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Synthesis, chemical structures elucidation and biological studies on the effect of some vital metal ions on vitamin A: Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) complexes

M. Zaky [1], M. Y. El-Sayed [1,2], S. M. El-Megharbel [1,3], S. A. Taleb [1], M.S. Refat [3,4]

[1] *Department of Chemistry, Faculty of Science, Zagazig University, Egypt*
[2] *Faculty of Applied Medical Science, Al Jouf University-Al Qurayate*
[3]*Department of Chemistry, Faculty of Science, Taif University, 888 Taif, Kingdom Saudi Arabia*
[4] *Department of Chemistry, Faculty of Science, Port Said, Port Said University, Egypt*

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Complexes of vitamin A as a pharmaceutical ligand with Ca(II), Mg(II), Zn(II), Fe(III) and VO(II), were synthesized and characterized by microanalysis, conductance, infrared and thermogravimetric (TG/DTG and DTA) measurements. The ligand can be coordinated as a monodentate ligand *via* the oxygen atom of the deprotonated hydroxyl group. Thermal degradation curves revealed that the uncoordinated water molecules are removed in a first stage while the decomposition of ligand besides coordinated water molecules took place in the second and subsequent steps. Vitamin A ligand, as well as its complexes were checked against some kinds of bacteria and fungi and produced a significant effect. The effect of kinetic thermodynamic parameters (E*, ΔH*, ΔS* and ΔG*) of the synthesized complexes upon the TG curves was calculated using Coats-Redfern and Horowitz-Metzger equations.

Keywords: Vitamin A complexes, Infrared spectra, Electronic spectra, Thermal analysis, Antimicrobial activity.

INTRODUCTION

Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to diseases. Well-known examples include pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to recognize, to understand at the molecular level, and to treat diseases caused by inadequate metal ion functions constitutes an important aspect of medicinal bioinorganic chemistry [1-5].

Metals and metal complexes have played a key role in the development of modern chemotherapy [6]. For example, anticancer platinum drugs appear in more chemotherapy regimes than any other class of anticancer agents and have substantially contributed to the success achieved in treating cancer over the past three decades. Metals can play an important role in modifying the pharmacological properties of known drugs coordinated to a metal. This is because the resulting pro-drugs have different physical and pharmacological properties, allowing the drug to be released in a controlled fashion or at specific location [7]. This approach may lead to the rescue of drugs that have failed because of poor pharmacology or high toxicity. Complexation of non-steroidal anti-inflammatory drugs to copper overcomes some of the gastric side effects of these drugs [8]. The release of cytotoxins such as nitrogen mustards from redox-active metals such as cobalt in the hypoxic regions of solid tumors has the potential to improve drug activity and reduce toxicity [9]. The metal-based drugs are also being used for the treatment of a variety of ailments, *viz.* diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases, as well as for diagnostics [10-12]. A number of drugs and potential pharmaceutical agents also contain metal-binding or metal-recognition sites, which can bind or interact with metal ions and potentially influence their bioactivities and might also cause damages on their target biomolecules. Numerous examples of these ‘‘metallodrugs’’ and ‘‘metallopharmaceuticals’’ and their actions can be found in the literature, for instance: (a) several anti-inflammatory drugs, such as aspirin and its metabolite salicylglycine [13-16], suprofen [17], and paracetamol [18] are known to bind metal ions and affect their antioxidant and anti-inflammatory activities; (b) the potent histamine-H2-receptor antagonist cimetidine [19] can form complexes with Cu^{2+} and Fe^{3+}, and the histidine blocker antiulcer drug famotidine can also form a stable complex with Cu^{2+} [20,21]; (c) the anthelmintic and fungistatic agent thiabendazole, which is used for the treatment of several parasitic diseases, forms a

* To whom all correspondence should be sent:
E-mail: msrefat@yahoo.com

Co^{2+} complex of 1:2 metal-to-drug ratio [22]; (d) the Ru^{2+} complex of the anti-malaria agent chloroquine exhibits activity two to five times higher than that of the parent drug against drug-resistant strains of *Plasmodium faciparum* [23]. However, it is known that some drugs act *via* chelation or by inhibiting metalloenzymes but most of the drugs act as potential ligands. A lot of studies are being carried out to ascertain how metal binding influences the activities of the drugs [24]. Metal complexes are gaining increasing importance in the design of drugs on coordination with a metal. Metal–organic frameworks are a burgeoning field in the last two decades, which not only stems from their tremendous potential applications in areas such as catalysis, molecular adsorption, magnetism, nonlinear optics, and molecular sensing, but also from their novel topologies and intriguing structural diversities [25-28]. On the other hand, many organic drugs, which possess modified pharmacological and toxicological properties, administered in the form of metallic complexes [29], have the potential to act as ligands and the resulting metal–drug complexes are particularly important both in coordination chemistry and biochemistry [30-34]. However, the study of metal–drug complexes is still in its early stages, thus representing a great challenge in current synthetic chemistry and coordination chemistry.

Vitamin A (Fig. 1) is an essential nutrient for humans because it cannot be synthesized *de novo* within the body. The term "vitamin A" is used generically for all derivatives (other than carotenoids) that have the biological activity of all-trans retinol. Forms of vitamin A include retinol, retinal (also called retinaldehyde), and various retinyl esters [35]. Retinoic acid can perform some but not all of the biological functions of vitamin A.

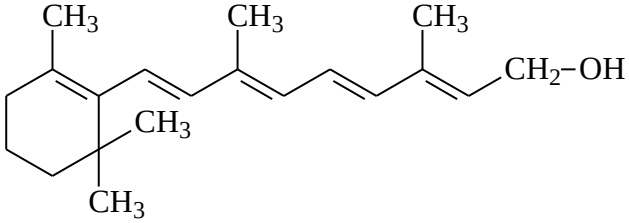

Fig. 1. Structure of vitamin A (Vit. A)

Vitamin A deficiency is a major nutritional disorder in many developing countries. It especially affects young children, in whom it can cause xerophthalmia and lead to blindness, and can also limit growth, weaken innate and acquired host defenses, exacerbate infection and increase the risk of death [36]. Researchers have succeeded in creating water-soluble forms of vitamin A, which they believed could reduce the potential for toxicity; however a study in 2003 found water-soluble vitamin A approximately 10 times as toxic as the fat-soluble vitamin [37]. Because vitamin A is fat soluble and can be stored primarily in the liver, routine consumption of large amounts of vitamin A over a period of time can result in toxic symptoms, including liver damage, bone abnormalities and joint pain, alopecia, headaches and vomiting, and skin desquamation. Hypervitaminosis A appears to be due to abnormal transport and distribution of vitamin A and retinoids caused by overloading of the plasma transport mechanisms [38]. Recently the interest in the trend of metal drug complexes has increased in order to achieve an enhanced therapeutic effect in combination with decreased toxicity. To the best of our knowledge, little attention has been paid to discuss the interaction between vitamin A and metal ions and the literature is still poor in such spectroscopic characterizations. The interpretations are based on the ability of the cited drug to form complex associations with vital metal ions like Ca(II), Mg(II), Zn(II), Fe(III) and VO(II). The spectral characteristics and the stability of the formed complex associates were also included.

MATERIALS AND METHODS

Materials

All chemicals used in this investigation were of highest purity grade (Merck). Selected metal salts like $CaCl_2$, $MgCl_2.6H_2O$, $ZnSO_4.H_2O$, $Fe(NO_3)_3.9H_2O$ and $VOSO_4.H_2O$ were used. Vitamin A was received from the Egyptian International Pharmaceutical Industrial Company (EIPICO.).

