of proton-ligand and metal-ligand stability constants. For each one of the binary, ternary and quaternary schemes, five solution mixture have been titrated against standardized sodium hydroxide (0.01M) solution, keeping total volume 50ml in every case and ionic strength 0.1M$NaNO_3$.

Solution A: 5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + Water
Solution B: 5 ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml L_1 (0.01M) + water
Solution C: 5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml L_1 (0.01M) + 5ml M_1 (II) (0.01M) + water
Solution D: 5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml L_1 (0.01M) + 5ml M_1 (II) (0.01M) + 5ml L_2 (0.01M) + water
Solution E: 5ml $NaNO_3$ (1.0M) + 5ml HNO_3 (0.02M) + 5ml L_1 (0.01M) + 5ml M_1 (II) (0.01M) + 5ml L_2 (0.01M) + 5 ml M_2 (II) (0.01M) + water.
Where M_1 (II) and M_2 (II) are Co/Ni/Cu and Zn, L_1 = Primary ligand and L_2= Secondary ligand.

The pH meter reading with continuous addition of alkali to the titration mixtures were noted, when the reading of pH meter equilibrated. The titration was suspended at the arrival of turbidity. The pH values were plotted averse the volume of sodium hydroxide and titration curves were obtained.

For evaluation of speciation constants by the SCOGS computer program[38] in a system of the two different metal ions M_1 and M_2 and two different ligands L_1 and L_2 in aqueous medium, complexation may be described according to following equilibrium.

$$pM_1+qM_2+rL_1+sL_2+tOH \rightleftharpoons (M_1)p(M_2)q(L_1)r\ (L_2)s(OH)t$$

The overall stability constant (β_{pqrst}) of chelates calculated by following realation:

$$\beta_{pqrst} = [(M1)p(M2)q(L_1)r(L_2)s(OH)t]/[M])^p[M2]^q[L_1]^r[L_2]^s[OH]^t$$

The above equation may be used to calculate the species distribution curves that provides the clues for the formation equilibria of the complexes.

Values of constants were supplied to the computer as input data to obtain distribution curves of the complexes occurring at different pH. Ionic product of water (kw) and activity coefficient of hydrogen ion under the experimental conditions were obtained from literature.

Results and Discussion

Pyrimidine base derivative (6-methyl-2-thiouracil) practiced in this study has three speciation sites (1) Nitrogen atoms (2) Sulphur atom (3) Oxygen atom , by only nitrogen and sulphur atom illustrate imperative significance as bonding metal sites[39]. According to investigational and literature[40] affirmation the protonation constant of 6-methyl-2-thiouracil is 7.71. The formation constant of thiouracil valuated by computer program of the titration data corresponds to the protonation of nitrogen atom (N_3) in Figure-1.

Figure-1: The structure of 6-methyl-2-thiouracil.

Based on proclaimed, it may be accomplished that alanine coordinate to metal ions as bidentate ligand through nitrogen atom of amino group (NH_2)[41] and oxygen atom of carboxylic (COOH) group in Figure-2. Amino acid unveil three possible structures in acidic,basic and neutral medium (Figure-3).

Figure-2: The structure of Alanine.

Figure-3: Zwitter ionic form of an amino acid.

Protonation constants for the ligands have been determined by Irving-Rossotti titration technique[32] and are presented in Table-1.

Cu(II)-Ni(II)–Alanine(Ala)-6-Methyl-2-Thiouracil(MTU) (1:1:1:1) system: Potentiometric improved titration and Species distribution curves for [Cu(II)-Ni(II)-Alanine-6-Methyl-2-Thiouracil] system are flashed in Figure-4 and Figure-5 independently. By solution titration curves it is distinctly announced that the curve E (quaternary) set apart from curve D (ternary) at pH ≈3.0, which confirm the complex formation in solution medium. The multimetal-multiligand complex formation equilibria are establish to assimilate multinuclear complex species; H_2L, HL (alanine), HL (thiouracil), binary, mixed ligand complex species, free transition metal ions, and metal hydroxo species in present media. The each one of the protonated ligand species are established to be shortening with increase in the pH range ≈ 3.0-7.4, which displays their engagement in the complex formation. [Cu(II)-Alanine], [Cu(II)-6-methyl-2-thiouracil] and [Cu(II)], [Ni(II)] exit in the contemporary system. The formation of metal ligand complexes is indicated by following:

$[HL_2]^- + Cu^{2+} \rightleftharpoons [Cu(II)\text{-}HL_2]^+$

$[HL_1]^- + Ni^{2+} \rightleftharpoons [Ni(II)\text{-}L_1] + H^+$

The binary complexes [Cu(II)-L_1] and [Cu(II)-L_2H]$^+$ are present in the appreciable amount. The binary complexation starts in the beginning of titration and the mentioned complexes attain maximum concentration at higher pH region. Mixed ligand complexes with Cu^{2+} (aq.) and Ni^{2+} (aq.) is found to be remarkable species in the higher pH range ≈ 7.7-9.3 as follows.

$[HL_1]^- + Cu^{2+} + [HL_2]^- \rightleftharpoons [Cu(II)\text{-}L_1\text{-}L_2H]^- + H^+$

$[HL_1]^- + Ni^{2+} + [HL_2]^- \rightleftharpoons [Ni(II)\text{-}L_1\text{-}L_2 H]^- + H^+$

Another form

$[Cu(II)\text{-}HL_2]^+ + [HL_1]^- \rightleftharpoons [Cu(II)\text{-}L_1L_2H]^- + H^+$

$[Ni(II)\text{-}L_1\text{-}L_2 H]^- + [HL_1]^- \rightleftharpoons [Ni(II)\text{-}L_1L_2H]^- + H^+$

For multimetal-multiligand system,the species distribution curves indicate the formation of heterobinuclear complex according to the following equilibrium:

$[HL_1]^- + Cu^{2+} + [HL_2]^- + Ni^{2+} \rightleftharpoons [Cu(II)\text{-}Ni(II)\text{-}L_1\text{-}L_2] + 2H^+$

The alternative equilibrium can be written as:

$[Cu(II)\text{-}L_1\text{-}HL_2]^- + Ni^{2+} \rightleftharpoons [Cu(II)\text{-}Ni(II)\text{-}L_1\text{-}L_2] + H^+$

Speciation curve shows that there is a concomitant decline in the concentration of Cu^{2+} and Ni^{2+} aqueous ions with the incline in the concentration of multimetal- multiligand complex species. Quaternary complex species is the predominant species in the present system. The complexation starts from the very beginning and the concentration of multinuclear species is increasing gradually with the gradual increase in pH attaining maximum value ≈ 95% at ≈ 7.0.

The Metal hydroxo species Cu(II)$(OH)_2$ and Ni (II)$(OH)_2$ exit in the pH range ≈ 7.0-9.3 involving the following equilibrium:

f equilibria can be written as:

$Cu^{2+} + 2H_2O \rightleftharpoons Cu(II)(OH)_2 + 2H^+$

$Ni^{2+} + 2H_2O \rightleftharpoons Ni(II)(OH)_2 + 2H^+$

Table-1: Stability constants and other related constants of Binary, Ternary, and Quaternary complex of L-2-Aminopropanoic acid (Alanine = A) and (6-methyl-2-thiouracill=B) with different metal ions in aqueous solution at 37±1^{0}C, I=0.1M $NaNO_3$ Stability constants and other related constants of Binary, Ternary, and Quaternary complex of L-2-Aminopropanoic acid (Alanine = A) and (6-methyl-2-thiouracill=B) with different metal ions in aqueous solution at 37±1^{0}C, I=0.1M $NaNO_3$.

