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COMPLEXATION AND MUTAGENICITY POTENTIAL STUDIES WITH *N*,*N*′-*bis*(2-HYDROXYNAPHTHALIN-1-CARBALDEHYDENE)-1,2-*bis*-(*P*-AMINOPHENOXY)ETHANE AND A NOVEL OXOVANADIUM(IV) COMPLEX

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A new oxovanadium(IV) complex of the Schiff base obtained by condensation of 1,2-*bis*(*p*-aminophenoxy)ethane with 2-hydroxynaphthalin-1-carbaldehyde was synthesized. The complex was characterized by elemental analysis, magnetic measurements, mass spectral data, UV–visible and IR spectra. Stability constants and thermodynamic values for complexation between $Cu(NO_3)_2$, $Zn(NO_3)_2 \cdot 6H_2O$, $Ni(NO_3)_2 \cdot 6H_2O$ and $VOSO_4 \cdot 5H_2O$ and the ligand in 80% dioxane/water were determined by conductance measurements. Ni(II) and Cu(II) complexes of the ligand synthesized by a previously described method were found to be mutagens on strain TA 100 in the presence and absence of S9 mix. These compounds are classified as mutagenic in the Ames test.

Keywords: Schiff-base complexes; Complexation studies; Mutagenic and Ames test; Oxovanadium(IV)

INTRODUCTION

In recent years the complexes of oxovanadium(IV) have received considerable attention. Oxovanadium(IV) chelating complexes containing tetradentate Schiff-base ligands derived from 1,2-diamines have been the subject of several recent reports [1]. These square-pyramidal complexes exhibit a strong tendency to remain five-coordinate in both donor and non-donor solvents [2].

The *Salmonella*/Microsome mutagenicity test has been used to determine the mutagenicity of complex environmental and biological mixtures. Many of the mutagenic components of these mixtures have also been characterized chemically. A considerable number of mutagens first detected by the Salmonella test have subsequently been shown

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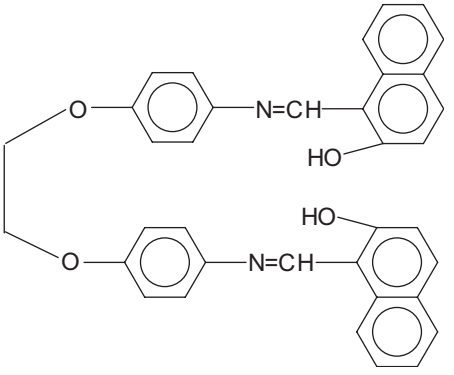

N,*N*′-*bis*(2-hydroxynaphthaline-1-carbaldehydene)-1,2-bis-(*p*-aminophenoxy)ethane (ligand).

to be carcinogenic [3]. Although some chemical carcinogens are non-genotoxic in conventional assays, DNA damage is considered as the initiating event by which a molecule causes hereditary effects and cancer [4]. Thus, the evaluation of the genotoxic potential of newly synthesized molecules constitutes one of the most important preliminary steps for safety assessment and regulatory control of chemicals. This evaluation is carried out mainly through *in vitro* assays [5]. The *in vitro* assessment of the genotoxic potential of a chemical is a multiple-step process requiring a 'funnel-shaped' screening strategy based on a battery of tests [6] from bacteria to mammals to assess point mutation as well as chromosomal damage. Upstream of such a strategy are the tests based on bacterial systems that allow a rapid (due to the growth rate of bacteria) and relatively straightforward method (due to biochemical selection of the mutants) of assessing mutagenic potential. The bacterial reverse mutagenicity test on *Salmonella typhimurium* strains developed in 1975 by Bruce Ames [7] (also called the Ames test) is one of the tests required by regulatory authorities and is usually used as an initial screen. A set of histidine-requiring strains is used for mutagenicity testing. Each test strain contains a different type of mutation in the histidine operon. In addition to the histidine mutation, test strains contain other mutations that greatly increase their ability to detect mutagens [3]. This test is designed for the detection of the mutagenicity potential of substances through the induction of reverse mutation in the histidine gene of modified *S. typhimurium* strains [8].