Preparation of solid complexes

The hygroscopic vitamin A complexes with the formulas: $[Ca(Vit.A)(Cl)(NH_3)_2\ (H_2O)_2].13H_2O$ (I), $[Mg(Vit.A)(Cl)(NH_3)_2(H_2O)_2].50H_2O$ (II), $[Zn(Vit.A)(SO_4)(NH_3)_2\ (NH_4)].20H_2O$ (III), $[Fe(Vit.A)(NO_3)_2(NH_3)(H_2O)_2].16H_2O$ (IV) and $[VO(Vit.\ A)(SO_4)(NH_4)].2NH_3.20H_2O$ (V) were prepared, employing a 1:1 (metal : Vit. A) ratio. The complexes were prepared by mixing equal volumes (20 ml) of distilled water solutions of $CaCl_2$ (0.111 g, 1.0 mmol), $MgCl_2.6H_2O$ (0.203 g, 1.0 mmol), $ZnSO_4.H_2O$ (0.180 g, 1.0 mmol), $Fe(NO_3)_3.9H_2O$ (0.404 g, 1.0 mmol) and $VOSO_4.H_2O$ (0.163 g, 1.0 mmol) with a methanol solution of Vit. A (0.286 g, 1.0 mmol). The mixtures were neutralized by titration against 5% alcoholic ammonia solution to adjust the pH at (7.0–9.0), then warmed at about ~ 60 ºC for about 3 h and left overnight to evaporate slowly at

room temperature. The obtained precipitates were filtered off, washed several times with minimum amounts of hot methanol and dried at 60 °C over anhydrous $CaCl_2$.

Preparations of stock solutions

Barium chloride solution

A 10 g of barium chloride dihydrate, $BaCl_2.2H_2O$, was weighed and dissolved in a minimum amount of distilled water. The volume was completed to 100 ml in a measuring flask to give a 10% solution.

Silver nitrate solution

A weight of 0.1701 g of $AgNO_3$ was dissolved in a small amount of distilled water and completed to 100 ml in a dark measuring flask to obtain an approximate 0.01 M solution.

Ammonium hydroxide solution

The stock solution of NH_4OH was prepared by taking 15 ml of concentrated NH_3 (33% v/v) in 35 ml distilled water. The volume was then completed to 100 ml by methanol to give an approximately (5% v/v) solution.

Apparatus and experimental conditions

Carbon, hydrogen and nitrogen content were determined using a Perkin-Elmer CHN Elemental Analyzer model 2400. The metal content was determined gravimetrically by converting the compounds into their corresponding oxides.

The Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) contents were determined gravimetrically by direct ignition of the complexes at 800 °C for 3 h till constant weight. The residues were then weighed in the form of metal oxides. Molar conductivities of freshly prepared 1.0×10^{-3} mol/l DMSO solutions of the complexes were measured using a Jenway 4010 conductivity meter. IR spectra were recorded on a Bruker FTIR spectrophotometer (4000 – 400 cm^{-1}) in KBr pellets. The UV-vis spectra were recorded in DMSO solvent with concentration of (1.0×10^{-3} M) for the free ligands and their complexes using a Jenway 6405 spectrophotometer with 1 cm quartz cell, in the range of 200-600 nm. ^{1}H-NMR spectra of the free ligands and their complexes were recorded on a Varian Gemini 200 MHZ spectrophotometer using DMSO-d_6 as solvent and TMS as internal reference. Thermogravimetric analysis (TGA, DTG and DTA) was carried out in the temperature range from 25 to 800 °C in a steam of nitrogen atmosphere by using a Shimadzu TGA-50 H thermal analyzer. The experimental conditions were: platinum crucible, nitrogen atmosphere with a 30 ml/min flow rate and heating rate of 10 °C/min.

In recent years there has been increasing interest in determining the rate-dependent parameters of solid-state non-isothermal decomposition reactions by analysis of TG curves [39-45]. Most commonly used methods are the differential method of Freeman and Carroll [39], the integral method of Coat and Redfern [40] and the approximation method of Horowitz and Metzger [43]. In the present investigation, the general thermal behavior of the vitamin A complexes in terms of stability ranges, peak temperatures and values of kinetic parameters are discussed. The kinetic parameters were evaluated using the Coats-Redfern equation:

$$\int_0^{\alpha} \frac{d\alpha}{(1-\alpha)^n} = \frac{A}{\varphi}\int_{T_1}^{T_2} \exp(-\frac{E^*}{RT})dt \qquad (1)$$

This equation on integration gives:

$$\ln[-\frac{\ln(1-\alpha)}{T^2}] = -\frac{E^*}{RT} + \ln[\frac{AR}{\varphi E^*}] \qquad (2)$$

A plot of the left-hand side (LHS) against 1/T was drawn. E^* is the energy of activation in J mol^{-1} and is calculated from the slop and A in (s^{-1}) from the intercept value. The entropy of activation ΔS^* in ($JK^{-1}mol^{-1}$) was calculated by using the equation:

$$\Delta S^* = R \ln(Ah/k_B T_s) \qquad (3)$$

where k_B is the Boltzmann constant, h is the Plank's constant and T_s is the DTG peak temperature [44].

The Horowitz-Metzger equation is an illustration of the approximation methods.

$$\log[\{1-(1-\alpha)^{1-n}\}/(1-n)] = E^*\theta/2.303RT_s^2 \quad \text{for } n\neq1 \qquad (4)$$

When n = 1, the LHS of equation 4 would be log[-log (1-α)]. For a first-order kinetic process the Horowitz-Metzger equation may be written in the form:

$$\log[\log(w_\alpha / w_\gamma)] = E^*\theta/2.303RT_s^2 - \log 2.303$$

where $\theta = T - T_s$, $w_\gamma = w_\alpha - w$, w_α = mass loss at completion of the reaction; w = mass loss up to time t. The plot of $\log[\log(w_\alpha / w_\gamma)]$ vs θ was drawn and was found to be linear. From its slope E^* was calculated. The pre-exponential factor, A, was calculated from the equation:

$$E^*/RT_s^2 = A/[\varphi \exp(-E^*/RT_s)]$$

The entropy of activation, ΔS^*, was calculated from equation 3. The enthalpy activation, ΔH^*, and Gibbs free energy, ΔG^*, were calculated from: $\Delta H^* = E^* - RT$ and $\Delta G^* = \Delta H^* - T\Delta S^*$, respectively.

Microbiological investigation

According to Gupta *et al.* 1995 [46], the hole well method was applied. The investigated isolates of bacteria and fungi were seeded in tubes with nutrient broth (NB) and Dox's broth (DB), respectively. The seeded (NB) for bacteria and (DB) for fungi (1 ml) were homogenized in the tubes with 9 ml of melted

(45 °C) nutrient agar (NA) for bacteria and (DA) for fungi. The homogenous suspensions were poured into Petri dishes. Holes (diameter 0.5 cm) were done in the cool medium. After cooling in these holes, about 100 µl of the investigated compounds were applied using a micropipette. After incubation for 24 h in an incubator at 37 °C and 28 °C for bacteria and fungi, respectively, the inhibition zone diameters were measured and expressed in cm. The antimicrobial activities of the investigated compounds were tested against some kinds of bacteria *as Escherichia coli* (Gram –ve) and *Staph albus* (Gram +ve), and some kinds of fungi as *Aspergillus flavus* and *Aspergillus niger*. In the same time with the antimicrobial investigations of the complexes, the pure solvent was also tested. The concentration of each solution was 1.0×10^{-3} mol/L. Commercial DMSO was employed to dissolve the tested samples.

RESULTS AND DISCUSSION

The reactions of vitamin A with the metal ions Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) gave colored solid complexes in moderate to good yields (65–85 %). The physical and analytical data, colors, percentage (carbon, hydrogen and nitrogen) and melting/decomposition temperatures of the compounds are presented in Table (1).

