

Zinc Complexes of Benzothiazole-derived Schiff Bases with Antibacterial Activity

ZAHID H. CHOCHAN^a, ANDREA SCOZZAFAVA^b and CLAUDIU T. SUPURAN^{b,*}

^aDepartment of Chemistry, Islamia University, Bahawalpur, Pakistan; ^bUniversity of Florence, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Via della Lastruccia 3, Rm 188, Polo Scientifico, 50019-Sesto Fiorentino, Firenze, Italy

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Reaction of 2-acetamidobenzaldehyde with 2-amino-, 2-amino-4-methyl-, 2-amino-4-methoxy-, 2-amino-4-chloro-, 2-amino-6-nitro- and 2-amino-6-methylsufonyl-benzothiazole afforded a series of Schiff bases. These compounds have been used for complexation reactions to obtain Zn(II) chelates having the same metal ion but different anions of the type $[Zn(L)_2]X_n$ [L = Schiff base derivative, X = SO₄, NO₃, C₂O₄ and CH₃CO₂ and n = 1 or 2] These complexes (Table I) have been characterized by physical, spectral, and analytical data. The Schiff bases act tridentately and their metal complexes were proposed to possess an octahedral geometry. To evaluate the antibacterial role of the anion, these compounds have been screened for antibacterial properties against pathogenic strains such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Keywords: Antibacterials; Benzothiazoles; Zinc complexes; Schiff bases

INTRODUCTION

Biological activity of benzothiazole and the compounds derived from it, such as 4-aryl-2-(2-hydroxy- α -substituted benzylamino)benzothiazole,¹ 2-(2-hydroxyphenyl/naphthyl)-3-(4-arylthiazol-2-yl)-4-thiazolidonebenzothiazole methiodide,² 2-aryl-4-(5-nitro-2-furyl)benzothiazole,³ acetoacetamido-benzothiazole⁴ and many chloro-, nitro-, hydroxy-, -methoxy, or -methyl substituted benzothiazoles⁵ have been thoroughly investigated. A bulk of research has indicated^{6–20} the relationship between metallo-organic and biological behavior of compounds containing the azomethine (CH=N) linkage. This activity is probably connected to their

ability^{21,22} to provide a site that leads to a potential system with a “locked geometry” via the coordination mechanism by which certain substrates become attached to this framework^{23,24} of the chelated compound and activate enzymatic reactions.^{25–27} The growing interest in this area and all these observations attracted our attention to commence a program to synthesize^{28,29} anti-bacterial benzothiazole-derived Schiff bases (L¹–L⁶) (Figure 1) and their metal chelates. In the present work we wish to highlight the participating antibacterial role of anions in such derivatives, by reporting metal chelates with previously synthesized^{30,31} ligands (L¹–L⁶) having the same cation (zinc) but different anions (such as sulfate, nitrate, acetate and oxalate). These newly synthesized metal complexes have been characterized by physical, spectral and analytical data and have been screened for their antibacterial activity against pathogenic bacterial species i.e. *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

MATERIALS AND METHODS

Chemistry

All chemicals and solvents used were of Analar grade. Zinc salts used were the sulfate, nitrate, acetate and oxalate. IR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer. UV-Visible spectra were obtained in DMF on a Hitachi U-2000 double-beam spectrophotometer. C, H and N analyses was carried out by Butterworth Laboratories Ltd, Middlesex, U.K. Conductances of