In the present paper, a VO(IV) complex of the Schiff base derived from 2-hydroxynaphthalin-1-carbaldehyde and 1,2-bis-(*p*-aminophenoxy)ethane is reported. Based on the physical and chemical data of this complex and adducts, schematic structures are proposed. To the best of our knowledge, this is the first report of this complex. Furthermore, we report the stability constants and thermodynamic values for complexation of Cu(II), Zn(II), Ni(II) and VO(IV) with ligands containing nitrogen and oxygen donor atoms in a 80% dioxane/water solvent.

EXPERIMENTAL

Material

N,*N*′-*bis*(2-hydroxynaphthalin-1-carbaldehydene)-1,2-bis-(*p*-aminophenoxy)ethane and its Ni(II) and Cu(II) complexes were synthesized by the method described in the

literature [1]. Media and buffer for the Ames test were prepared as described previously [3], with chemicals from Difco or Merck. The positive controls used were 2-aminoflourene (2-Af) and daunomycin (for the TA 98 strain), sodium azide (for the TA 100 strain), and DMSO was used as solvent (all from Sigma). All experiments in the presence of S9 mix were conducted in parallel on the same day with all strains.

Reagent and Measurements

The electronic spectra of the complexes in the UV–Vis region were recorded in DMF solutions using a Shimatzu Model 160 UV–Vis spectrophotometer. The IR spectra of the complex were recorded in KBr pellets with a Midac 1700 instrument. Magnetic susceptibilities were determined on a Sherwood Scientific magnetic susceptibility balance (Model N0: MK1) at room temperature (23°C) using $Hg[Co(SCN)_2]$ as the calibrant [8]. Elemental analyses were conducted on a Carlo Erba instrument. Mass spectra were measured on Micromass Zapspec.

Synthesis of the VO(IV)L Complex

The salt $VOSO_4 \cdot 5H_2O$ (20.00 mmol) was dissolved in hot methanol (50 ml), and a mixture of NEt_3 (40 mmol) and the ligand (20.00 mmol; 11.04 g) in DMF (50 ml) was added and stirred for a period of 10 min. The mixture was kept hot (60–64°C) and stirred for 2–3 h. The solid complexes that separated out after 24 h were filtered and washed with diethyl ether, hot water and ethanol. The resulting solid was recrystallized in 25 ml DMSO/25 ml DMF and dried over anhydrous $CaCl_2$ *in vacuo* at room temperature. The yield was 70%. The complex decomposes at 275–278°C and is almost insoluble in water but partially soluble in polar solvents (DMSO and DMF). MS: (m/z) 552 (58%, M^+), 551 (33%, M − 1), 262 (56%), 155 (100%), 106 (36%).

Conductometry

High purity $Cu(NO_3)_2$, $Zn(NO_3)_2 \cdot 6H_2O$, $Ni(NO_3)_2 \cdot 6H_2O$ (Fluka; 99%) and $VOSO_4 \cdot 5H_2O$ (Fluka; 96%) were used without further purification. The water used in the conductometric studies was redistilled from alkaline potassium permanganate; the conductivity was less than $6 \times 10^{-7}\,S\,cm^{-1}$.

Conductances were measured at 25 ± 0.05°C using a glass vessel (Ingold type) with an external jacket connected to a thermostated water bath (25 ± 0.05°C) and a conductivity cell (Cole-Parmer 19050-66) with a cell constant of $0.3162\,cm^{-1}$. The conductivity was measured with a Suntex conductometer, Model Sc-170.