The found and calculated percentages of elemental analysis CHN are in good agreement and prove the suggested molecular formulas of the obtained vitamin A complexes. The complexes have low melting points (lower than 100 °C). The molar conductivities of the compounds in DMSO ranged (7-47) Ω^{-1} cm^2 mol^{-1}, showing that they were of non-electrolytes nature. Vit. A ligand behaves as a monodentate ligand and coordinates to the metal ions through the oxygen of the hydroxyl group upon deprotonation. Isolated Vit. A complexes are in 1:1 molar ratio of (M:Vit. A) where M=Ca(II), Mg(II), Zn(II), Fe(III) and VO(II).

Molar conductivities

Conductivity measurements have frequently been used to predict the structure of metal chelates within the limits of their solubility. They provide a method of testing the degree of ionization of the complexes. The more molecular ions a complex liberates in solution, the higher will be its molar conductivity and *vice versa* [47]. The molar conductivity values for the Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) complexes of vitamin A in DMSO solvent (1.00×10^{-3} M) were found to be in the range (7–47) Ω^{-1} cm^2 mol^{-1} at 25°C, suggesting them to be non-electrolytes [48], as shown in Table (1). Hence, the molar conductance values indicate that no ions are present outside the coordination sphere so the Cl^-, SO_4^{--} and NO_3^- ions may be inside the coordination sphere or absent.

The obtained results were strongly matched with the elemental analysis data where Cl^-, SO_4^{--} and NO_3^- ions are detected in case of Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) complexes after

Table 1. Elemental analysis and physical data of vitamin A complexes

Complex	M wt. g/mole	m.p./ °C	color	% C		% H		% N		% M		Λm (Ω^{-1} cm^2 mol^{-1})
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
[Ca(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].13H_2O ($C_{20}H_{65}O_{16}N_2Cl$ Ca)	664.5	Low melting points < 100	Pale yellow	36.11	35.54	9.78	9.52	4.21	4.01	6.02	5.89	35
[Mg(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].50H_2O ($C_{20}H_{139}O_{53}N_2Cl$ Mg)	1314.5		Pale yellow	18.25	18.56	10.57	10.49	2.13	2.48	1.82	1.77	47
[Zn(Vit. A)$(SO_4)(NH_3)_2(NH_4)$].20H_2O ($C_{20}H_{79}O_{25}N_3S$ Zn)	858.4		Yellow	27.95	27.56	9.20	9.22	4.89	5.07	7.62	7.55	7
[Fe(Vit. A)$(NO_3)_2(NH_3)(H_2O)_2$].16H_2O ($C_{20}H_{68}O_{25}N_3$ Fe)	806		Brown	29.77	30.20	8.43	8.59	5.21	4.82	6.94	6.86	14
[VO(Vit. A)$(SO_4)(NH_4)$].2NH_3.20H_2O ($C_{20}H_{79}O_{25}N_3S$ VO)	860		Dark green	27.90	26.37	9.18	9.05	4.88	5.22	7.79	7.71	11

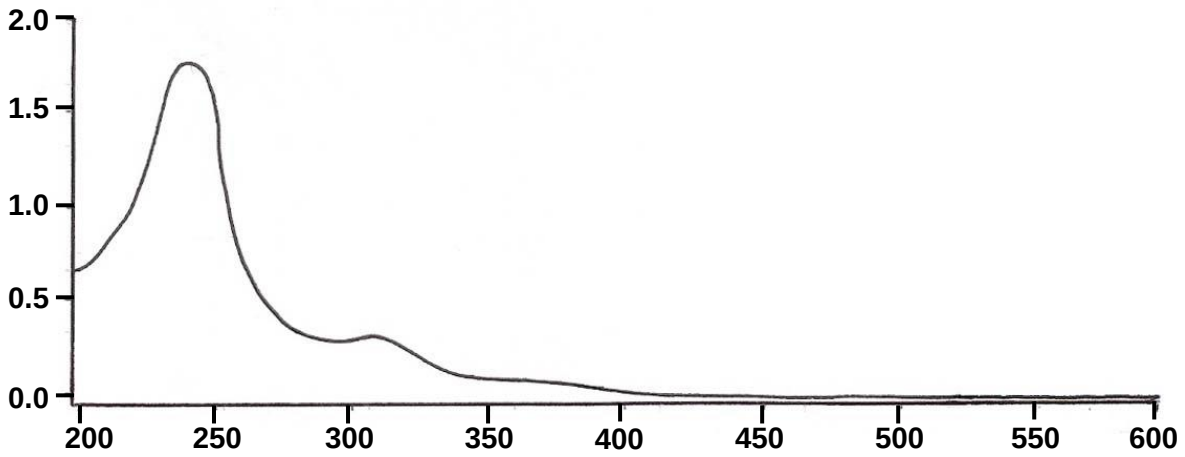

Fig. 2. Uv/vis electronic spectra of the Fe(III)/Vit. A complex.

degradation of these complexes by using nitric acid, and precipitation of Cl^- and SO_4^{--} by addition of $AgNO_3$ and $BaCl_2$ solutions, respectively, to the solutions of the mentioned complexes in nitric acid. NO_3^- ions were also detected using infrared spectral data. The above complexes are hygroscopic, insoluble in water, partially soluble in alcohol and most of organic solvents and soluble in DMSO, DMF and concentrated acids.

Electronic absorption spectra

The formation of the Ca(II), Mg(II), Zn(II), VO(II) and Fe(III) complexes with vitamin A was confirmed by UV-Vis spectra as well. Fig. (2) shows the electronic absorption spectra of the Fe(III) complex in DMSO in the 200–600 nm range.

It can be seen that the free vitamin A has one distinct absorption band at 350 nm which may be attributed to n→π* intra-ligand transition. In the spectra of the Fe(III) complex this band is clearly blue shifted to 312 nm, where the Fe(III) complex shows two bands at 241 and 312 nm assigned to π→π* and n→π* respectively, suggesting that the ligand is deprotonated and the lone pair of electrons on the oxygen atom of the OH group participates in the complexation. The electronic absorption spectrum of the Fe(III) complex in DMSO solution has two bands at 375 and 435 nm and a weak band at 480 nm assigned to the charge transfer transition from metal-to-ligand and a d-d transition band, respectively.

Infrared spectra

The infrared spectra of vitamin A free ligand and its complexes are shown in Fig. (3) and Table (2).

The spectra are similar but there are some differences which could give information on the type of coordination. The IR spectrum of vitamin A shows a very strong broad band at 3406 cm^{-1} which is assigned to ν(O-H) stretching vibration of an alcoholic OH group. Ionization of the alcoholic OH group with subsequent ligation through oxygen atom seems a plausible explanation [49]. It is difficult to distinguish between the ν(OH) of the alcoholic group of vitamin A and the stretching vibrational bands of water molecules of the complexes due to the overlapping values, and their appearance in one place. To ascertain the involvement of ν(OH) of the alcoholic group of vitamin A in the coordination process, the stretching vibration bands of ν(C-O) in all vitamin A complexes were followed. The examination of these complexes showed that the ν(C-O) is shifted to the lower wavenumbers from 1073 and 1176 cm^{-1} in case of free ligand to (1035-1084) cm^{-1} and (1075-1157) cm^{-1} in the complexes. This result indicates that the alcoholic group participates in the complexation [50, 51] and vitamin A acts as a monodentate ligand.

