PHYSICOCHEMICAL STUDIES OF METAL COMPLEXES OF DRUG DIAZEPAM (7-CHLORO-1-METHYL-5-PHENYL-3H-1, 4-BENZODIAZEPINE-2-ONE) IN SOLID STATE

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ABSTRACT

Thermogravimetric analyses have been used to evaluate kinetic parameters of metal complexes of diazepam. The thermal decomposition of metal complexes of diazepam drug is kinetically of zero order and the activation energy for the decomposition process lies in the range of 4-14 kcal mol^{-1}. I R spectra indicate that the metal complexes exist with monomeric structure through metal nitrogen bonding of 1, 4-N atom of ligand molecule.

Key words: Diazepam, Physicochemical, Mn (II), Cu (II), Zn (II), Co (II).

INTRODUCTION

The drug diazepam, a benzodiazepine drug, is among the most frequently prescribed drugs for the treatment of sleep disturbance, anxiety[1] and is used in medicines as tranquilizing and sedative hypnotic agents[2]. 1, 4-Benzodiazepine can act as a monodentate, bidentate or as bridging ligand in bonding[3]. The stereochemistry and chemical reactivity studies of its coordination compounds with transition metal ions help us to determine the relationship between the chemical structure and biological activity of drugs. Although a good deal of research work has been reported[4-6] for the characterization of the metal complexes of diazepam, but particularly no attention has been devoted to the study of their thermal and isothermal decomposition. The structure of ligand (diazepam) is given in Fig. 1.

EXPERIMENTAL

All the chemicals used were of AR grade and purified by standard methods. Metal complexes were prepared by the mixing of equimolar solutions of ligand (diazepam) and

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metal nitrate solutions. The 1 : 1 stiochiometric ratio was confirmed by Fengers mass estimation method[7]. The complexes were purified by recrystallization and TLC. The thermogravimetric analysis of metal complex was carried out at a constant heating rate 10^0C/min up to temperature 1000^0C on a TGA instrument Model Perkin-Elmer (Pyris Diamond). I R spectra of metal complexes were recorded on Perkin-Elmer–842 spectrophotometer.
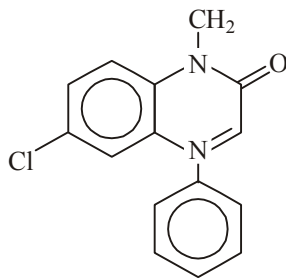
Fig. 1: Diazepam (7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepine-2-one)

RESULTS AND DISCUSSION

The band at 1608 cm^{-1} in the free ligand is attributed to v (C = N)[8,9], which undergoes shifting to lower region in all the complexes, indicating the participation of azomethine nitrogen N (4) in complexation. In all the complexes, the band assigned to v (N-CH$_3$) in ligand (1428 cm^{-1}) shows a lowering as compared to the ligand indicating the involvement of N (1) atom also in coordination. The band attributed to the vibrational mode v (C = O) appearing at (1680 cm^{-1}) in the ligand shows a small positive shift in all the complexes. The presence of new bands in the region 515 cm^{-1}-313 cm^{-1} in all the complexes is attributed to v (M-N) linkage[10,11].

The results of thermogravimetric analysis of metal complexes were recorded, which show that the final residue was the metal carbide as well as well as metal oxide and weight of residue was in good agreement with the theoretically calculated weight of metal carbide as well as metal oxide. The residue left have higher weight[9] than metal oxide, probably it shows the presence of metal carbide formed simultaneously on heating the complexes at about 1000^0C. The thermal decomposition of metal complexes can be expressed as-

It was found that the order of reaction for the decomposition of metal complexes is zero and the value of energy of activation obtained from Freeman-Carrolls[10], Horowitz-Metzger's[11] and Coats-Redfrern's[12] equations are -

Table 1: Decomposition Scheme of M (II) Complexes

Decomposition Scheme	Mn (II)		Cu (II)		Co (II)		Zn (II)	
	T	WL	T	WL	T	WL	T	WL
M ($C_{16}H_{13}ClN_2O$)(NO_3)$_2$ →								
M (C_9H_5NO)(NO_3)$_2$ →	206-324	13.89 (14.40)	194-393	13.02 (13.28)	106-206	13.78 (13.23)	195-439	29.64 (30.65)
MO + MC$_3$ + other volatile oxides of C, H, N →	510-660	26.29 (26.74)	488-586	32.18 (32.47)	397-586	26.51 (26.01)	516-662	26.15 (25.81)
MO + MC$_3$	1003	53.42 (42.98)	1004	48.31 (49.03)	9008	55.17 (56.37)	1005	38.55 (34.89)