The solutions were prepared at a constant 1 : 1 ratio of metal–salt to ligand (L) in a 80% dioxane/water mixture. All solutions were prepared in a dry box and transferred to the dried conductivity cell. The atmosphere was replaced by nitrogen gas. After the cell was thermally equilibrated in a water bath, the resistance of the solution was measured. $\log K_e$ values for the reaction of the ligand with the cations were determined by a conductometric procedure outlined previously [9]. Results are reported as the average, and standard deviation from the average, of four to six independent experimental determinations.

S. Typhimurium Strain

Strains TA 98 and TA 100, as recommended by the Organisation for Economic Co-operation and Development (OECO) guidelines, were used in this study. The strains were purchased from the laboratory of Dr Bruce Ames (University of California, Berkeley, CA, USA), and their genetic backgrounds [10,11] were controlled every 6 months as described previously [2].

Ames Test: Treatment and Plating

The Ames test was performed according to the OECD guidelines [12]. Two different treatments were used: without metabolic activation (−S9 mix) and with metabolic activation (+S9 mix). S9 mix is mammalian liver tissue that is used in the Ames test to provide a first approximation to mammalian metabolism. S9 mix, used routinely for general mutagenesis screening, was prepared according to Maron and Ames [3].

The direct plating test protocol (2) was used. The bacterial strains were exposed to a range of concentrations of the test compounds in the absence or presence of S9 mix in a soft agar overlay. Briefly, for each Petri plate, 100 µl of a 13-h culture of the strains were mixed in 2 ml of top agar with the 100 µl of test compound formulation and, for the activated tests, with 500 µl of S9 mix in the following order: test compound, top agar, bacteria, S9 mix (activated assay only). The tubes were swirled and poured onto 90-mm Petri plates. The culture plates were incubated at 37°C for 48–72 h.

Scoring and Positive Criteria

The revertants obtained at each concentration and treatments were scored manually in the Ames test. The acute observation, under a magnifying glass, of the bacterial lawn in each culture dish was used to check for possible toxicity of the treatment.

RESULTS AND DISCUSSION

The analytical data for the ligand and its complex are listed in Table I. The ligand, on interaction with $VOSO_4 \cdot 5H_2O$, yields VO(IV)L. The analytical data for this complex are presented in Tables I and II. The metal to ligand ratio of the VO(IV)L complex was found to be 1 : 1. Its structure is presumably based on the square pyramid [1] (Fig. 1).

TABLE I The colours, formulas, formula weights, yields, melting points and elemental analyses of the ligand and its complex

Compound	*FW* ($g\,mol^{-1}$)	*Mp* (°C)	*Yield* (%)	*Elemental analyses %* *Calculated* (*found*)			Λ_M ($\Omega^{-1}cm^{-2}mol^{-1}$)	μ_{eff} (BM)
				C	*H*	*N*		
Ligand (H_2L) (yellow) $C_{36}H_{28}N_2O_4$	552.00	240.0	82.0	78.26 (78.08)	5.07 (5.16)	5.07 (5.13)	–	–
VO(IV)L (brown) $C_{36}H_{26}N_2O_5V$	616.90	275.0–278.0	70.0	70.03 (69.76)	4.19 (4.25)	4.52 (4.30)	5.0	1.74

TABLE II Some IR frequencies (in cm^{-1}) of the Schiff base and its complex

Ligand	*[VO(IV)L]*	*Assignment*
2887 m	–	Intramolecular H-bonded –OH
1616 s	1620s	central C=N stretching
1285 m	1291s	phenolic C–O stretching
–	968w	V=O stretching
–	504w	ν(M–N)
	450w	ν(M–O)

s, strong; m, medium; w, weak.

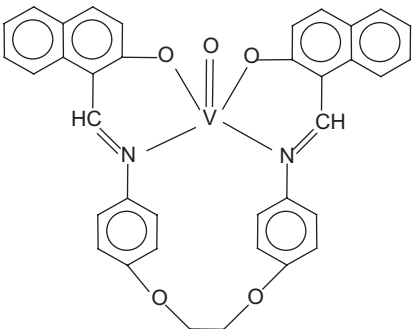

FIGURE 1 Suggested structure of the square pyramidal VO(IV)L {[*N*,*N*′-*bis*(2-hydroxynaphthalin-1-carbaldehydene)-1,2-*bis*-(*p*-aminophenoxy)ethane]oxovanadium(IV)} complex of the ligand.