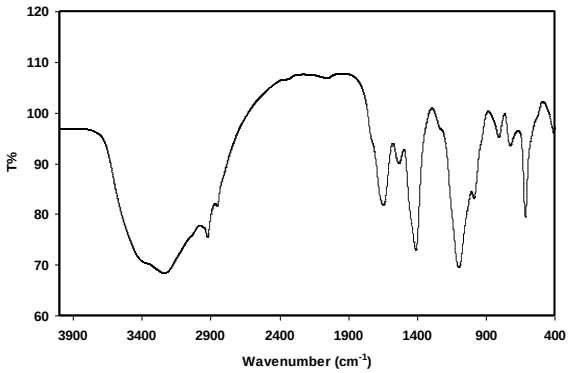

Fig. 3. IR spectrum of the VO(II)/Vit. A complex

Table 2. IR frequencies (cm^{-1}) of vitamin A and its metal complexes

Compound	ν(O-H)	ν(NH); NH_3 and NH_4	δ(NH); NH_3 and NH_4	ν (C-H) aliphatic	ν (C-O)	ν (M-O)	ν (M-N)
Vitamin A	3406	---	---	2955 2929	1176 1073	---	---
$[Ca(Vit.\ A)(Cl)(NH_3)_2(H_2O)_2].13H_2O$	3423	3230	1640	2925 2900	1157 1038	540	490
$[Mg(Vit.\ A)(Cl)(NH_3)_2(H_2O)_2].50H_2O$	3410	3220	1637	2923 2857	1075 1035	613	477
$[Zn(Vit.\ A)(SO_4)(NH_3)_2(NH_4)].20H_2O$	3395	3190	1647	2922 2855	1143 1084	520	488
$[Fe(Vit.\ A)(NO_3)_2(NH_3)(H_2O)_2].16H_2O$	3383	3170	1652	2924 2900	1150 1037	596	505
$[VO(Vit.\ A)(SO_4)(NH_4)].2NH_3.20H_2O$	3410	3160	1649	2926 2857	1101	560	412

The presence of water molecules in the above mentioned complexes is ascertained by the presence of a broad band of strong intensity in the (3383-3423) cm^{-1} region which may be assigned to the OH stretching vibration for the coordinated and uncoordinated water molecules in the vitamin A complexes. The angular deformation motions of the coordinated water can be classified into four types of vibrations: δ_b(bend), δ_r(rock), δ_t(twist) and δ_w(wag). The assignments of these motions in all isolated complexes are as follows, the bending motion, $\delta_b(H_2O)$ at (1637–1652) cm^{-1}, the rocking motion, $\delta_r(H_2O)$ at (750–850) cm^{-1}, the wagging motion, $\delta_w(H_2O)$ at (581–619) cm^{-1}, the twisting motion, $\delta_t(H_2O)$ at (625–690) cm^{-1} [49]. It should be mentioned here that these assignments for both the bond stretches and angular deformation of the coordinated water molecules fall in the frequency regions reported for related aquo-complexes. The vitamin A complexes show new bands in the range of (3160-3230) cm^{-1} which can be assigned to the stretching vibration of ν(N-H) of NH_3 and NH_4 groups; the absence of these bands in the spectrum of the free ligand supports our explanation. Also bending motions of *δ*(NH) were observed in the range of (1637–1652) cm^{-1}. The ν(V=O) stretching vibration in the vanadyl complex is observed as an expected band at 989 cm^{-1}, which is in good agreement with those known for many vanadyl complexes [52]. The coordination of a nitrato anion to the Fe(III) ions was also supported by the IR spectrum of the ferric complex, where the nitrato complex displayed two bands due to $\nu_{as}(NO_2)$ at 1542 cm^{-1} and $\nu_s(NO_2)$ at 1381 cm^{-1} assigned to a monodentate group [53]. It is worth mentioning that the test for the presence of sulfato group in the VO(II) and Zn(II) complexes gave a positive result; this conclusion was supported by the two detected infrared frequency bands at about 1100 and 600 cm^{-1} overlapping with angular deformation motions of the coordinated water molecules. Participation of both oxygen (hydroxyl group) and nitrogen (NH_3 and/or/ NH_4) is also confirmed by the appearance of new bands in the complexes within the (520-613) and (410-505) cm^{-1} regions which may be assigned to the ν(M-O) and ν(M-N) stretching vibrations respectively [54,55].

^{1}H-NMR spectra

The ^{1}H-NMR data of vitamin A and its Fe (III) complex are listed in Table (3) and shown in Fig. (4) as an example. ^{1}H-NMR spectrum of vitamin A shows a signal at δ = (~ 9) ppm, which is assigned to the proton of the alcoholic OH group which disappears in the Mg(II) complex.

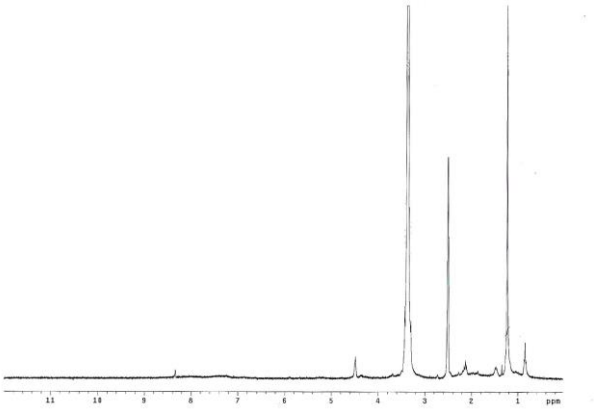

Fig. 4. 1H-NMR spectrum of the Mg(II)/Vit. A complex

The disappearance of the signal of the proton of the hydroxyl group in the ^{1}H-NMR spectrum of the complex confirms that the hydroxyl group contributes to the complexation between vitamin A and Mg(II) ion [56]. The proton NMR spectrum for the Mg(II) complex shows singlets at 3.29 and 3.42 ppm. These singlets are not observed in the free ligand spectrum and can be assigned to protons of H_2O molecules, thus supporting the complex formula.

Thermal analysis

The obtained vitamin A complexes were studied by thermogravimetric (TG), differential thermogravimetric (DTG) and DTA analysis from ambient temperature to 800 ºC in a N_2 atmosphere. The TG curves were drawn as mg mass loss *versus* temperature and DTG curves were drawn as rate of mass loss *versus* temperature. The thermoanalytical results are summarized in Table (4).

[Ca(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].13H_2O complex

The thermal decomposition of the Ca(II) complex of vitamin A with the general formula [Ca(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].13H_2O occurs in four steps. The first degradation step takes place within the temperature range of 25-145 ºC at DTG_{max}=59 ºC and DTA= 60 ºC (endo) and it corresponds to the loss of 8 molecules of hydration water(uncoordinated water) with an observed weight loss of 20.05% (calcd.=21.67%). The activation energy of this step is 20 K J mol^{-1}. The second step occurs within the temperature range of 145-275 ºC at DTG_{max}=225 ºC which is assigned to the loss of 3 molecules of hydration water (uncoordinated water) with a weight loss (obs =7.99%, calcd.=8.12%). The activation energy of this step is 74 K J mol^{-1}. The third step occurs within the temperature range of 275-440 ºC at DTG_{max}=367 ºC and DTA=415 ºC (exo) which is assigned to the loss of 4 molecules of hydration water

Table 3. 1H-NMR spectral data of vitamin A and its Mg(III) complex

Compound	δ ppm of hydrogen					
	H; $\underline{C}H_3$	H; $\underline{C}H_2$	H; $\underline{C}H$	H; $H_2\underline{O}$	H; $\underline{N}H_3$	H; $\underline{O}H$
Vitamin A	1.0	1.50	1.6-1.65-1.8-1.9-2.0	---	---	~ 9
Mg(II) complex	1.05 – 0.84	1.23	1.34-1.47-1.86-2.10-2.13	3.29 - 3.42	4.48	---

Table 4. Thermal data of vitamin A complexes.