T = Temperature range (°C) ; WL = Weight loss (%) Found/(Cal.) ; M = Mn (II), Cu (II), Co (II) and Zn (II)

Table 2: Energy of activation of Mn (II), Zn (II), Cu (II) & Co (II) complexes in Kcal mol^{-1} from different equations

Metal complexes	Freeman-Carolls	Coat-Redferns	Horowitz-Metzgers
Mn- DZ complex	10.97	11.26	11.39
Zn- DZ complex	10.26	12.83	12.19
Cu- DZ complex	9.09	11.78	10.28
Co- DZ complex	9.46	13.04	11.95

Table 3

Metal complexes	Activation energy (E) (K cal mol^{-1})	Activation entropy ΔS (e.u.)	Free energy of activation, ΔG (K cal mol^{-1})
Mn- DZ complex	9.08	56.79	43.17
Zn- DZ complex	8.29	56.83	40.71
Cu- DZ complex	8.27	56.98	41.97
Co- DZ complex	9.08	57.16	45.31

The values of energy of activation obtained from these equations are in complete agreement. The usual zero order rate law expression is -

$$\frac{dw}{dt} = K \qquad ...(1)$$

On comparing with the Arrhenious equation :

$$k = Z \exp^{(-E/RT)} \qquad ...(2)$$

or $\qquad\qquad$ log dw/dt = - E/2.303 RT + log Z

The values of energy of activation E were obtained from the slope (-E/2.303R) of the plots of log (dw/dt) vs (T^{-1}) and the values of entropy of activation ΔS for metal complexes are obtained from the relation -
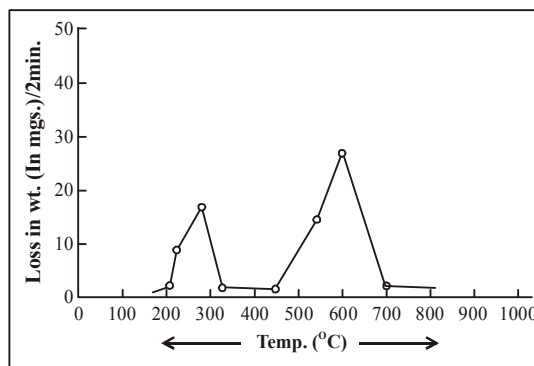
$$\Delta S = 2.303 \ R \ \log (Zh/KT_s) \qquad ...(3)$$

Where K is the Boltzman constant, h is Planck's constant and T$_s$ is the temperature for peak decomposition. The free energy of activation ΔG is calculated using the equation -
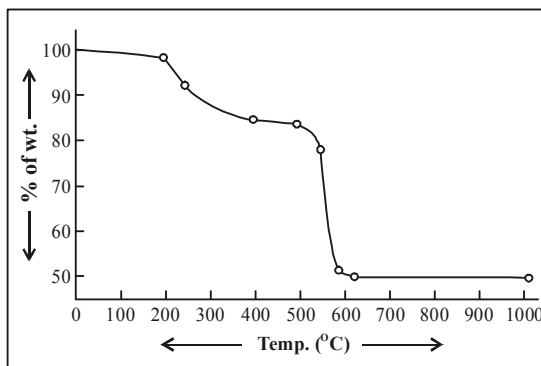
$$\Delta G = E - T_s \, (\Delta S) \qquad \qquad ...(4)$$
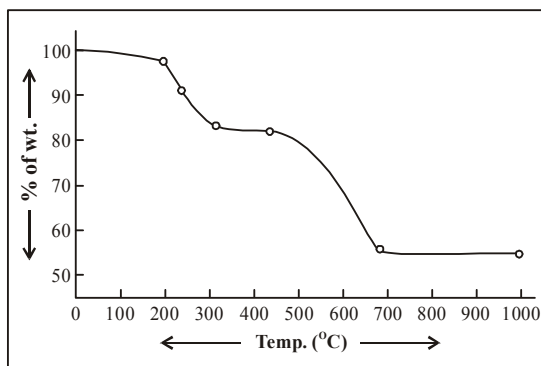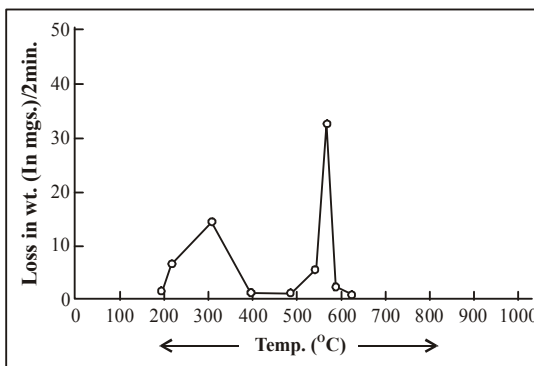