Important IR bands of the Schiff-base ligand and its complex are given in Table II. The broad band of the Schiff base at 2887 cm^{-1} is assigned to the stretch of the intramolecular hydrogen-bonded –OH group. Similar bands were observed at the same frequency in the IR spectra of salicylideneanilines [1,13–19]. This band disappeared in the IR spectrum of the complex. The band at 1285 cm^{-1} is ascribed to the phenolic C–O stretching vibration [1]. This band is found at 1291 cm^{-1} in the IR spectrum of the complex. This shift suggests that the *o*-OH group of the Schiff-base moiety has taken part in complex formation. Coordination through the imine nitrogen is inferred from the shift in the absorbance at 1616 cm^{-1} for the ligand to 1620 cm^{-1} for the complex [1,14–19]. Conclusive evidence of the bonding is also shown by the observation that new bands in the spectrum of the metal complex appear at 450 cm^{-1} and 504 cm^{-1} assigned to M–O and M–N stretching vibrations, respectively, and these are not observed in the spectra of the ligand [1,14–19]. The ν(V=O) band appears in the expected range [2] at 968 cm^{-1}.

The electronic spectrum of the complex was recorded in 10^{-3} M DMF at room temperature. The spectra of the two free Schiff bases exhibit two absorption bands in the regions 250–270 nm ($\varepsilon = 2600\,l\,mol^{-1}\,cm^{-1}$) and 310–320 nm ($\varepsilon = 550\,l\,mol^{-1}\,cm^{-1}$). These bands are attributed to $\pi \rightarrow \pi^*$ transitions, the first with the benzene ring and the second with the imino group. In the complex, the imino $\pi \rightarrow \pi^*$ transition is shifted to longer wavelength as a consequence of coordination when binding with the metal, confirming the formation of a Schiff-base metal complex [7,2–6,14–19].

CALCULATIONS

When the Schiff-base ligand (L) forms a 1:1 complex with the metal ion (M^{m+}), the equilibrium equation is written as [1]:

$$\begin{array}{ccccc} M^{m+} & + & L & \rightleftharpoons & ML^{m+} \\ \alpha[M]_t & & [L]_t - (1-\alpha)[M]_t & & (1-\alpha)[M]_t \end{array} \quad (1)$$

where M^{m+}, L, $[M]_t$, $[L]_t$ and α are the cation, ligand compound, total concentration of the metal salt and the Schiff-base ligand, and fraction of free cations, respectively. Thus, the complex formation constant (K_{ML}) is defined by

$$\begin{aligned} K_{ML} &= [ML^{m+}]/[M^{m+}][L] \\ &= 1-\alpha/\alpha[L] \end{aligned} \quad (2)$$

The apparent conductivity (κ_{app}) of the metal nitrate (M_nA_m) solution in the presence of ligand L is given by

$$\kappa_{app} = \kappa_{MnAm} + \kappa_{MnLAm} \quad (3)$$

where A^{n-} denotes an anion, κ_{MnAm} and κ_{MnLAm} refer to conductivities of the electrolyte and the ligand compound–electrolyte complex, respectively. The molar conductivities are

$$\begin{aligned} \Lambda_{MnAm} &= \kappa_{MnAm}/[M^{m+}] \\ &= \kappa_{MnAm}/\alpha[M]_t \end{aligned} \quad (4)$$

and

$$\begin{aligned} \Lambda_{MnLAm} &= \kappa_{MnLAm}/[ML^{m+}] \\ &= \kappa_{MnLAm}/(1-\alpha)[M]_t \end{aligned} \quad (5)$$

where Λ_{MnAm} and Λ_{MnLAm} designate molar conductivities of the electrolyte and the ligand compound–electrolyte complex, respectively. The apparent molar conductivity of the metal salt, is defined as

$$\begin{aligned} \Lambda_{app} &= \kappa_{app}/[M]_t \\ &= \alpha\Lambda_{MnAm} + (1-\alpha)\Lambda_{MnLAm} \end{aligned} \quad (6)$$

