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Synthesis, Characterization and Biocidal Studies of Rare Earth Metal Complexes of Diazepam

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ABSTRACT

Complexes of diazepam (DZM) with the metal nitrates of thorium, uranium and cerium have been synthesized and characterized by elemental analysis, IR spectra and pH metric analysis. In the view of above studies complexes were found to have the general composition $[L(M_1)(NO_3)_4]$, $[L(M_2)(NO_3)_2]$ *and* $[L(M_3)(NO_3)_4]$. *Where, L= ligand (DZM),* M_1 *= Th(IV),* M_2 *=* UO_2*(II) and* M_3 *= Ce(IV). The ligand act as a bi-dentate chelating agent and the complexes were proposed to be the octahedral in geometry. The ligand and its metal complexes were screened for their antimicrobial activities on bacteria (E. coli, S. typhi, B. subtitilis, S. aureus) and fungi (A. niger, F. species, P. triticena, A. flavous).*

Keywords: Diazepam (DZM), Antimicrobial Studies, Metal complexes.

INTRODUCTION

Diazepam [7-chloro-1methyl-5-phenyl-3H-1, 4 benzodiazepine-2-one] is a physiologically active agent. This is one of the most prescribed 1, 4 benzodiazepine drug ligand which has the hypnotic, tranquillizing[1-5] and anticonvulsant properties[6-9]. Its application has been reported widely in the treatment of sleep disturbance and anxiety[10]. This Schiff base and its metal complexes have the antimicrobial tendency to inhibit the growth of bacteria and fungi. DZM and its metal derivatives have been extensively studied in recent years because of its capability to form the organometallic compounds. The presence of azomethine group in metal derivatives of Schiff base has been reported[11]. Keeping the above facts in mind and the continuation of recent work on transition metal complexes, the synthesis, characterization and antimicrobial activity of DZM and its complexes with thorium, uranium and cerium have been reported in present paper. The structure of ligand diazepam is given in figure1.

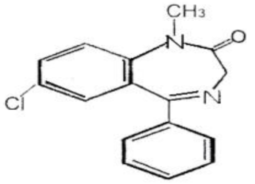


Fig.1Diazepam

MATERIALS AND METHODS

All the chemicals used were of AR grade. Ligand as well as its metal complexes prepared and analyzed by standard methods. IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. Potentiometric analysis has been carried out by Elico-120 pH-meter.

Preparation of stock solution: The stock solution of metal nitrates was prepared in double distill water. The metal content of these solution were standardized by using standard methods[12-15]. Stock solution of diazepam was prepared by dissolving the weighed amount of ligand in chloroform.

Preparation of complexes: The complexes were prepared by mixing the solution of metal nitrates and ligand DZM in the molar ratio 1:1. Few drops of KNO_3 were added in mixture with continuous mixing of 0.1N solution of caustic soda. The colored complexes were filtered and washed with warm water followed by ethanol and dried in oven until the complexes free from moisture. Recrystallisation of the complexes was done with ethanol. Purity of the complexes has been checked by TLC.

RESULTS AND DISCUSSION

All the synthesized derivatives are found to be stable at room temperature. Elemental analysis of the ligand DZM and its metal derivatives is shown in table1. Potentiometric titration has been carried out in the ratio of 1:1 of ligand and metal nitrates. In the given figures the curve a, b and c shows the curves of metal nitrates, ligand (DZM) and metal complexes respectively. Curve (a) in fig. 2 to 4 indicates the correlation of metal ion to the salt formation. In all the figures curve (c) indicates the inflection of DZM with metal nitrates of thorium, uranium and cerium. Inflection clearly indicates the formation of metal-drug derivative by the titration. pH of the solution was maintained between 8 to 9. Stoichiometry ratio is further confirmed by Job`s method[16,17].