*Corresponding author. E-mail: claudiu.supuran@unifi.it

TABLE I Physical and analytical data of the Zn(II) chelates

Metal Chelate	M.P (°C) (decomp)	Calc (Found)%			Yield (%)
		C	H	N	
(1) [Zn(L ¹) ₂](NO ₃) ₂ C ₃₂ H ₂₆ ZnN ₈ O ₈ S ₂ [779.4]	208–210	49.3 (49.6)	3.3 (3.5)	14.4 (14.6)	62
(2) [Zn(L ¹) ₂]SO ₄ C ₃₂ H ₂₆ ZnN ₆ O ₆ S ₃ [751.4]	215–217	51.1 (51.2)	3.5 (3.9)	11.2 (11.5)	61
(3) [Zn(L ¹) ₂]C ₂ O ₄ C ₃₄ H ₂₆ ZnN ₆ O ₆ S ₂ [773.4]	205–207	54.9 (55.2)	3.5 (3.2)	11.3 (11.6)	60
(4) [Zn(L ¹) ₂](CH ₃ CO ₂) ₂ C ₃₆ H ₃₂ ZnN ₆ O ₆ S ₂ [773.4]	220–222	55.9 (55.5)	4.1 (4.0)	10.9 (10.6)	61
(5) [Zn(L ²) ₂](NO ₃) ₂ C ₃₆ H ₃₀ ZnN ₈ O ₈ S ₂ [831.4]	202–204	52.0 (52.4)	3.6 (3.8)	13.5 (13.7)	60
(6) [Zn(L ²) ₂]SO ₄ C ₃₆ H ₃₀ ZnN ₆ O ₆ S ₃ [803.4]	218–220	53.8 (53.6)	3.7 (3.3)	10.5 (10.4)	60
(7) [Zn(L ²) ₂]C ₂ O ₄ C ₃₈ H ₃₀ ZnN ₆ O ₆ S ₂ [795.4]	207–209	57.3 (57.7)	3.8 (3.5)	10.6 (10.9)	62
(8) [Zn(L ²) ₂](CH ₃ CO ₂) ₂ C ₄₀ H ₃₆ ZnN ₆ O ₆ S ₂ [753.1]	218–220	58.2 (58.5)	4.4 (4.8)	10.2 (10.0)	61
(9) [Zn(L ³) ₂](NO ₃) ₂ C ₃₆ H ₃₀ ZnN ₈ O ₁₀ S ₂ [863.4]	209–211	52.3 (52.4)	3.5 (3.4)	13.0 (13.3)	60
(10) [Zn(L ³) ₂]SO ₄ C ₃₆ H ₃₀ ZnN ₆ O ₈ S ₃ [835.4]	222–224	51.7 (51.5)	3.6 (3.9)	10.0 (11.2)	62
(11) [Zn(L ³) ₂]C ₂ O ₄ C ₃₈ H ₃₀ ZnN ₆ O ₈ S ₂ [827.4]	206–208	55.1 (55.0)	3.6 (3.5)	10.2 (10.5)	61
(12) [Zn(L ³) ₂](CH ₃ CO ₂) ₂ C ₄₀ H ₃₆ ZnN ₆ O ₈ S ₂ [857.4]	215–217	56.0 (56.3)	4.2 (4.1)	9.9 (9.7)	61
(13) [Zn(L ⁴) ₂](NO ₃) ₂ C ₃₂ H ₂₄ ZnN ₈ O ₈ S ₂ [712.9]	208–210	44.8 (44.7)	3.0 (3.5)	13.8 (13.9)	62
(14) [Zn(L ⁴) ₂]SO ₄ C ₃₂ H ₂₄ ZnN ₆ O ₆ S ₃ [784.9]	215–217	48.9 (49.2)	3.1 (3.2)	10.7 (10.5)	61
(15) [Zn(L ⁴) ₂]C ₂ O ₄ C ₃₂ H ₂₄ ZnN ₆ O ₆ S ₂ [776.9]	205–207	52.5 (52.6)	3.1 (3.5)	10.8 (10.5)	60
(16) [Zn(L ⁴) ₂](CH ₃ CO ₂) ₂ C ₃₆ H ₃₀ ZnN ₆ O ₆ S ₂ [806.9]	220–222	52.5 (52.8)	3.7 (3.9)	10.4 (10.3)	61
(17) [Zn(L ⁵) ₂](NO ₃) ₂ C ₃₂ H ₂₄ ZnN ₁₀ O ₁₂ S ₂ [869.4]	202–204	44.2 (44.0)	2.8 (2.5)	16.1 (16.5)	60
(18) [Zn(L ⁵) ₂]SO ₄ C ₃₂ H ₂₄ ZnN ₈ O ₁₀ S ₃ [841.4]	218–220	45.6 (45.9)	2.9 (3.7)	13.3 (13.0)	60
(19) [Zn(L ⁵) ₂]C ₂ O ₄ C ₃₄ H ₂₄ ZnN ₈ O ₁₀ S ₂ [833.4]	207–209	49.0 (49.5)	2.9 (3.2)	13.4 (13.5)	62
(20) [Zn(L ⁵) ₂](CH ₃ CO ₂) ₂ C ₃₆ H ₃₀ ZnN ₈ O ₁₀ S ₂ [863.4]	218–220	50.0 (50.2)	3.5 (3.2)	13.0 (13.3)	61
(21) [Zn(L ⁶) ₂](NO ₃) ₂ C ₃₄ H ₃₀ ZnN ₈ O ₁₂ S ₄ [935.4]	209–211	43.6 (43.9)	3.2 (3.5)	12.0 (12.1)	60

the metal complexes were determined in DMF on a Hitachi YSI-32 model conductometer. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