Hence Eq. (2) can be transformed into

$$K_e = (\Lambda_{MnAm} - \Lambda_{app})/(\Lambda_{app} - \Lambda_{MnLAm})[L]$$

where $[L] = [L]_t - [M]_t(\Lambda_{MnAm} - \Lambda_{app})/(\Lambda_{MnAm} - \Lambda_{MnLAm})$

Furthermore, the differences in complexing ability between the Schiff base and metal ion are discussed based on the thermodynamic equation:

$$\Delta G_c^o = -2.303RT \log K_e$$

where ΔG_c^o is the Gibbs free energy of complexation in 80% dioxane/water.

Complexation in 80% Dioxane/Water Mixture

In this study, we used 80% dioxane/water mixture as a solvent because of the very low dielectric constant. A high dielectric constant gives rise to ion pair aggregation which can affect ion pair solvation in an unfavourable way. Dioxane could take part among the water molecules although such an inclusion breaks the intramolecular hydrogen bonds which mainly compute with the dipolar power of the Schiff-base ligand to bind the cation in the mixture. This solvent seems to be a suitable medium with respect to alcohols to observe the main effect.

Dielectric saturation makes the effective dielectric constant much smaller than the macroscopic one; therefore, external solvation of a contact ion pair is more effective in polar solvents. On coordination with the Schiff-base ligand some solvent should be removed and this process requires more energy for methanol than for dioxane. The experimental molar conductance equations and all the calculations for the stability constants have been published in our previous work [20,21]. All experimental studies have been made using a 1:1 ratio of the metal ion and Schiff-base ligand. The stability constants of Cu(II), Zn(II), Ni(II) and VO(IV) complexes with the synthesized Schiff-base ligand are shown in Table III. The κ_{app} *versus* $[M^{m+}]$ plots in Figures 2–5 show a decrease in κ_{app} with an increase in M^{m+} concentration except for the VO(IV) and Zn(II) systems. This indicates that complexation occurs between the Schiff-base ligand and Cu(II) and Ni(II) metal ions, and that these complexes are less mobile than free Cu(II) and Ni(II) metal ions. The κ_{app} *versus* $[M^{m+}]$ plots of the VO(IV)L and Zn(II)L systems show an increase in κ_{app} as the M^{m+} concentration increases. This indicates that the Schiff-base ligand forms a complex with VO(IV) and Zn(II), and that the Schiff-base ligand VO(IV) and Zn(II) complexes are more mobile than the VO(IV) and Zn(II) ions; consequently, using 80% dioxane/water, the conductometric determinations of the complex formation constants for VO(IV)L and Zn(II)L systems were impossible [18].

The largest complex formation constant was found for Cu(II) (Figures 2–5). The significantly larger stability constant of the Cu(II) complexes in comparison to the other ion complexes may be explained by assuming a partial participation of the nitrogen and oxygen atoms of the ligand in the binding of the central Cu(II) cation, which possesses a higher electron-acceptor power. This assumption is also supported by the direction of the Gibbs free enthalpy changes. In the metal series from Zn(II),

TABLE III $\log K_e$ and $-\Delta G_c^o$ values for the interaction of ligand with $Cu(NO_3)_2$, $Zn(NO_3)_2 \cdot 6H_2O$, $Ni(NO_3) \cdot 6H_2O$ and $VOSO_4 \cdot 5H_2O$ in 80% dioxane/water at 25°C by a conductometric study