Compound	Steps	TG, temp. range (ºC)	DTG_{max} (ºC)	DTA (ºC)	TG weight loss (%)		Assignments
					Calcd.	Found	
[Ca(Vit.	1	25-145	59	60	21.67	20.05	$8H_2O$
A)(Cl)$(NH_3)_2(H_2O)_2$].13H_2O	2	145-275	225	---	8.12	7.99	$3H_2O$
($C_{20}H_{65}O_{16}N_2Cl$ Ca)	3	275-440	367	415	21.44	21.71	$4H_2O+2NH_3+HCl$
	4	440-580	511	513	20.46	21.27	C_9H_{28} (organic moiety)
		Final residue = CaO + 11C (found =28.98% , Calcd.=28.29%)					
[Mg(Vit.	1	30-140	70	71	28.75	28.80	$21H_2O$
A)(Cl)$(NH_3)_2(H_2O)_2$].50H_2O	2	140-210	184	---	17.80	18.02	$13H_2O$
($C_{20}H_{139}O_{53}N_2Cl$ Mg)	3	300-370	334	---	13.69	12.92	$10H_2O$
	4	370-465	420	440	13.54	13.51	$8H_2O+2NH_3$
	5	465-580	534	539	14.94	14.80	$HCl+C_{11}H_{28}$ (organic moiety)
		Final residue = MgO + 9C (found =11.95% , Calcd.=11.25%)					
[Zn(Vit.	1	48-190	81	82	14.67	15.30	$7H_2O$
A)$(SO_4)(NH_3)_2(NH_4)$].20H_2O	2	225-350	292	---	10.48	11.06	$5H_2O$
($C_{20}H_{79}O_{25}N_3S$ Zn)	3	350-400	345	354	12.58	11.89	$6H_2O$
	4	475-570	537	539	19.57	18.20	$2H_2O+2NH_3+H_2SO_4$
	5	700-800	749	---	24.81	23.87	$C_{13}H_{31}N$ (organic moiety)
		Final residue = ZnO + 7C (found =19.68% , Calcd.=19.26%)					
[Fe(Vit.	1	50-125	80	---	3.34	3.27	$1.5H_2O$
A)$(NO_3)_2(NH_3)(H_2O)_2$].16H_2O	2	125-220	187	196	17.86	17.51	$8H_2O$
($C_{20}H_{68}O_{25}N_3$ Fe)	3	220-325	284	302	28.90	28.67	$8.5H_2O+NH_4NO_3$
	4	325-430	366	372	26.55	26.62	$C_{11}H_{28}N\ O_{2.5}$ (organic moiety)
		Final residue = $FeO_{1.5}$ + 9C (found =23.93% , Calcd.=23.32%)					
[VO(Vit.	1	45-140	66	---	4.18	3.79	$2H_2O$
A)$(SO_4)(NH_4)$].2NH_3.20H_2O	2	140-310	266	262	31.39	30.99	$15H_2O$
($C_{20}H_{79}O_{25}N_3S$ VO)	3	310-360	341	339	14.06	14.72	$3NH_4OH+CH_4$
	4	360-510	454	460	32.32	32.78	$C_{13}H_{26}O_4S$ (organic moiety)
		Final residue = VO_2 + 6C (found =17.54% , Calcd.=18.02%)					

exo=exothermic peak, endo=endothermic peak.

(2 uncoordinated and 2 coordinated) +2(NH_3) gas+HCl with a weight loss (obs.=21.71%, calcd.=21.44%). The large number of water molecules can participate in intermolecular hydrogen bonding which in some cases causes an increase in the temperature for weight losses [57]. The activation energy of this step is 99.7 K J mol^{-1}. The fourth step occurs within the temperature range of 440-580 °C at DTG_{max}=511 °C and DTA=513 °C (exo) which is assigned to the loss of C_9H_{28} (organic moiety) with a weight loss (obs.=21.27%, calcd.=20.46%); the activation energy of this step is 192 K J mol^{-1}. CaO+11C are the products remaining stable till 800 °C as a final residue.

[Mg(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].50H_2O complex

The thermal decomposition of the Mg(II) complex of vitamin A with the general formula [Mg(Vit. A)(Cl)$(NH_3)_2(H_2O)_2$].50H_2O occurs in five steps. The first degradation step takes place within the temperature range of 30-140 °C at DTG_{max}=70 °C and DTA=71 °C (endo) and it corresponds to the loss of 21 molecules of hydration water (uncoordinated water) with an observed weight loss of 28.80% (calcd.=28.75%); the activation energy of this step is 44.1 K J mol^{-1}. The second step occurs within the temperature range of 140-210 °C at DTG_{max}=184 °C which is assigned to the loss of another 13 molecules of hydration water (uncoordinated water) with a weight loss (obs.=18.02%, calcd.=17.80%); the activation energy of this step is 84.5 K J mol^{-1}. The third step occurs within the temperature range of 300-370 °C at DTG_{max}=334 °C which is assigned to the loss of 10 molecules of hydration water (uncoordinated water) with a weight loss (obs.=12.92%, calcd.=13.69%); the activation energy of this step is 164 K J mol^{-1}. The fourth step occurs within the temperature range of 370-465 °C at DTG_{max}=420 °C and DTA=440 °C (exo) which is assigned to the loss of 8 molecules of hydration water (6 uncoordinated and 2 coordinated) +2(NH_3) gas molecules with a weight loss (obs.=13.51%, calcd.=13.54%); the activation energy of this step is 268 K J mol^{-1}. The remaining several water molecules not liberated till higher temperature back to the hydrogen bonding between the water molecules [57]. The fifth step occurs within the temperature range of 465-580 °C at DTG_{max}=534 °C and DTA=539 °C (exo) which is assigned to the loss of HCl+$C_{11}H_{28}$ (organic moiety) with a weight loss (obs.=14.80%, calcd.=14.94%). MgO+9C are the products remaining stable till 800 °C as a final residue.

[Zn(Vit. A)$(SO_4)(NH_3)_2(NH_4)$].20H_2O complex

The thermal decomposition of the Zn(II) complex of vitamin A with the general formula [Zn(Vit. A)$(SO_4)(NH_3)_2(NH_4)$].20H_2O occurs in six steps. The first degradation step takes place within the temperature range of 48-190 °C at DTG_{max}=81 °C and DTA=82 °C (endo) and it corresponds to the loss of 7 molecules of hydration water with an observed weight loss of 15.30% (calcd.=14.67%); the activation energy of this step is 44.9 K J mol^{-1}. The second step occurs within the temperature range of 225-320 °C at DTG_{max}=292 °C which is assigned to the loss of another 5 molecules of hydration water with a weight loss (obs.=11.06%, calcd.=10.48%); the activation energy of this step is 102 K J mol^{-1}. The third step occurs within the temperature range of 320-400 °C at DTG_{max}=345 °C and DTA=354 °C (endo) which is assigned to the loss of 6 molecules of hydration water with a weight loss (obs.=11.89%, calcd.=12.58%); the activation energy of this step is 144 K J mol^{-1}. The fourth step occurs within the temperature range of 475-570 °C at DTG_{max}=537 °C and DTA=539 °C (exo) which is assigned to the loss of 2 molecules of hydration water +2 NH_3 molecules+H_2SO_4 with a weight loss (obs.=18.20%, calcd.=19.57%); the activation energy of this step is 263 K J mol^{-1}. The fifth step occurs within the temperature range of 700-800 °C at DTG_{max}=749 °C which is assigned to the loss of $C_{13}H_{31}N$ (organic moiety) with a weight loss (obs.=23.87%, calcd.=24.81%). ZnO+7C are the products remaining stable till 800 °C as a final residue.