Preparation of the Schiff Base Ligands

2-[(2-METHYLCARBONYLAMINO)PHENYLMETHYLIDINAMINO]BENZOTHAZOLE (L¹)

2-Aminobenzothiazole (1.5 g, 9.9 mM) in ethanol (10 ml) was added to a hot ethanol solution (30 ml) of 2-acetamidobenzaldehyde (1.6 g, 9.8 mM). Then 2–3 drops of conc. H₂SO₄ were added and the mixture refluxed for 2 h. On cooling, a solid product was formed which was filtered, washed with ethanol, then with ether and dried. Crystallization from hot ethanol gave L¹. The same method was applied for the preparation of L²–L⁶ by using the corresponding reagents in the molar ratio.³¹

PREPARATION OF ZN(II) COMPLEX

A warm ethanol solution (20 ml) of the Schiff base ligand (5 mM) was added to a magnetically stirred

solution of Zn(II) salt (2.5 mM) in ethanol (25 ml). The mixture was refluxed for 1 h and cooled to room temperature, when a solid product precipitated. The product thus obtained was filtered, washed with ethanol, then with ether and dried. Crystallization from aqueous ethanol (30:70) gave the desired metal complexes.

Antibacterial Studies

The ligand/complex (30 µg) in DMF (0.01 ml) was mounted as a paper disc [prepared from blotting paper (3 mm diameter)] with the help of a micropipette. The discs were left in an incubator for 48 h at 37°C and then applied onto the bacteria grown on agar plates.

Minimal agar was used for the growth of specific bacterial species. For the preparation of agar plates for *Escherichia coli*, MacConkey agar (50 g) obtained from Merck Chemical Company, was suspended in freshly distilled water (1 L). It was allowed to soak for 15 min and then boiled on a water bath until the agar was completely dissolved. The mixture was autoclaved for 15 min at 120°C and then poured into previously washed and sterilized Petri dishes and stored at 40°C for inoculation of the bacterial strains using a platinum wire loop.

Sterilized forceps were used for application of the paper disc on the previously inoculated agar plates. After the discs were applied, the plates were incubated at 37°C for 24 h. The zone of inhibition around the disc was then measured (in mm).

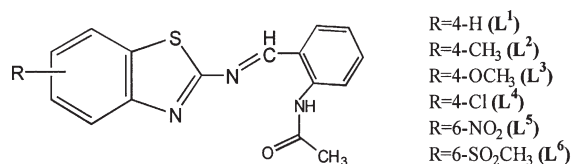


FIGURE 1 Structure of the Schiff bases.

RESULTS AND DISCUSSION

Chemistry

The Schiff bases (L^1-L^6) (Figure 1) were prepared by refluxing an appropriate amount of 2-acetamidobenzaldehyde with 2-aminobenzothiazole and its substituted 4-methyl, 4-methoxy-, 4-chloro-, 6-nitro- and 6-(methylsulfonyl) derivatives, respectively, in hot ethanol in a 1:1 molar ratio. The structures of these Schiff bases were established utilizing their IR, NMR, and microanalytical data and have been reported³¹ earlier.

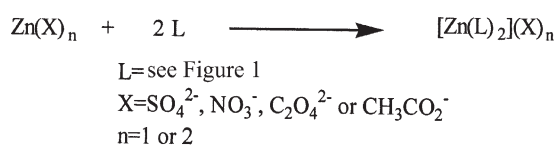
The Schiff bases (L^1-L^6) were used for the complexation reaction with Zn(II) salts containing different anions such as sulfate, nitrate, acetate and oxalate. All of the newly synthesized metal complexes were air and moisture stable and were prepared (Table I) by the stoichiometric reaction of the corresponding Zn(II) salt and the corresponding Schiff base in molar ratios M: L of 1: 2 (Scheme 1).

The complexes are amorphous solids, which decompose above 200°C. They are insoluble in common organic solvents such as ethanol, methanol, chloroform or acetone, but soluble in DMSO and DMF. Molar conductance values of the soluble complexes in DMF showed values (98–112 ohm⁻¹ cm² mol⁻¹) indicating³² that they were electrolytes.