Value	*Cu(II)*	*Zn(II)*	*Ni(II)*	*VO(IV)*
$\log K_e$	4.59 ± 0.18	–	3.46 ± 0.07	–
$-\Delta G_c^o$	6264.27 ± 0.08	–	4718.28 ± 0.04	–

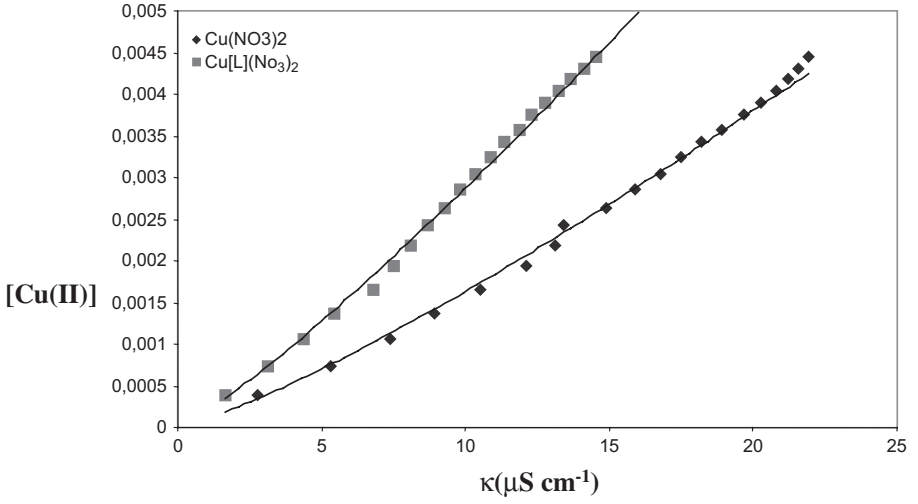

FIGURE 2 Plot of [Cu(II)] ($mol\,l^{-1}$) *vs.* observed conductivity, $\kappa\,(\mu S\,cm^{-1})$, of $Cu(NO_3)_2$ with L in 80% dioxane/water mixtures at 25°C.

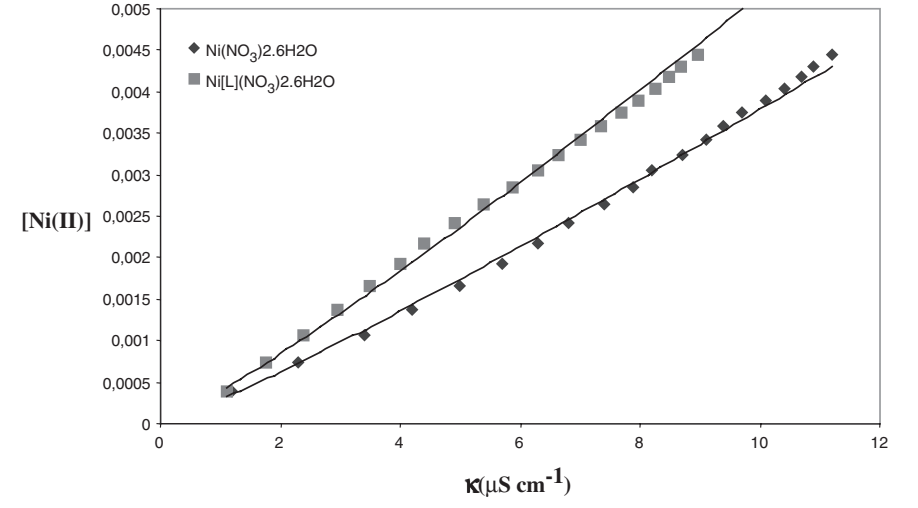

FIGURE 3 Plot of [Ni(II)] ($mol\,l^{-1}$) *vs.* observed conductivity, $\kappa\,(\mu S\,cm^{-1})$, of $Ni(NO_3)_2 \cdot 6H_2O$ with L in 80% dioxane/water mixtures at 25°C.