[Fe(Vit. A)$(NO_3)_2(NH_3)(H_2O)_2$].16H_2O complex

The thermal decomposition of the Fe(III) complex of vitamin A with the general formula [Fe(Vit. A)$(NO_3)_2(NH_3)(H_2O)_2$].16H_2O occurs in four steps. The first degradation step takes place within the temperature range of 50-125 °C at DTG_{max}=80 °C and it corresponds to the loss of 1.5 molecules of hydration water (uncoordinated water) with an observed weight loss of 3.27% (calcd.=3.34%); the activation energy of this step is 71.4 K J mol^{-1}. The variation from one molecule to one and half water molecules is assigned to the hygroscopic nature of the vitamin A complexes. The second step occurs within the temperature range of 125-220 °C at DTG_{max}=187 °C and DTA=196 °C (exo) which is assigned to the loss of another 8 molecules of hydration water (uncoordinated water) with a weight loss (obs =17.51%, calcd.=17.86%); the activation energy of this step is 88.4 K J mol^{-1}. The third step occurs within the temperature range of 220-325 °C at DTG_{max}=284 °C and DTA=302 °C (exo) which is assigned to the loss of 8.5 molecules of hydration water+NH_4NO_3 with a weight loss (obs.=28.67%, calcd.=28.90%); the

activation energy of this step is 97.7 K J mol^{-1}. The fourth step occurs within the temperature range of 325-430 °C at DTG_{max}=366 °C and DTA=372 °C (exo) which is assigned to the loss of $C_{11}H_{28}NO_{2.5}$ (organic moiety) with a weight loss (obs.=26.62%, calcd.=26.55%); the activation energy of this step is 123 K J mol^{-1}. $FeO_{1.5}$+9C are the products remaining stable till 800 °C as a final residue.

[VO(Vit. A)(SO_4)(NH_4)].2NH_3.20H_2O complex

The thermal decomposition of the VO(II) complex of vitamin A with the general formula [VO(Vit. A)(SO_4)(NH_4)].2NH_3.20H_2O occurs in four steps. The first degradation step takes place within the temperature range of 45-140 °C at DTG_{max}=66 °C and it correspond to the loss of 2 molecules of hydration water (uncoordinated water) with an observed weight loss of 3.79% (calcd.=4.18%); the activation energy of this step is 51.6 K J mol^{-1}.The second step occurs within the temperature range of 140-310 °C at DTG_{max}=266 °C and DTA=262 °C (endo) which is assigned to the loss of another 15 molecules of hydration water with a weight loss (obs.=30.99%, calcd.=31.39%); the activation energy of this step is 100 K J mol^{-1}. The third step occurs within the temperature range of 310-360 °C at DTG_{max}=341 °C and DTA=339 °C (endo) which is assigned to the loss of 3 NH_4OH and CH_4 gas with a weight loss (obs.=14.72%, calcd.=14.06%); the activation energy of this step is 181 K J mol^{-1}. Concerning retained ammonia molecules over water till DTG of 341 °C, the combination between water molecules and ammonia to give 3NH_4OH alterated to 3NH_3 + 3H_2O. The fourth step occurs within the temperature range of 360-510 °C at DTG_{max}=454 °C and DTA=460 °C (exo) which is assigned to the loss of $C_{13}H_{26}O_4S$ (organic moiety) with a weight loss (obs.=32.78%, calcd.=32.32%); the activation energy of this step is 149 K J mol^{-1}. VO_2+6C are the products remaining stable till 800 °C as a final residue. It can be noted that the increase in the number of water molecules favors the formation of intermolecular hydrogen bonding which pushes up the temperature range for losing water molecules.

Kinetic studies

The kinetic parameters such as activation energy (*ΔE**), enthalpy (*ΔH**), entropy (*ΔS**) and free energy change of the decomposition (*ΔG**) were evaluated graphically, as shown in Figs. (5, 6) by employing the Coats–Redfern and Horwitz–Mitzger relations [43,40].

The calculated values of *E**, *A*, *ΔS**, *ΔH** and *ΔG** for the decomposition steps of vitamin A complexes are given in Table (5). The most significant result is the considerable thermal stability of the Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) complexes evidenced by the high values of the activation energy of decomposition. The second essential result is that the entropy change *ΔS** for the formation of the activated complexes from the starting reactants has in most cases negative values. The negative sign of *ΔS** suggests that the thermodynamic behavior of all vitamin A complexes is non-spontaneous (more ordered) and the degree of structural "complexity" (arrangement, "organization") of the activated complexes is lower than that of the starting reactants, hence the thermodynamic behavior of all complexes is endothermic ($\Delta H > 0$) and endergonic ($\Delta G > 0$), during the reactions. The thermodynamic data obtained with the two methods are in harmony with each other. The correlation coefficients of the Arrhenius plots of the thermal decomposition steps were found to lie in the range from 0.9628 to 0.9999, showing a good fit with the linear function. The thermograms and the calculated thermal parameters for the complexes show that the stability of these complexes depends on the nature of the central metal ion. The thermal stability of the metal complexes was found to increase periodically with the increase in atomic number of the metal and the larger value of charge/radius ratio [58].

Microbiological investigation of the vitamin A complexes

Antibacterial and antifungal activities of vitamin A complexes are carried out against some kinds of bacteria as *Escherichia coli* (Gram –ve) and *Staph albus* (Gram +ve), as well as some kinds of fungi as *Aspergillus niger* and *Aspergillus flavus*. The antimicrobial activity was estimated based on the size of the inhibition zone. The free vitamin A was found to have the lowest activity against the four types of bacteria and fungi, while the Zn(II) complex was found to have the highest activity. The biological activities increase in the following order: Zn(II)/Vit.A > Fe(III)/Vit.A > VO(II)/Vit.A > Mg(II)/Vit.A > Ca(II)/Vit.A. The data are listed in Table (6) and are shown in Fig. (7), the activity is verified with different metal ions containing the respective complexes, thus chelation increases lipophilic character in the complexes and results in enhancement of activity.

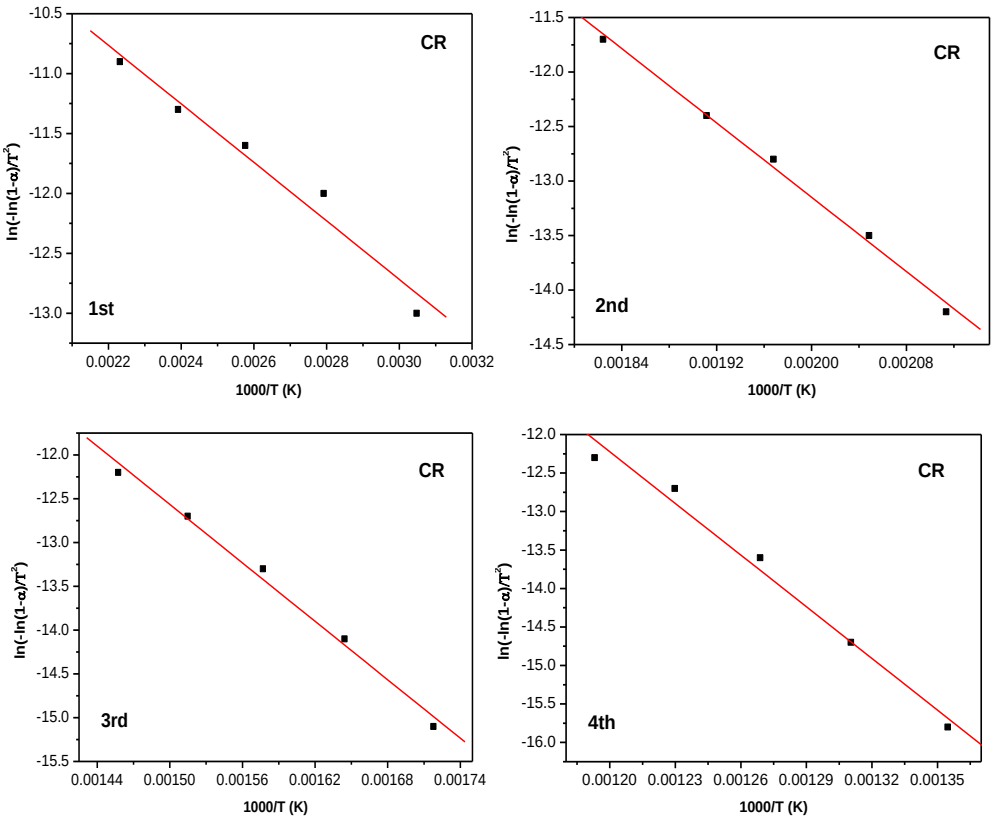

Fig. 5. Coats-Redfern (CR) plots of the first, second, third and fourth thermal decomposition steps of the Ca(II)/Vit. A complex