Proton-ligand formation constants (logβ_{00rst})						
Alanine(Ala)	H_2L	11.99				
	HL	9.69				
6-methyl-2-Thiouracil (MTU)	HL	7.94				
Hydrolytic constants (logβ_{p000t}/logβ_{0q00t})						
	Cu	Ni	Zn	Co		
$M(OH)^+$	6.29	8.10	7.89	8.23		
$M(OH)_2$	13.10	16.87	14.92	17.83		
Metal – ligand constants (logβ_{p0r00}/logβ_{0qr00}/logβ_{p00s0}/logβ_{0q0s0}): Binary systems						
ML_1	8.21	6.85	5.93	5.01		
ML_2	7.29	6.73	6.11	5.87		
Metal – ligand constants (logβ_{p0rs0} / logβ_{0qrs0}): Ternary systems						
ML_1L_2	13.46	11.57	10.93	9.85		
Metal – ligand constants (logβ_{pqrs0}): Quaternary systems						
	Cu-Ni	Cu-Zn	Cu-Co	Ni-Zn	Ni-Co	Zn-Co
$M_1M_2L_1L_2$	22.34	21.08	19.84	18.96	17.89	16.72

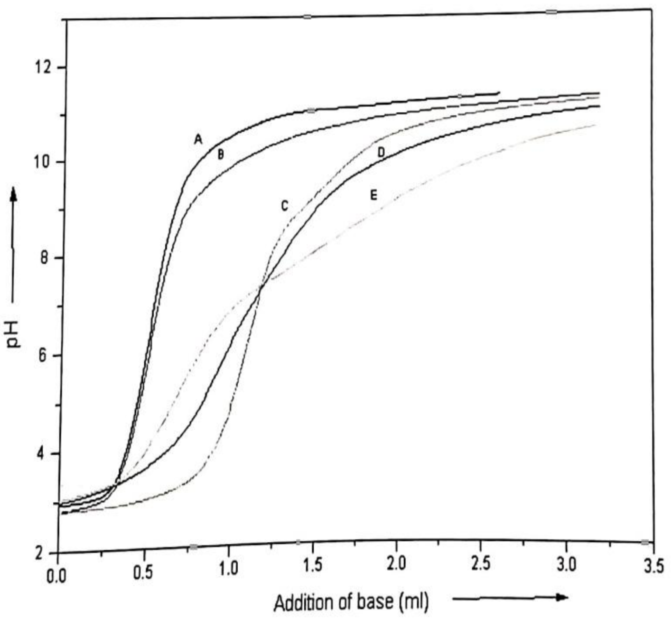

Figure-4: Potentiometric titration curves of 1:1:1:1 Cu(II)-Ni(II)-Alanine-6-Methyl-2-Thiouracil system; (A) Acid (B) Alanine (C) Cu(II)-Alanine (D) Cu(II)-Alanine-6-Methyl-2-Thiouracil (E) Cu(II)-Ni(II)-Alanine-6-Methyl-2-Thiouracil.

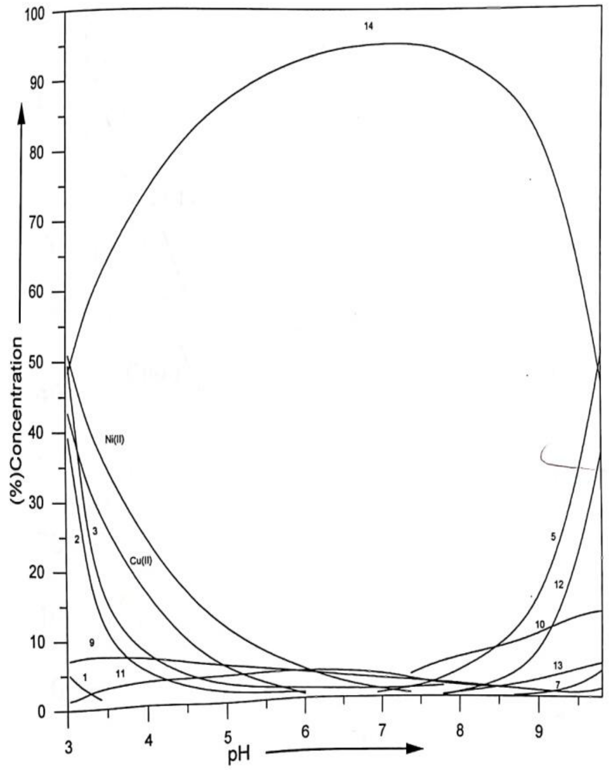

Figure-5: Distribution Curves of 1:1:1:1 Cu(II)-Ni(II)- Alanine-6-Methyl-2-Thiouracil system; (1) H_2L (2) HL (3) HL (4) $Cu(OH)^+$ (5) $Cu(OH)_2$ (6) $Ni(OH)^+$ (7) $Ni(OH)_2$ (8) CuL_1 (9) CuL_2 (10) NiL_1 (11) NiL_2 (12) CuL_1L_2 (13) NiL_1L_2 (14) $CuNiL_1L_2$.