VO(IV) and Ni(II) to Cu(II), the free enthalpy changes become more negative, and this indicates the greatest coordination of the metal ion during complex formation with the Schiff-base ligand (Table III).

Mutagenicity Potential Studies

As indicated in Table IV, the ligand, its Ni(II) complex and its Cu(II) complex are mutagenic on strain TA 98 in the presence and absence of S9 mix. In *S. typhimurium* TA 100, the ligand was found to be weakly mutagenic in the absence of S9 mix but

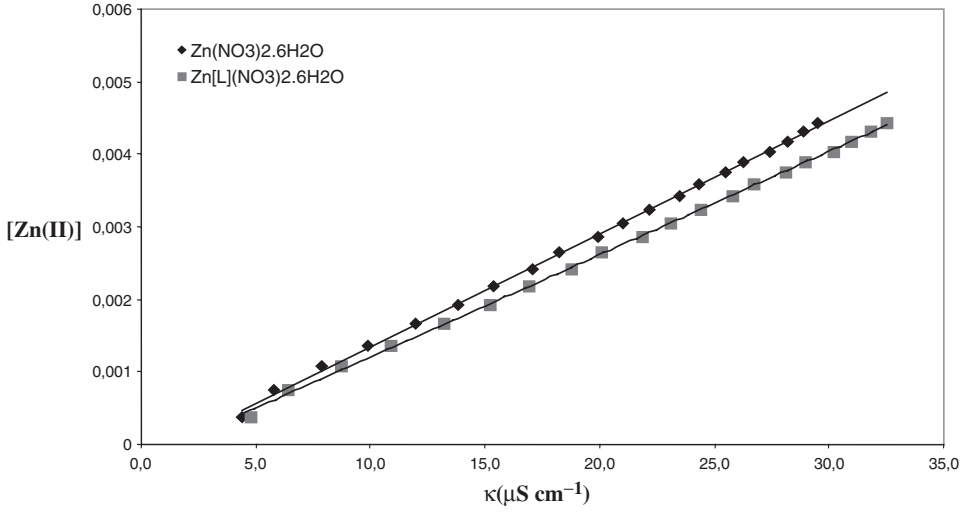

FIGURE 4 Plot of [Zn(II)] (mol l^{-1}) *vs*. observed conductivity, κ ($\mu S\,cm^{-1}$), of $Zn(NO_3)_2 \cdot 6H_2O$ with L in 80% dioxane/water mixtures at 25°C.

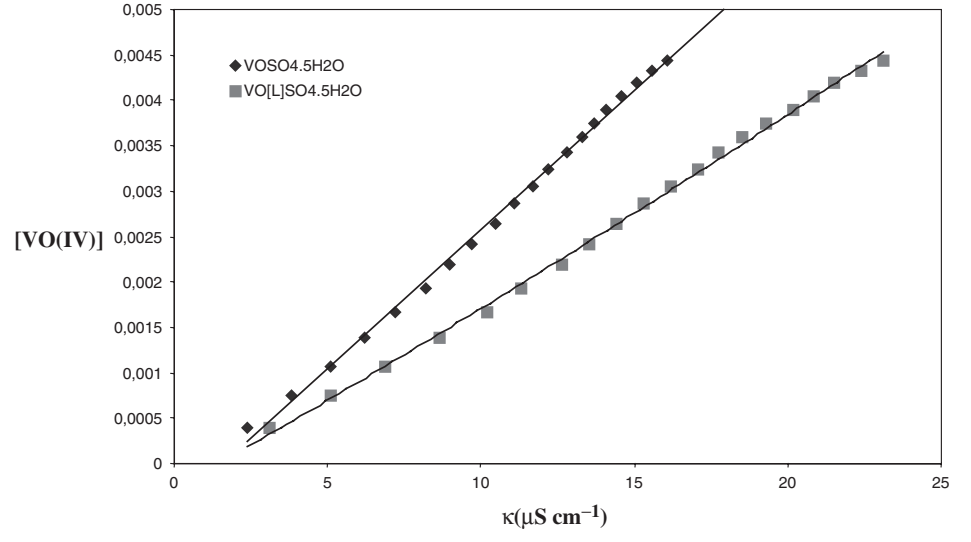

FIGURE 5 Plot of [VO(IV)] (mol l^{-1}) *vs* observed conductivity, κ ($\mu S\,cm^{-1}$), of $VOSO_4 \cdot 5H_2O$ with L in 80% dioxane/water mixtures at 25°C.