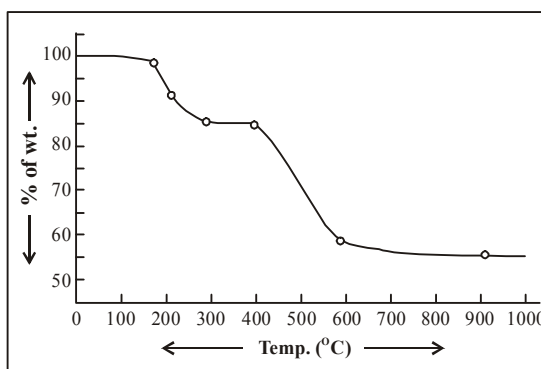**Fig. 2(a): Thermolysis curve of 1 : 1 Mn^{2+}-DZ complex**

Fig. 2(b): D. T. G. record for 1 : 1 Mn^{2+}-DZ complex
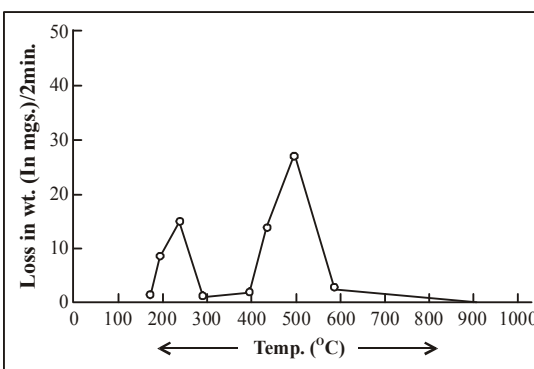

Fig. 3(a): Thermolysis curve of 1 : 1 Cu^{2+}-DZ complex
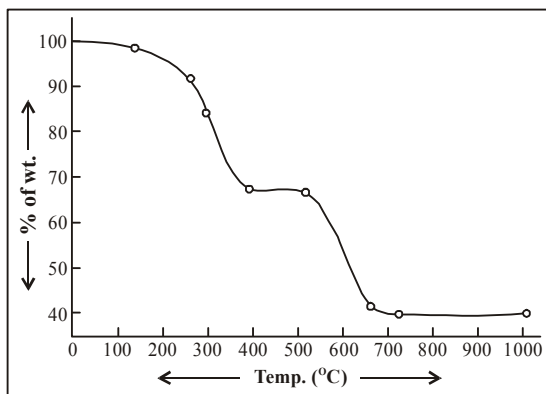

Fig. 3(b): D. T. G. record for 1 : 1 Cu^{2+}-DZ complex
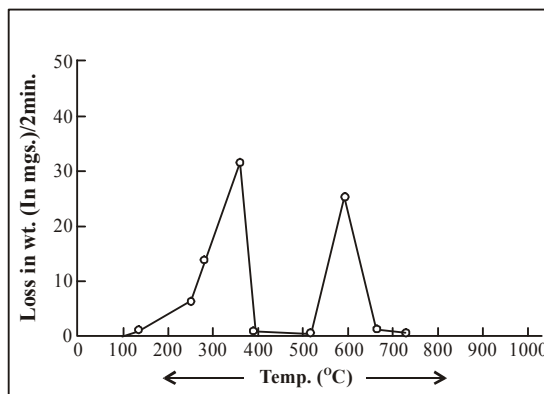

