Ligand substitution reactions of a phenolic quinolyl hydrazone; oxidovanadium (IV) complexes

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Abstract

Background: Quinoline ring has therapeutic and biological activities. Quinolyl hydrazones constitute a class of excellent chelating agents. Recently, the physiological and biological activities of quinolyl hydrazones arise from their tendency to form metal chelates with transition metal ions. In this context, we have aimed to study the competency effect of a phenolic quinolyl hydrazone (H2L; primary ligand) with some auxiliary ligands (Tmen, Phen or Oxine; secondary ligands) towards oxidovanadium (IV) ions.

Results: Mono- and binuclear oxidovanadium (IV) complexes were obtained from the reaction of a phenolic quinolyl hydrazone with oxidovanadium (IV)- ion in absence and presence of N,N,N′,N′-tetramethylethlenediamine (Tmen), 1,10-phenanthroline (Phen) or 8-hydroxyquinoline (Oxine). The phenolic quinolyl hydrazone ligand behaves as monobasic bidentate (NO- donor with O- bridging). All the obtained complexes have the preferable octahedral geometry except the oxinato complex (2) which has a square pyramid geometry with no axial interaction; the only homoleptic complex in this study.

Conclusion: The ligand exchange (substitution/replacement) reactions reflect the strong competency power of the auxiliary aromatic ligands (Phen/Oxine) compared to the phenolic quinolyl hydrazone (H2L) towards oxidovanadium (IV)- ion; (complexes 2 and 3). By contrast, in case of the more flexible aliphatic competitor (Tmen), an adduct was obtained (4). The obtained complexes reflect the strength of the ligand field towards the oxidovanadium (IV)- ion; Oxine or Phen >> phenolic hydrazone (H2L) > Tmen.

Background

The heterocyclic hydrazones constitute an important class of biologically active drug molecules which have attracted attention of medicinal chemists due to their wide ranging pharmacological properties including iron scavenging and anti-tubercular activities [1-4]. Literature survey revealed that quinolyl hydrazones have anticancer and anti-inflammatory activities [1]. Quinolyl hydrazones are known to function as chelating agents and have versatile modes of bonding [5-7]. Recently, the physiological and biological activities of quinolyl hydrazones arise from their tendency to form metal chelates with transition metal ions [3,4]. On the other hand, vanadium is a versatile bio-essential element capable of existing in a wide range of oxidation states spanning between 3- and 5+, that advances the usefulness of this element in the biological milieu [8]. Current focus in the coordination chemistry of vanadium has been the subject of extensive research, stimulated by the potential pharmacological effects such as action against diabetes [8-11] and cancer [12,13], the stimulation of phosphomutases and isomerases as well as the ability of vanadium in the inhibition of sodium potassium ATPase enzymes [14,15] provide great impetus in vanadate-phosphate analogy [11]. This work is aimed to study the competency of a phenolic quinolyl hydrazone [5]; 4-[(2-(4,8-dimethylquinolin-2-yl)hydrazono)methyl] benzene-1,3-diol (H2L; primary ligand) with some auxiliary ligands (Tmen, Phen or Oxine; secondary ligands) towards oxido-vanadium (IV)- ion (Scheme 1).

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Results and discussion

Effect of solvent on the spectra of the hydrazone

In this study, the electronic absorption spectra of the hydrazone (2 × 10⁻⁵ M) were recorded in solvents of various polarities (Table 1 and Figure 1). The hydrazone displays mainly three bands, the shortest UV- bands (λ₁ = 247-266 and λ₂ = 308-369 nm) are best ascribed to π-π* transitions of the aromatic system and they are solvent sensitive bands whereas, the longest UV- band (λ₃ = 370 nm) is a strong broad band reflecting its charge transfer (CT) nature [6,7]. Most bands suffered a red shift on increasing the solvent polarity. Also, the less intense n-π* transitions are hidden under the more intense CT bands, increasing the solvent polarity. Also, the less intense n-(CT) nature [6,7].

Table 1 Electronic spectral data* of the hydrazone in various solvents.

| Solvent     | DMSO | DMF | 2-Propanol | MeOH | EtOH | Acetone | Dioxane | THF | Ethyl ether | Benzene | Ethyl acetate |
|-------------|------|-----|------------|------|------|---------|---------|-----|-------------|---------|--------------|
| λ₁          | 265  | 265 | 247        | — — | — — | — —     | 258     | — — | — —         | 261     | — —          |
| ε₁          | 17927| 17288| 20629      | — — | — — | — —     | 17191   | — — | — —         | 21080   | 14888        |
| λ₂          | 364  | 321 | 308        | 312 | 322 | 335     | 351     | 369 | 345         | 343     | 347          |
| ε₂          | 19104| 17688| 18887      | 18034| 18089| 17391   | 22614   | 13575| 19566       | 17421   | 18592        |
| λ₃          | — — | 372 | 372        | 370 | 369 | 367     | — —     | — — | — —         | — —     | — —          |
| ε₃          | — — | 19040| 19329      | 19580| 19416| 18148   | — —     | — — | — —         | — —     | — —          |