TABLE .1

S.No.	Compound	Molecular Formula	Color	% Analysis			
				C	H	N	Metal
1.	Diazepam	$C_{16}H_{13}N_2ClO$	White	67.62 (67.44)	4.24 (4.57)	9.43 (9.83)	-
2.	DZM-$Th(NO_3)_4$	$[C_{16}H_{13}N_2ClO.\ Th(NO_3)_4]$	Shiny Yellow	25.21 (25.10)	1.49 (1.70)	11.12 (10.98)	30.24 (30.33)
3.	DZM-$UO_2(NO_3)_2$	$[C_{16}H_{13}N_2ClO.\ UO_2(NO_3)_2]$	Yellow	28.46 (28.29)	1.85 (1.91)	8.43 (8.25)	34.85 (35.06)
4.	DZM-$Ce(NO_3)_4$	$[C_{16}H_{13}N_2ClO.\ Ce(NO_3)_4]$	Cream Yellow	28.24 (28.53)	1.98 (1.93)	12.62 (12.48)	20.57 (20.82)

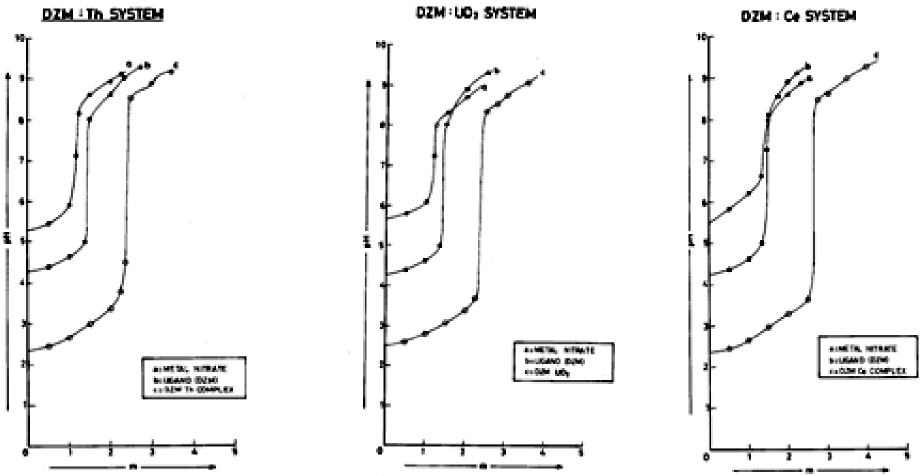
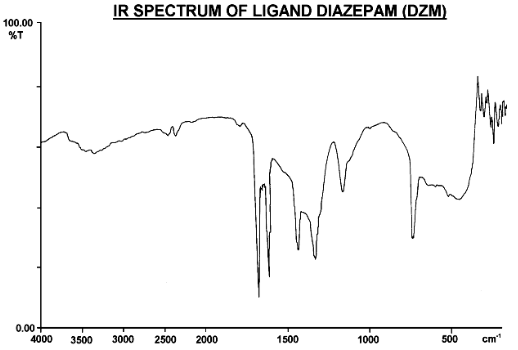
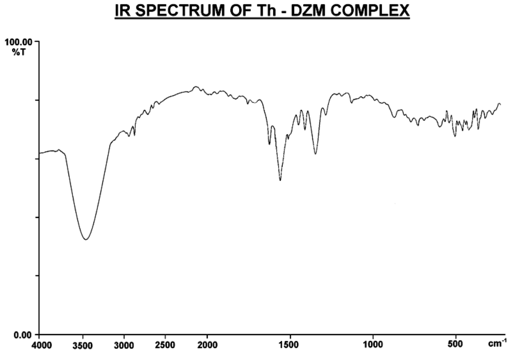


Fig. 2 Fig. 3 Fig. 4

Fig. 2-4. Potentiometric titrations

Spectral study i.e. Infrared Spectroscopy (fig.5) was recorded on Perkin–Elmer 842 spectrophotometer. The infrared spectrum of DZM exhibits the band in the region of 3412 cm^{-1}, 1680 cm^{-1}, 1608 cm^{-1}, 1428 cm^{-1}, 1332 cm^{-1} and 740 cm^{-1} which may be assigned as (HC-OH), (C=O), (C=N), (N-CH_3), -CH stretching and –Cl group respectively[18-25]. In the IR spectra of thorium, uranium and cerium complexes, the band attributed to the vibration mode. (C=N) peak appears at 1603 cm^{-1}, 1605 cm^{-1}, and 1626 cm^{-1} respectively showing the lower shifting in thorium and uranium complexes but positive shifting in cerium complex as compared to the ligand indicating that the azomethine nitrogen $N_{(4)}$ involve in the complexation. The peak of (C=O) group at 1680 cm^{-1} on vibrational mode in DZM exhibits a small positive shift during complexation. (C=O) band shifted to 1694 cm^{-1}, 1689 cm^{-1} and 1685 cm^{-1} respectively. The presence of (N-CH_3) group is suggested by the bands in thorium, uranium and cerium complexes at 1418 cm^{-1}, 1426 cm^{-1} and 1422 cm^{-1} respectively as compared to ligand (1428 cm^{-1}). The presence of new bands in thorium complex at 527 cm^{-1} and 385 cm^{-1}, in uranium complex at 504 cm^{-1} and 307 cm^{-1} and in cerium complex at 514 cm^{-1} and 458 cm^{-1} indicates the M–N linkage. Other strong bands at 1376 cm^{-1} and 858 cm^{-1} in thorium complex, 1385 cm^{-1} and 835 cm^{-1} in uranium complex and 1383 cm^{-1} in Ce(IV) complex suggest the presence of mono-dentate nitrate group in complexes[26] in the coordination sphere.