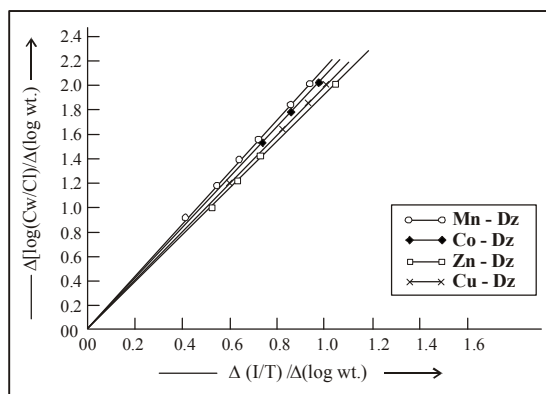**Fig. 4(a): Thermolysis curve of 1 : 1 Co^{2+}-DZ complex**
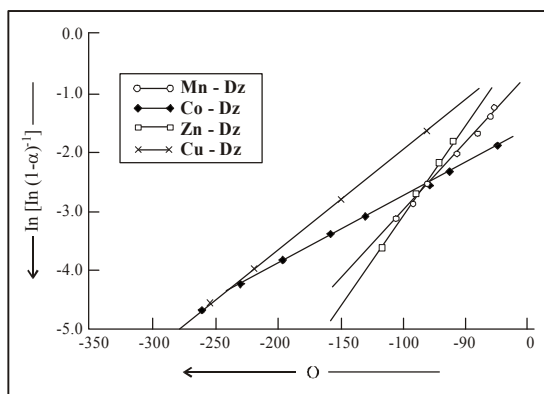

Fig. 4(b): D. T. G. record for 1 : 1 Co^{2+}-DZ complex

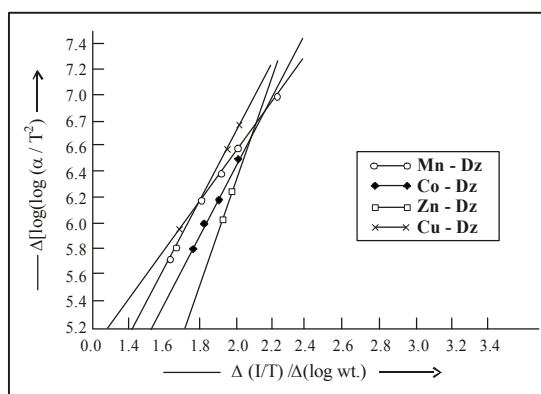**Fig. 5(a): Thermolysis curve of 1 : 1 Zn²⁺-DZ complex**

Fig. 5(b): D. T. G. record for 1 : 1 -Zn²⁺-DZ complex

Fig. 6: Freeman-Caroll's plot

Fig. 7: Horowitz-Metzger's plot

Fig. 8: Coats-Redfern's plot

REFERENCE

1. J. Bruhwyler and A. Hassoun, J. Anal. Toxicol., **16(4)**, 244 (1992).

2. H. Scultz, Benzodiazepines Springer Verlag, Heidelberg (1982).

3. E. Forizs, L. David, O. Cozar, C. Crauum and M. Kilyen, J. Mol. Structure, **408/409**, 195 (1997).

4. J. A. Real, J. Borras, M. C. Munoz and A. Mosset, Studies on Metal – Drug Complexes, J. Inorg. Biochem., **31**, 221 (1987).

5. A. Mosset, J. P. Tuchagues, J. A. Bonnet and P. Sharrode, Solution and Solid State Structure Study of Copper (II) Complex of Diazepam, Inorg. Chem., **19**, 290 (1980).

6. M. Cusmano, A. Gianetto, P. Ficcara and S. Tomassini, J. Chem. Soc., Dalton Trans., 1581 (1991).

7. P. Job, Ann., **9**, 113 (1928).

8. N. B. Colthup, L. H. Daly and S. E. Wiberley, Introduction to IR and Raman Spectroscopy, Academic Press, New York (1964).

9. L. J. Bellamy, The IR Spectra of Complex Molecules, Wiley, New York (1966).

10. A. K. Narula, J. Indian Chem. Soc., **68**, 313 (1999).

11. K. Nakamoto, J. Fujita and H. Murata, J. Amer. Chem. Soc., **80**, 4817 (1958).

12. H. D. Duan, W. G. Hou, Y. M. Wu, S. H. Han and L. Z. Wang, J. Indian Chem. Soc., **79**, 509 (2002).

13. E. S. Freeman and B. J. Caroll, Ohys. Chem., **62**, 394 (1958).

14. H. H. Horowitz and G. Metzger, Anal. Chem., **35**, 1464, (1963).

15. A. W. Coats and J. P. Redferns, Nature, **68**, 209 (1964).