IR spectra of the Schiff bases showed the absence of bands at 1730 and 3425 cm⁻¹ due to carbonyl $\nu(C=O)$ and $\nu(NH_2)$ stretching vibrations and, instead, a strong new band appeared at ~ 1635 cm⁻¹ assigned³³ to the azomethine $\nu(HC=N)$ linkage. This suggested that the amino and aldehyde moieties of the starting reagents no longer existed and had been converted into their corresponding Schiff bases (Figure 1). The IR spectra of the Zn(II) chelates (Table II) indicated that the Schiff bases were coordinated to the metal atom in three ways, thus representing the ligands acting in a tridentate manner. The band appearing at 1635 cm⁻¹ due to the azomethine was shifted to lower frequency by ~ 10 –15 cm⁻¹ indicating³⁴ participation of the azomethine nitrogen in the complexation. The band at 1615 cm⁻¹ assigned to the benzothiazole ring $\nu(C=N)$ nitrogen also shifted to lower frequency by ~ 15 –20 cm⁻¹ which was indicative of the involvement of the ring nitrogen of the benzothiazole moiety in chelation. A medium strong band appearing at 3190 cm⁻¹ assigned to $\nu(NH)$ remained unchanged thus providing a clue

TABLE II IR and electronic spectral data of the complexes

	IR (cm ⁻¹) ^a	λ_{max} (cm ⁻¹)
(1)	3190 (s, NH), 1625 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28455 (CT)
(2)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28610 (CT)
(3)	3190 (s, NH), 1625 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28545 (CT)
(4)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28480 (CT)
(5)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28555 (CT)
(6)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28495 (CT)
(7)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28515 (CT)
(8)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28570 (CT)
(9)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28525 (CT)
(10)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28540 (CT)
(11)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28480 (CT)
(12)	3190 (s, NH), 1625 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28455 (CT)
(13)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28610 (CT)
(14)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28545 (CT)
(15)	3190 (s, NH), 1620 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28480 (CT)
(16)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28555 (CT)
(17)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28495 (CT)
(18)	3190 (s, NH), 1625 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M - N), 455 (ms, M - O).	28515 (CT)



SCHEME 1

TABLE II – *continued*

	IR (cm ⁻¹) ^a	λ_{\max} (cm ⁻¹)
(19)	3190 (s, NH), 1620 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28570 (CT)
(20)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28525 (CT)
(21)	3190 (s, NH), 1620 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28540 (CT)
(22)	3190 (s, NH), 1620 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28480 (CT)
(23)	3190 (s, NH), 1625 (s, HC=N), 1600 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28495 (CT)
(24)	3190 (s, NH), 1620 (s, HC=N), 1605 (s, C=N), 1670, 1535 (s, CONH), 530 (ms, M – N), 455 (ms, M – O).	28495 (CT)

^a s = sharp, ms = medium sharp.

that this NH group is not involved in the coordination. However, a band at 1685 cm⁻¹ assigned³³ to the amido group $\nu(-CONH)$ in the Schiff bases was not found at the same frequency and shifted to lower frequency by 10–15 cm⁻¹ indicating, in turn, the coordination of the amido oxygen $\nu(-C=O)$ to the zinc metal. Further conclusive evidence of the coordination of these Schiff bases with the zinc metal atom was shown by the appearance of weak low-frequency new bands at 525 and 455 cm⁻¹ assigned³⁴ to the zinc–nitrogen $\nu(Zn-N)$ and zinc–oxygen $\nu(Zn-O)$ respectively. These new bands were observable only in the spectra of the metal complexes and not in the spectra of its uncomplexed Schiff bases, thus confirming the participation of these hetero groups (O or N) in the complexation.

The nature of the ligand field around the metal ion and the geometry of the metal complex were further deduced from their properties. All Zn(II) complexes were found diamagnetic. Their electronic spectra did not show any d–d bands but were only dominated by charge transfer bands. The charge transfer band at 28, 455–28610 cm⁻¹ was assigned³⁵ to E_g →²T_{2g} indicating³² their possible octahedral environment.