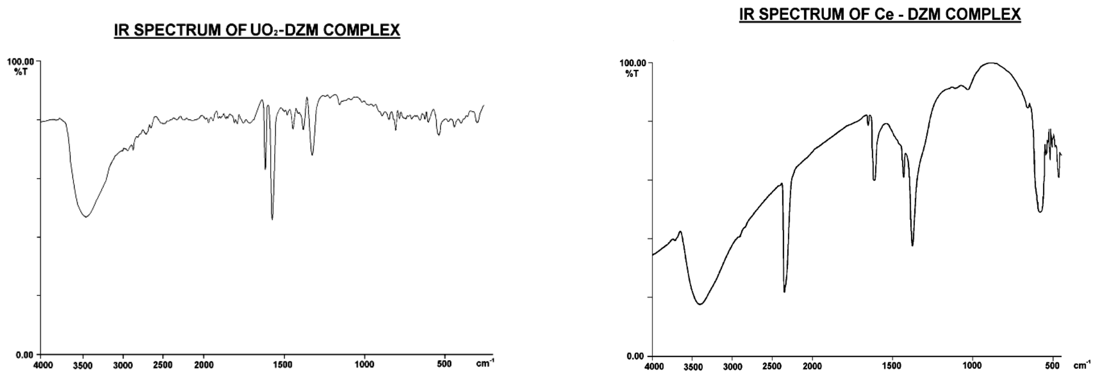


Fig5. IR Spectra

TABLE – 2

S.NO.	COMPOUND	(C=O)	(C=N)	(N-CH_3)	(-NO_3)	(M-N)
1.	Diazepam (DZM)	1680	1608	1428	-	-
2.	DZM + Th complex	1694	1603	1418	1376, 858	527, 385
3.	DZM + UO_2 complex	1689	1605	1426	1385, 835	504, 307
4.	DZM + Ce complex	1685	1626	1422	1383	514, 458

The tentative structure of complexes are shown in figs. 6, 7 and 8 on the basis of elemental analysis and IR spectral study.

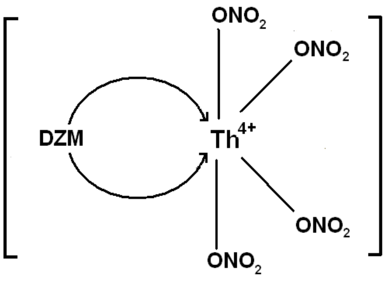


Fig.5

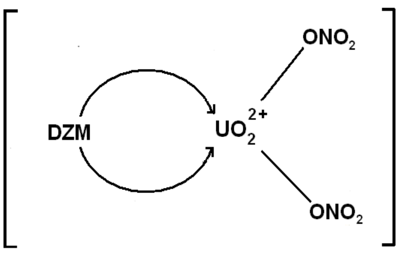


Fig.6

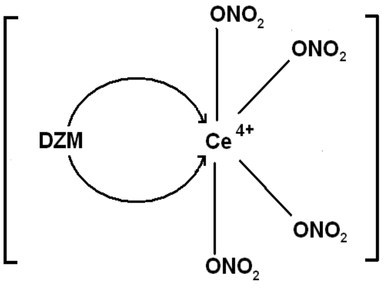
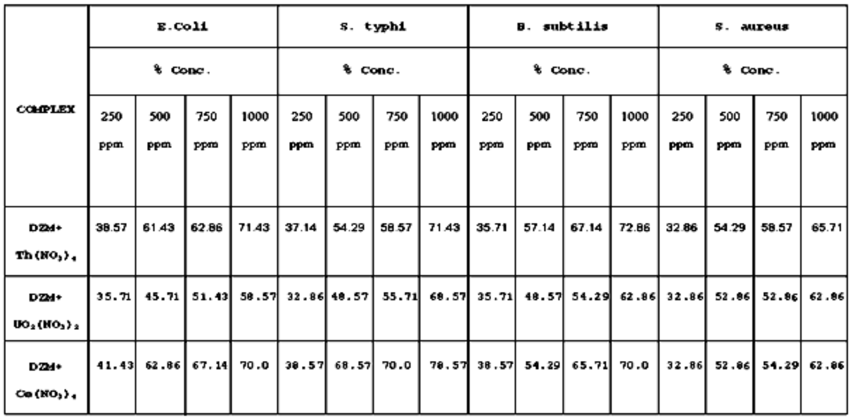