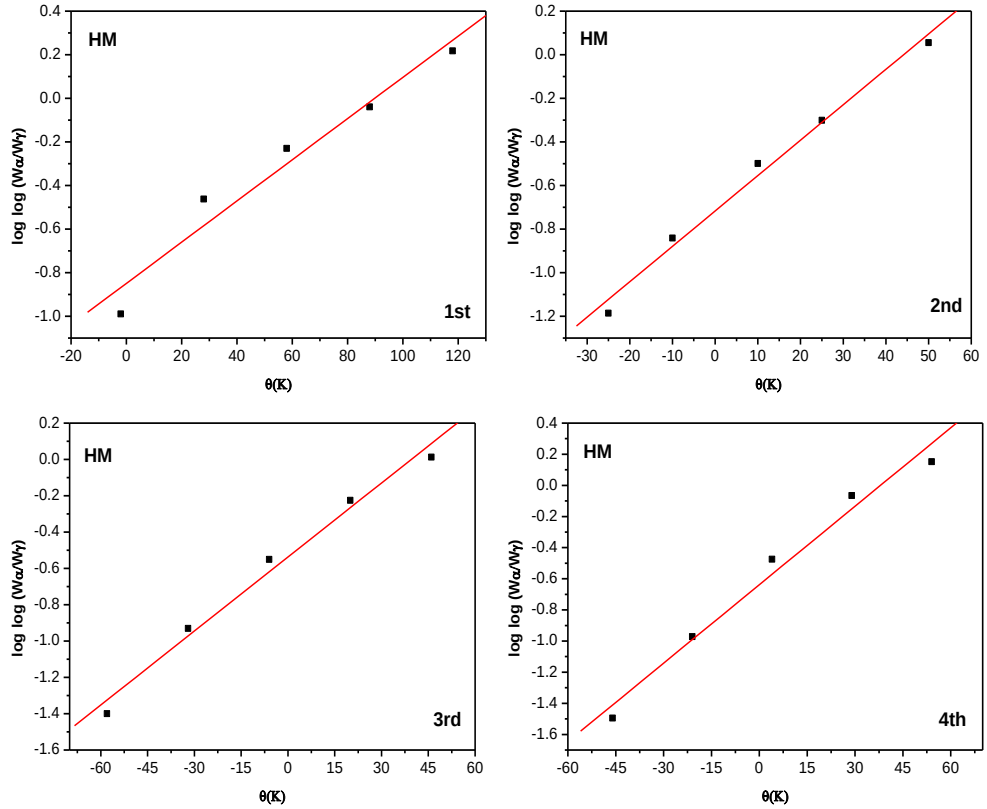

Fig. 6. Horowitz-Metzger (HM) plots of the first, second, third and fourth thermal decomposition steps of the Ca(II)/Vit. A complex

Table (5): Kinetic and thermodynamic parameters of the thermal decomposition of vitamin A complexes

Complex	Stage	Method	Parameter					R
			E (J mol^{-1})	A (s^{-1})	ΔS (J mol^{-1} K^{-1})	ΔH (J mol^{-1})	ΔG (J mol^{-1})	
Ca(II)	1 st	CR	2.03E+04	2.78E+00	-2.37E+02	1.76E+04	9.59E+04	0.98295
		HM	1.97E+04	7.18E+00	-2.29E+02	1.70E+04	9.27E+04	0.9774
	2 nd	CR	7.08E+04	1.04E+05	-1.53E+02	6.67E+04	1.43E+05	0.99746
		HM	7.72E+04	1.15E+06	-1.33E+02	7.30E+04	1.39E+05	0.99991
	3 rd	CR	9.25E+04	1.71E+05	-1.51E+02	8.72E+04	1.84E+05	0.99575
		HM	1.07E+05	3.87E+06	-1.25E+02	1.01E+05	1.81E+05	0.99241
	4 th	CR	1.86E+05	1.26E+10	-5.96E+01	1.80E+05	2.26E+05	0.99221
		HM	1.98E+05	1.45E+11	-3.93E+01	1.91E+05	2.22E+05	0.98946
Mg(II)	1 st	CR	4.27E+04	1.08E+04	-1.69E+02	3.98E+04	9.78E+04	0.9689
		HM	4.55E+04	9.96E+04	-1.50E+02	4.27E+04	9.43E+04	0.96461
	2 nd	CR	7.86E+04	8.21E+06	-1.16E+02	7.48E+04	1.28E+05	0.99124
		HM	9.05E+04	2.84E+08	-8.67E+01	8.67E+04	1.26E+05	0.99174
	3 rd	CR	1.59E+05	3.29E+11	-3.03E+01	1.53E+05	1.72E+05	0.99366
		HM	1.69E+05	4.96E+12	-7.78E+00	1.64E+05	1.69E+05	0.99208
	4 th	CR	2.62E+05	8.36E+14	3.25E+01	2.56E+05	2.29E+05	0.99963
		HM	2.75E+05	7.73E+15	5.10E+01	2.68E+05	2.27E+05	0.99841
Zn(II)	1 st	CR	4.41E+04	1.03E+04	-1.70E+02	4.12E+04	1.01E+05	0.9628
		HM	4.57E+04	6.08E+04	-1.55E+02	4.28E+04	9.76E+04	0.96425
	2 nd	CR	9.46E+04	4.86E+06	-1.22E+02	8.99E+04	1.59E+05	0.99486
		HM	1.11E+05	1.80E+08	-9.22E+01	1.06E+05	1.58E+05	0.99292
	3 rd	CR	1.42E+05	4.19E+09	-6.68E+01	1.37E+05	1.78E+05	0.99044
		HM	1.47E+05	2.96E+10	-5.05E+01	1.42E+05	1.73E+05	0.98735
	4 th	CR	2.53E+05	2.04E+14	2.07E+01	2.47E+05	2.30E+05	0.99821
		HM	2.74E+05	6.26E+15	4.92E+01	2.68E+05	2.28E+05	0.99883
Fe(III)	1 st	CR	7.02E+04	1.17E+08	-9.19E+01	6.73E+04	9.97E+04	0.98551
		HM	7.26E+04	9.49E+08	-7.45E+01	6.96E+04	9.59E+04	0.97885
	2 nd	CR	8.18E+04	1.52E+07	-1.11E+02	7.80E+04	1.29E+05	0.99895
		HM	9.50E+04	8.10E+08	-7.80E+01	9.11E+04	1.27E+05	0.99717
	3 rd	CR	9.15E+04	2.52E+06	-1.28E+02	8.69E+04	1.58E+05	0.99382
		HM	1.04E+05	5.85E+07	-1.01E+02	9.95E+04	1.56E+05	0.99332
	4 th	CR	1.22E+05	5.59E+07	-1.03E+02	1.17E+05	1.83E+05	0.99414
		HM	1.25E+05	1.58E+08	-9.43E+01	1.20E+05	1.80E+05	0.99286
VO(II)	1 st	CR	5.11E+04	2.42E+05	-1.43E+02	4.83E+04	9.68E+04	0.97166
		HM	5.21E+04	1.46E+06	-1.28E+02	4.93E+04	9.27E+04	0.9723
	2 nd	CR	9.40E+04	8.39E+06	-1.17E+02	8.95E+04	1.53E+05	0.99492
		HM	1.07E+05	2.59E+08	-8.88E+01	1.03E+05	1.50E+05	0.99333
	3 rd	CR	1.79E+05	1.11E+13	-1.19E+00	1.74E+05	1.74E+05	0.98955
		HM	1.84E+05	6.20E+13	1.31E+01	1.79E+05	1.71E+05	0.98833
	4 th	CR	1.42E+05	1.24E+08	-9.74E+01	1.36E+05	2.07E+05	0.99851
		HM	1.56E+05	1.31E+09	-7.78E+01	1.49E+05	2.06E+05	0.99856

r = correlation coefficient of the linear plot

.**Table (6):** Antimicrobial data of vitamin A complexes

Compound	Diameter of inhibition zone (cm)			
	E. coli	*Staph albus*	*Aspergillus niger*	*Aspergillus flavus*
Control	0	0	0	0
Vitamin A	0	0	0	0
Ca(II) complex	0	0	0.3	0
Mg(II) complex	0	0	0.5	0.2
Zn(II) complex	0	0.5	0.5	0.5
Fe(III) complex	0	0.2	0.4	0.4
VO(II) complex	0	0.2	0.3	0.4