* in nm and ε in (cm mol/L)⁻¹.
the quinoline and 1,10-phenanthroline rings are shifted to higher wave numbers for the former and to lower wave numbers for the latter, suggesting the participation of the heterocyclic N-atoms in the chelation [19]. Also, their intensities are greatly altered. The sulfato-complexes (1, 3, 4) showed the ν(S-O) stretches as strong bands around 1100 cm⁻¹ [21]. The characteristic ν(V = O) stretches [20,22] were observed at 984, 1010, 854 and 975 cm⁻¹; respectively. The higher value at 1010 cm⁻¹ is for the penta-coordinated oxinato-complex (2) which is most probably due to the strong O→V bonding [20], supporting the non axial interaction (Figure 2c). In contrast, the lower values for the hexa-coordinated complexes (1, 3, 4) suggest an axial interaction which lying trans to V = O (Figure 2a,b). In general, the ν(V = O) stretches are highly affected by the axial interactions trans to V = O stretches [20]. However, this could be explained by using the well known Ballhausen-Gray molecular orbital (M.O.) energy level diagram [23]; (Figure 2).

Conductivity and magnetic measurements
The molar conductance values of the current chelates in DMF (1 mmol/L) were measured at room temperature and the results are listed in Table 3. The values reflect the non-electrolytic nature of all complexes. The oxidovanadium (IV) complexes (1-4); d¹⁻ system exhibit μ_eff values in the range 1.27-1.90 B.M. (Table 3) indicating the presence of one unpaired electron. The subnormal μ_eff values indicate VO—VO interactions in the solid state; supporting the binuclear nature of the complexes (1 and 4).

Electronic spectra
Solution electronic spectra of the complexes in DMF (Table 3) are more or less similar and show a series of bands within the range 267-341 nm due to intra-ligand transitions. Unfortunately, although the oxidovanadium (IV)-complexes (1-4) are the easiest of the d¹⁻ systems to use experimentally, the interpretation of the spectra has been complicated by the deviation of the complexes from regular octahedral stereochemistry [24]. Three bands are normally observed around 485, 460 and 430 nm in case of the phenolic complexes (1) and (4). On a simple crystal field model, these bands would be interpreted as the transitions from the 2B₂-grount term to the 2E, 2B₁ and 2A₁⁻ terms [24], respectively. However, such a treatment does not give a good quantitative fit to the spectra and the axial π-bonding must be taken into account. In case of the oxinato (2) and Phen (3)

Table 2 Physical and analytical data of the complexes.

| No.  | Reactants                  | Complex (F.W.) | Color          | % Yield | Elemental Analysis; % Found/(Calc.) | C     | H     | N     |
|------|----------------------------|----------------|----------------|---------|-------------------------------------|-------|-------|-------|
| 1    | H₂L + VO SO₄              | [VO₂(H₂L)_2(MeOH)]₂SO₄.2MeOH (970.78) | Olive green    | 36      | 49.44 (49.49) 7.92 (7.98) 8.70 (8.66) |
| 2    | H₂L + VO SO₄ + Oxine      | [VO(Oxinate)₂]·1/4 H₂O (359.74) | Olive green    | 40      | 60.12 (60.09) 3.59 (3.50) 8.31 (7.80) |
| 3    | H₂L + VO SO₄ + Phen       | [VO(Phen)₂(SO₄)]21/2 H₂O.41/4 MeOH (704.63) | Olive green    | 61      | 47.97 (48.15) 5.45 (5.44) 7.95 (7.95) |
| 4    | H₂L + VO SO₄ + Tmen       | [VO₂(H₂L)₂(Tmen)]SO₄.6H₂O (1066.92) | Coffee brown   | 70      | 47.18 (47.28) 5.62 (5.67) 10.60 (10.51) |
complexes, only the transition $^2B_2 \rightarrow ^2A_1$ was observed at 412 and 341 nm, respectively.

**ESR spectroscopy**

To obtain further information about the stereochemistry as well as the magnetic properties of the complexes, the ESR spectra of a powdered sample of complexes 1 and 4 were recorded at room temperature (Figure 3). The shape and the features of the obtained spectra are consistent with the Oh-geometry around the metal ion. The ESR spectrum of the adduct (4) displayed one strong signal with $g_{\text{eff}} = 2.094$ and a shoulder at $g = 2.44$. Also, a very weak signal at ~1700 Gauss due to the forbidden $\Delta M_s = \pm 2$ transition, characteristic of dimeric vanadyl (II) -complexes. This is consistent with the lower $\mu_{\text{eff}} = 1.27$ B.M. (Table 3). In contrast, the ESR spectrum of the phenolic complex (1) displayed the high field component at $g_{\perp} = 2.084$ and the low field component at $g_{11} = 2.208$; $g_{\text{eff}} = 1/3 (g_{11} + 2g_{\perp}) = 2.125$. The positive contribution in the $g_{\text{eff}}$ value than that of the free electron ($g_e = 2.0023$) indicates an increase in the covalency of the bonding. In axial symmetry, the value of the exchange interaction parameter; $G = (g_{11} \cdot g_e)/(g_{\perp} \cdot g_e) = 2.518$ indicates a considerable OV—VO interaction which is also consistent with the lower $\mu_{\text{eff}} = 1.59$ B.M. (Table 3) as well as the absence of hyperfine coupling. The latter is attributed to either the simultaneous flipping of neighboring electron spins or the strong exchange interaction [25].