Antibacterial Properties

The title Schiff bases and their Zn(II) chelates were evaluated for antibacterial activity against the strains *E. coli* (a), *S. aureus* (b) and *P. aeruginosa* (c). The evaluation studies of these ligands have been reported elsewhere³⁰ and their Zn(II) chelates in the present studies were tested at a concentration of

30 $\mu\text{g}/\text{mL}$ [which, expressed in molarity is: (1) 38.5 mM, (2) 40.0 mM, (3) 38.8 mM, (4) 38.8 mM, (5) 36.0 mM, (6) 37.3 mM, (7) 37.7 mM, (8) 39.8 mM, (9) 34.7 mM, (10) 36.0 mM, (11) 36.3 mM, (12) 35.0 mM, (13) 42.0 mM, (14) 36.2 mM, (15) 38.6 mM, (16) 37.2 mM, (17) 34.5 mM, (18) 35.7 mM, (19) 36.0 mM, (20) 35.0 mM, (21) 32.7 mM, (22) 33.1 mM, (23) 33.4 mM, (24) 32.3 mM, respectively], in DMF using the paper disc diffusion method.^{36–41} The diameter (mm) of the susceptibility zones were measured and the results are shown in Table III. The susceptibility zones measured were the clear zones around the discs killing the bacteria. The solubilities of the compound in the test media were within the concentration range used in the experiments.

All the Schiff bases and their zinc complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The present studies were carried out to elucidate the role of anions (counter part of the metal ion) on antibacterial activity. The antibacterial results

TABLE III Antibacterial Activity Data for the ligands and complexes investigated here

Schiff Base/Complex/Metal salt	Microbial Species		
	a	b	c
L ¹	++	+++	++
L ²	++	++	+
L ³	+	++	++
L ⁴	++	++	+++
L ⁵	+++	+	++
L ⁶	++	++	++
(1)	++++	++++	++++
(2)	+++	++	+++
(3)	+++	++++	+++
(4)	++	+++	++++
(5)	++++	+++	+++
(6)	+++	+++	+++
(7)	++++	+++	++
(8)	+++	+++	+++
(9)	++++	+++	++
(10)	+++	+++	+++
(11)	+++	++++	+++
(12)	+++	+++	++++
(13)	++++	+++	+++
(14)	+++	+++	+++
(15)	+++	+++	++++
(16)	+++	+++	+++
(17)	+++	++++	++++
(18)	+++	++++	++
(19)	++++	+++	+++
(20)	++	+++	++
(21)	++++	++++	+++
(22)	+++	++++	+++
(23)	+++	++++	+++
(24)	+++	+++	+++
Zn(CH ₃ CO ₂) ₂ ·2H ₂ O	-	+	+
ZnSO ₄ ·H ₂ O	-	+	-
Zn(NO ₃) ₂ ·6H ₂ O	+	-	+
ZnC ₂ O ₄	+	+	+

a = *Escherichia coli*. b = *Staphylococcus aureus*. c = *Pseudomonas aeruginosa*. Inhibition zone diameter mm (% inhibition): +, 6–10 (27–45%); ++, 10–14 (45–64%); +++, 14–18 (64–82%); +++++, 18–22 (82–100%). Percent inhibition values are relative to inhibition zone (22 mm) of the most active compound denoted as 100% inhibition.

reported in Table III, show that when the same Zn(II) metal chelate having different anions e.g., nitrate, sulfate, acetate or oxalate was individually tested for antibacterial activity, the degree of potency varied. Comparing the results of our previous studies³⁰ in which the same Zn(II) chelates as chloride anion were screened for their bactericidal activity against the same tested bacterial species under the same conditions, the activity/potency of the chelated complex having nitrate as anion (in the present studies) was found to be more bactericidal (82–95%) than the complex having an anion other than nitrate. Similarly, the same complex with oxalate anion was observed to be more antibacterial (64–80%) than the complex having acetate (45–64%) or sulfate anions (27–45%). From the obtained data, it was generally observed that the order of potency in comparison to the Zn(II) chelates having chloride anion reported^{30,31} earlier and in the present studies evaluated for anions other than chloride was found to follow: nitrate > oxalate > acetate > chloride > sulfate.

In the light of the above observations, it is evident that anions do affect the antibacterial activity of the chelated complex. It is suggested that the positive charge of the metal ion is partially shared with the donor atoms and there is π -electron delocalization over the whole chelate ring system having counter anions, which effectively influence the solubility mechanism of the complex. This, in turn increases the lipophilic character of the metal chelate and favors its greater permeation through the lipid layer of the bacterial membrane. The obtained data (Table III) shows that chelates having a nitrate anion were more antibacterial because of their greater solubility. Apart from this, other factors such as conductivity and dipole moment of anions also effect the presence of the metal ion that may possibly increase this activity upon chelation. The individual zinc salts, however, in tests under similar conditions using DMF as well as water showed negligible activity (6–10%) against the same test species.

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