mutagenic in the presence of S9 mix. Its Ni(II) and Cu(II) complexes were found as mutagens on strain TA 100 in the presence and absence of S9 mix.

TA 100 detects mutagens that cause base-pair substitutions. TA 98 detects various frameshift mutagens, which can stabilize the shifted pairing that often occurs in repetitive sequences or 'hot spots' of DNA [3]. Millers, Boyland, Magee and other workers made major contributions to the understanding that many mutagens and carcinogens must be converted by enzymes in the liver or other tissues to an active (electrophilic) form that is the true mutagen and carcinogen. For this reason, mammalian liver tissue is added to the test to provide a first approximation to mammalian metabolism [22].

TABLE IV Historical values obtained from each *Salmonella* strain in the Ames test

Compound ($\mu g\,l^{-1}$)		*Tester strains*			
		TA 98		*TA 100*	
		$-S9$ ($\bar{X} \pm SD$)	$+S9$ ($\bar{X} \pm SD$)	$-S9$ ($\bar{X} \pm SD$)	$+S9$ ($\bar{X} \pm SD$)
Control		40 ± 12	50 ± 20	172 ± 74	208 ± 68
Daunomycin		1054 ± 360			
Sodium azide				897 ± 262	
Ligand	8	377 ± 151	1192 ± 272	260 ± 87	496 ± 128
	16	528 ± 161	1065 ± 288	318 ± 112	506 ± 157
	24	711 ± 215	1028 ± 291	214 ± 94	504 ± 171
	33	515 ± 185	1184 ± 289	170 ± 81	492 ± 130
Ni(II)	5	521 ± 241	1197 ± 321	427 ± 142	538 ± 165
	10	464 ± 184	1146 ± 286	355 ± 102	515 ± 174
	15	368 ± 149	1127 ± 320	304 ± 78	508 ± 108
	20	549 ± 186	1166 ± 316	677 ± 121	518 ± 139
Cu(II)	8	340 ± 145	1127 ± 386	288 ± 72	496 ± 188
	16	437 ± 158	1145 ± 391	234 ± 68	506 ± 170
	24	343 ± 171	1133 ± 364	274 ± 81	526 ± 181
	33	256 ± 96	1174 ± 308	262 ± 74	520 ± 217

$\bar{X}$, mean; SD, standard deviation.

The results obtained in the Salmonella assay (Ames test) in the presence of S9 mix indicate that all substances tested induce a frameshift mutation (TA 98) and base-pair substitution mutations (TA 100) through their different metabolites, which can cause different types of DNA adducts. Mutations induced by genotoxic agents are consequences of DNA damage. Lesions caused by genotoxic agents belong to two classes. Miscoding lesions directly modify the pairing properties of a base. Many other lesions destroy coding altogether, including most DNA adducts, apurinic and aprimidinic sites, strand breaks, cross-links and gaps. In the Salmonella assay, each strain presents a certain specificity with respect to the type of mutagen to which it responds and also provides some information on the mode of action of the compound tested [23]. Despite their relatively recent appearance, bacterial tests provide important information in the search for, and study of, genotoxic agents. The assembly of tests into batteries will, in particular, provide information on the type of lesion produced, the mutagenic specificity and the metabolism of these compounds. These compounds could be classified as mutagenic according to the Ames test. Vanadium is not clastogenic and only weakly mutagenic. No data exist to indicate that vanadium is carcinogenic in animals or man [24].

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