Fig.7

Antimicrobial Activity: The ligand DZM and its metal complexes were tested for their anti-bacterial and anti-fungal activity. The ligand and metal complexes were screened against the bacteria (*E. coli*, *S. typhi*, *B. subtilis* and *S. aureus*) and fungi (*A. niger*, *A. flavous*, *P. triticena* and *F. species*). The comparative study clearly shows that the metal complexes have the enhanced antimicrobial activity in comparison of drug ligand DZM. The results of antimicrobial activities are given in table 3 and table 4.

TABLE 3

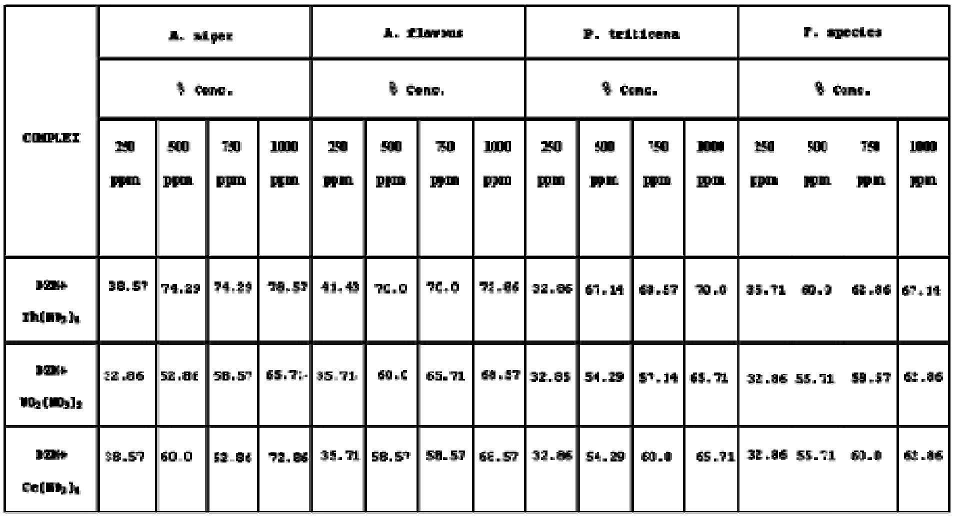
Percentage of zone of inhibition of DZM-metal complexes against bacteria:-



COMPLEX	E.Coli				S. typhi				B. subtilis				S. aureus			
	% Conc.				% Conc.				% Conc.				% Conc.			
	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm
DZM+ $Th(NO_3)_4$	38.57	61.43	62.86	71.43	37.14	54.29	58.57	71.43	35.71	57.14	67.14	72.86	32.86	54.29	58.57	65.71
DZM+ $UO_2(NO_3)_2$	35.71	45.71	51.43	58.57	32.86	48.57	55.71	68.57	35.71	48.57	54.29	62.86	32.86	52.86	52.86	62.86
DZM+ $Ce(NO_3)_4$	41.43	62.86	67.14	70.0	38.57	68.57	70.0	78.57	38.57	54.29	65.71	70.0	32.86	52.86	54.29	62.86

TABLE-4

Percentage ofzone of inhibition of DZM-metal complexes against fungus :-



COMPLEX	A. niger				A. flavus				P. triticena				F. species			
	% Conc.				% Conc.				% Conc.				% Conc.			
	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm	250 ppm	500 ppm	750 ppm	1000 ppm
DZM+ $Th(NO_3)_4$	38.57	74.29	74.29	78.57	41.43	76.0	76.0	71.86	32.86	67.14	68.57	70.0	35.71	60.0	62.86	67.14
DZM+ $UO_2(NO_3)_2$	32.86	52.86	58.57	65.71	35.71	60.0	65.71	68.57	32.85	54.29	57.14	65.71	32.86	55.71	58.57	62.86
DZM+ $Ce(NO_3)_4$	38.57	60.0	52.86	72.86	35.71	58.57	58.57	66.57	32.86	54.29	60.0	65.71	32.86	55.71	60.0	62.86

APPLICATIONS

Result shows that the Th (IV) complex of DZM is much active on bacteria and fungi in comparison of uranium and cerium complex. Thorium complex shows its effectiveness more towards the bacteria *E. coli* and *B. subtilis* and fungus *A. niger*.