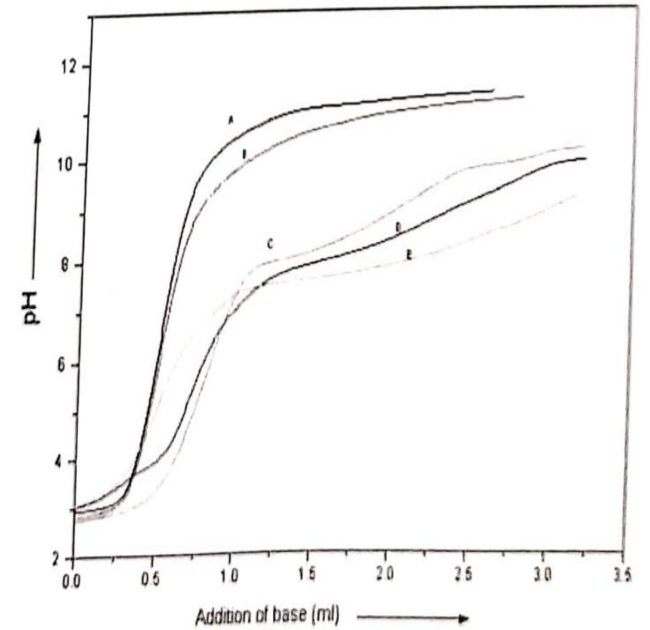

Figure-6: Potentiometric titration curves of 1:1:1:1 Zn(II)-Co(II)-Alanine-6-Methyl-2-Thiouracil system; (A) Acid (B) Alanine (C) Zn(II)-Alanine (D) Co(II)-Alanine-6-Methyl-2-Thiouracil (E) Zn(II)-Co(II)-Alanine-6-Methyl-2-Thiouracil.

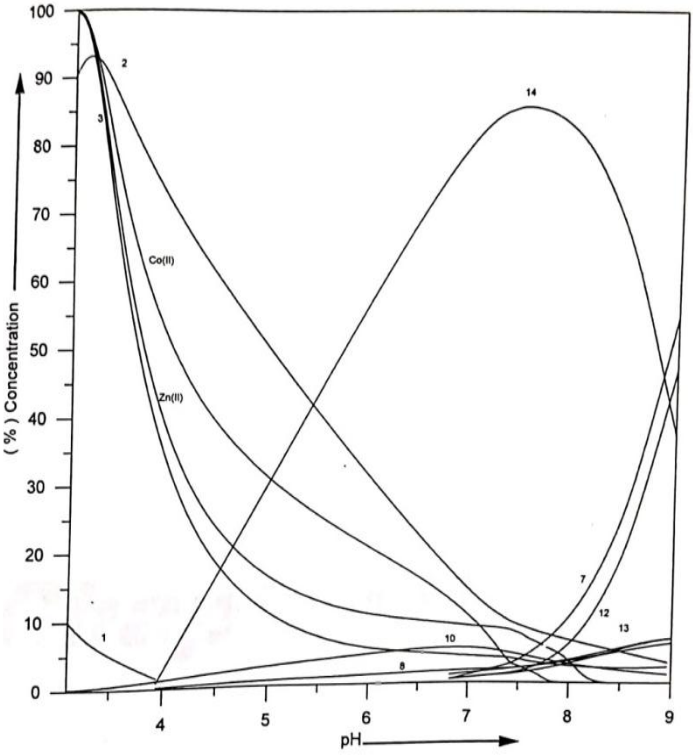

Figure-7: Distribution Curves of 1:1:1:1 Co(II)-Zn(II)-Alanine-6-Methyl-2-Thiouracil system; (1) H_2L_1(2)HL_1 (3) HL_2 (4) $Co(OH)^+$ (5) $Co(OH)_2$ (6) $Zn(OH)^+$ (7) $Zn(OH)_2$ (8) CoL_1 (9) CoL_2 (10) ZnL_1 (11) ZnL_2 (12) CoL_1L_2 (13) ZnL_1L_2 (14) $CoZnL_1L_2$.