Structure of the vitamin A complexes

The structures of the complexes of vitamin A with Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) ions were confirmed by the elemental analysis, IR, ^{1}H-

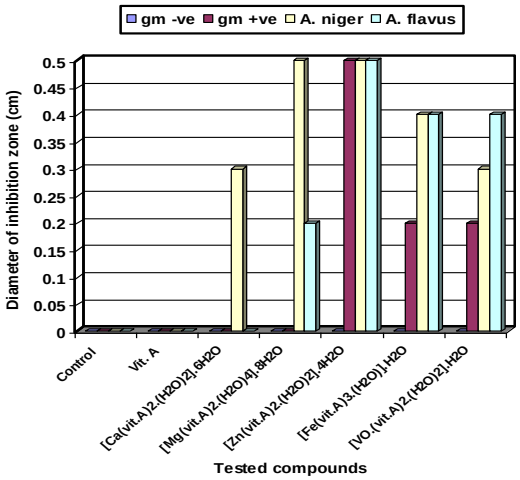

Fig. 7. Statistical representation of the biological activity of Vit. A and its complexes.

NMR, molar conductance, UV-Vis and thermal analysis data. Thus, from the IR spectra, it is concluded that vitamin A behaves as a mono-dentate ligand coordinated to the metal ions *via* the deprotonated hydroxyl oxygen atom. The structures of the investigated complexes are shown in Figs. (8-12).

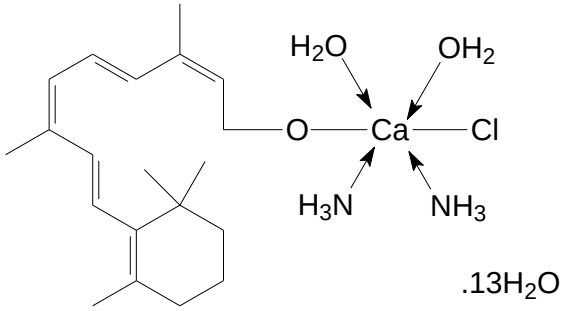

Fig. 8. Suggested structure of the Ca(II) complex of vitamin A

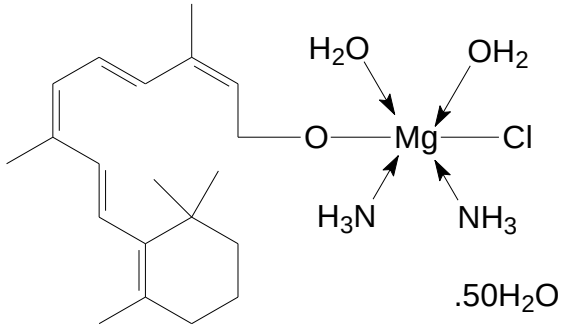

Fig. 9. Suggested structure of the Mg(II) complex of vitamin A

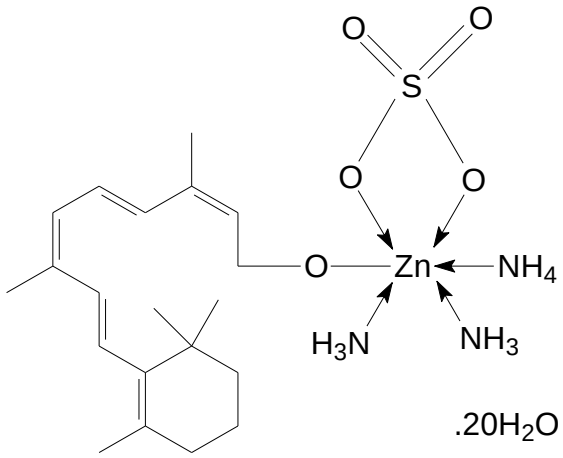

Fig. 10. Suggested structure of the Zn(II) complex of vitamin A

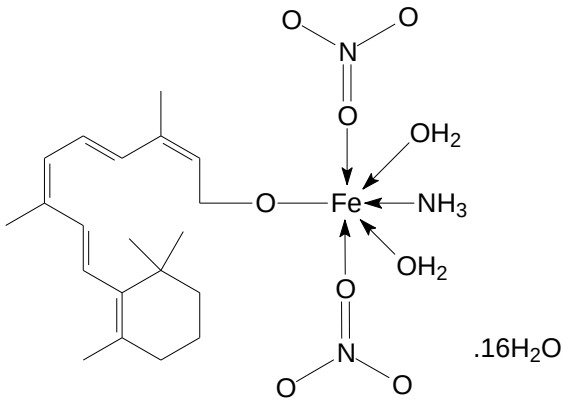

Fig. 11. Suggested structure of the Fe(III) complex of vitamin A

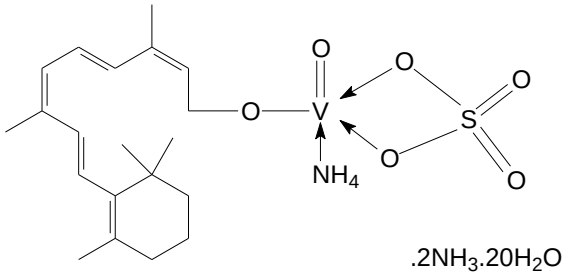

Fig. 12. Suggested structure of the VO(II) complex of vitamin A

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СИНТЕЗ, ИЗЯСНЯВАНЕ НА ХИМИЧНИТЕ СТРУКТУРИ И БИОЛОГИЧНИ ИЗСЛЕДВАНИЯ ВЪРХУ ЕФЕКТА НА НЯКОИ ВАЖНИ МЕТАЛНИ ЙОНИ НА ВИТАМИН А: Ca (II), Mg (II), Zn (II), Fe(III) И VO(II) КОМПЛЕКСИ

М. Заки[1], М. И. Ел-Саид[1,2], С. М. Ел-Мегарбел[1,3], С. Або Талеб[1], M. S. Refat[3,4]

1 Катедра по химия, Научен факултет, Университет Загазиг, Египет
2 Факултет за приложни медицински науки, Университет Ал-Джуф-Ал Караят
3Катедра по химия, Научен факултет, Университет Таиф, 888 Таиф, Кралство Саудитска Арабия
4 Катедра по химия, Научен факултет, Порт Саид, Университет Порт Саид, Египет

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(Резюме)

Комплекси на витамин А като фармацевтичен лиганд с Ca (II), Mg (II), Zn (II), Fe (III) и VO (II), бяха синтезирани и охарактеризирани с микроанализ, проводимост, инфрачервена спектроскопия и термогравиметрични (TG / DTG и DTA) измервания. Лигандът може да се координира като монодентатен лиганд чрез кислородния атом на депротонирана хидроксилна група. Кривите на термичното разграждане разкриха, че некоординираните водни молекули са премахнати в първия етап, докато разлагането на лиганда, освен координирани водни молекули, намира място при втория и следващите етапи. Витамин А като лиганд, както и неговите комплекси бяха проверени срещу някои видове бактерии и гъбички и показаха значителен ефект. Ефектът от кинетични термодинамични параметри (E*, AH*, ΔS* и ΔG*) на синтезираните комплексите върху TG кривите бяха изчислени с помощта на уравненията на Coats-Redfern and Horowitz-Metzger.