CONCLUSIONS

The ligand diazepam forms the complexes on reaction with metal salts. The analytical and spectral investigations reveal that the complexes have been formed with the molecular formula of $[L(M_1)(NO_3)_4]$, $[L(M_2)(NO_3)_2]$ and $[L(M_3)(NO_3)_4]$ where L= ligand (DZM), M_1= Th(IV), M_2= UO_2(II) and M_3= Ce(IV). The antimicrobial studies show that the complexes are more bioactive than the parent ligand. Further investigations on exploiting the antibacterial activities of the complexes are in progress.

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REFERENCES

[1] W. J. Geary, *Coord. Chem. Rev*. **1971**, 7, 81.
[2] C. Preti and G. Tosi, *J. Coord. Chem.* **1979**, 8, 223.
[3] C. Preti and G. Tosi, Transition Met. Chem. **1978**, 3, 246.
[4] G. Minghetti, M. L. Ganadu, C. Foddai, M. A. Cinellu, F. Demartin and M. Manassero, *Inorg. Chim. Acta,* **1984**, 86, 93.
[5] M. A. Cinellu, M. L. Ganadu, G. Minghetti, F.Cariati, F. Demartin and M. Manassero, *Inorg. Chim. Acta,* **1984**, 86, 93.
[6] W. Schollek, W. D. Horst, W. Schlosser, *Adv. Pharmacol. Chemother.*, **1979**, 16,45-87.
[7] F. C. Colpaert, NIDA Res. Monogr., 116, 245-266, *Drug Discrim. Appl. Drug Abuse Res.* **1991.**
[8] S. D. Iversen, *Br. Assoc. Psychopharmacol. Monogr*.**1985**, 6, 75-88.
[9] M. Buehrer, P. O. Maitre, C. Crevoisier, D. R. Stanski, *Clin. Pharmacol. Ther., (St. Louis),* **1990**, 48(5), 555-567.
[10] J. Bruhwyler, A. Hassoun, *J. Anal. Toxicol*., **1992**, 16(4), 244-252.
[11] W. F. Snyth, Voltametric Determination of Molecules of Biological Significances, P.13-31, Wiley, Chichester**1992**.
[12] A. I. Vogel, "A Text Book of Quantitative Inorganic Analysis" E. L.B. S., **1962**, p.358.
[13] A. I. Vogel, ibid, p.525.
[14] A. I. Vogel, ibid, p.351.
[15] A. I. Vogel, ibid, p.533.
[16] A. J. Thomson, R. J Williams, P. Resolva, *Struc. Bonding*, **1962**, 11, 1, P. Job, Anu, **1928**, 9, 113.
[17] J. Fenger, K. E. Siekirsha and B. S. Jenson, *Inorg. Nucl. Chem.* 1928, 33, 113.
[18] J. H. Quasted, *J. Gen. Microbial*, **1966**, 45, 14.
[19] A. W. Baura, W. M. Kirby, J. C. Sherries and M. Turk, *Am. J. Clin. Pathol*. **1966**, 45, 493.
[20] R. M. Silverstein, Spectrometric Identification of Organic Compounds 6th Edn. John Wiley, **1991**, 123.
[21] K. Nakamoto, Fujita, H. J. Murata, *Amer. Chem. Soc.* **1958**, 80, 4817.
[22] K. Nakanishi, Infrared Spectra of Inorganic and Coordination Compound, Wiely, New-York, **1970**.
[23] M. J. M. Camphell and R. J.Grzesjwaik, *Inorg. Nucl. Chem*. **1968**, 30, 1865.
[24] B. Chatterjee, *Coord. Chem. Rev*. **1978**, 26, 281.
[25] K. Nakamoto, Spectroscopy and Structure of Metal Chelate Compounds, John Wiley, New-York, **1968**.
[26] S. N. Chaube, J. P. Srivastava and L. K. Mishra, *Inorganic Chem. Acta*. **1977**, 23, 1.