Zn(II)-Co(II)-Alanine(Ala)-6-Methyl-2-Thiouracil(MTU) (1:1:1:1) system: pH titration curves and speciationn curves for [Zn(II)-Co(II)-Alanine-6-Methyl-2-Thiouracil] system are presented in Figure-6 and Figure-7 respectively. Multinuclear species, protonated species; H_2L,HL(Ala), HL(MTU), binary, ternary, free metal ions and hydroxo species exist in considerable amount throughout the entire pH range. The binary complex species [Zn(II)-Ala], [Co(II)-Ala] are existing in the higher pH range ≈7.0,while [Zn(II)-MTU], and [Co(II)-MTU] species are absent throughout the entire pH range. The complex formation equilibria of binary complexes are as follows:

$$[HL_1]^- + Zn^{2+} \rightleftharpoons [Zn(II)\text{-}L_1] + H^+$$
$$[HL_1]^- + Co^{2+} \rightleftharpoons [Co(II)\text{-}L_1] + H^+$$

The formation of ternary complex species ZnL_1L_2 and CoL_1L_2 occurs in higher pH region ≈ 6.7-9.0. The concentration of mixed ligand complexes incline with increase in pH and attains maximum concentration ≈ 45% and 09% respectively, according to following equilibria:

$$[HL_1]^- + Zn^{2+} + [HL_2]^- \rightleftharpoons [Zn(II)\text{-}L_1\text{-}HL_2]^- + H^+$$
$$[HL_1]^- + Co^{2+} + [HL_2]^- \rightleftharpoons [Co(II)\text{-}L_1\text{-}HL_2]^- + H^+$$

For multimetal-multiligand system formation curves indicate the complex formation equilibria as follows:

$$[HL_1]^- + Zn^{2+} + [HL_2]^- + Co^{2+} \rightleftharpoons [Zn(II)\text{-}Co(II)\text{-}L_1\text{-}L_2] + 2H^+$$

The another form of equilibrium may be represented as:

$$[Zn(II)\text{-}L_1\text{-}HL_2]^- + Co^{2+} \rightleftharpoons [Zn(II)\text{-}Co(II)\text{-}L_1\text{-}L_2] + H^+$$

The distribution curves clearly reveal that the concentration of free metal ions continuously fall with increase in pH, which shows involvement of free metal ions in the formation of multinuclear complexes. The complexation starts at very low pH region and concentration of quaternary complexes with increase in pH and attains maximum value ≈ 85% at pH 7.5. The appearance of metal hydroxo species indicates the dissociation of quaternary complex. The formation of hydroxo species is as follows.

$$Co^{2+} + 2H_2O \rightleftharpoons Co(II)(OH)_2 + 2H^+$$

Figure-8: Proposed Hexacoordinated solution structure of Mixed ligand M(II)-Alanine-6-Methyl-2-Thiouracil complex.

Figure-9: Proposed Tetracoordinted solution structure of Mixed ligand M(II)-Alanine-6-Methyl-2-Thiouracil complex

Figure-10: Proposed Solution structure of Quaternary M_1 (II)-M_2(II)-Alanine-6-Methyl-2-Thiouracil complex.

Conclusion

Metals having maximum logβ value of M-L_1 complex will be the foremost to connect with ligand L_1 which further ties to additional ligand L_2 to satisfy its chelation. The active sites of ligands still left free which will be occupied by another metal ion. In all the binary, ternary, and quaternary systems of present study following possibilities for the binding of ligands with various metal ions taken understudy may be speculated. Refined values of binary, ternary and quaternary constants are listed in Table-1, which are in rational agreement with those in literature. The overall stability constants of mixed metal-mixed ligand [Ala-MTU-M_1-M_2] systems have been found to supervene the ensuing order Cu-Ni> Cu-Zn > Cu-Co > Ni-Zn > Ni-Co > Co-Zn. On the basis of stability constants of mixed complexes and multimetal multiligand complexes the plausible solution structure are as succeeds.

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