**Mass spectra**

The mass spectra of complexes 2 and 3 showed the molecular ion peaks at $m/z = 356$ and 698 and the base peaks at 145 and 46, respectively, confirming their formulae weights (Table 2). The Oxinato- complex (2) showed the molecular ion peak at 356 which agree well with the formula weight of the non-hydrated complex (F.W. = 355.24); [(VO) (Oxinate) 2]. Furthermore, the base peak at 145 which is identical to the charged Oxine species- provides strong evidence for the structure of the Oxinato complex (Scheme 2).

**Thermal properties of the complexes**

TGA data of the complexes (1-4) showed good agreement with the results of elemental analyses. The decomposition occurs in two or three steps according to the nature of each complex. Attempts to generalize the thermal degradation patterns were unsuccessful indicating that there is no simple relation or general trend for explaining these thermal degradations. However, the decomposition ends with the formation of (VO)2 for the phenolic binuclear complexes 1 and 4. The Phen complex (3) decomposes into two stages and undergoes a structural rearrangement upon thermal degradation [26-28]; (Scheme 3). This structural rearrangement was confirmed from the considerable decrease of the values of $A$, $E^*$ and $\Delta H^*$ for the second stage than that for the first stage; Table 4. Also, the only adduct in this study;
[(VO)2 (HL)2 (Tmen) SO4].6H2O (4) undergoes another structural rearrangement as shown in Scheme 4.

**Experimental**

**Materials**
The chemicals used in this investigation were of the highest purity available (Merck, BDH, Aldrich and Fluka). They included vanadyl sulfate monohydrate, N, N,N',N'- tetramethylethylenediamine (Tmen), 1,10-phenanthroline (Phen) or 8-hydroxyquinoline (Oxine), o-toluidine, ethyl acetacetate, POCl3, sulfuric acid, hydrazine hydrate and 2,4-dihydroxybenzaldehyde. Organic solvents were reagent grade chemicals and were used without further purification.

**Physical measurements**
Microanalyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. Thermal analyses (TG-DSC) were carried out on a Shimadzu-50 thermal analyzer in nitrogen atmosphere and a heating rate of 20°C/min using the TA-50 WS1 program. Electronic spectra were recorded on a Jasco V-550 UV/VIS spectrophotometer. IR spectra were recorded on a Bruker Vector 22 spectrometer using KBr pellets. ESR spectra were recorded on a Bruker Elexys, E 500 operated at X-band frequency. Mass spectra were recorded at 70 eV on a gas chromatographic GCMSQP 1000-EX Shimadzu mass spectrometer. Molar conductance was measured as DMF solutions on the Corning conductivity meter NY 14831 model 441. Magnetic susceptibility was measured at room temperature using a Johnson Matthey, MKI magnetic susceptibility balance. Melting points were determined using a Stuart melting point apparatus.

**Preparation of the phenolic hydrazone**
An ethanolic mixture of 2-hydrazinyl-4,8-dimethyl quinoxaline (0.01 mol) and 2,4-dihydroxybenzaldehyde (0.012 mol) was refluxed for 1/2 h. The formed yellow compound was filtered off, washed with ethanol and crystallized from ethanol as described in our previous publication [5].

**Synthesis of the complexes (1-4)**
A methanolic solution of VOSO4.H2O was added gradually to a methanolic solution of the phenolic hydrazone in absence (complex 1) and in presence of Oxine, Phen or Tmen (complexes 2-4) at the mole ratio 1: 1: 1. The reaction mixture was refluxed until the solid complex was precipitated. Then, the isolated complexes were filtered off, washed with methanol, then diethyl ether and

| Table 4 Thermodynamic and kinetic parameters of complex 3. |
|-------------------|-----------------|-----------------|-----------------|-----------------|
| Stage  | T (K) | A × 10^{-9} sec^{-1} | E* | ΔH* | ΔG* | ΔS* |
| 1st    | 427   | 38.251                | 20.233 | 16.69 | 36.004 | 45.234 |
| 2nd    | 625   | 14.133                | 12.118 | 6.931 | 42.344 | 56.662 |

* E*, ΔH* and ΔG* are in kJ mol^{-1} while ΔS* is in J mol^{-1} K^{-1}.

Scheme 2: The mass fragmentation pattern of complex 2.
finally dried in vacuo. The obtained complexes (Table 2) are colored and quite stable in atmospheric conditions. The complexes are insoluble in water and most common solvents; but they are soluble in DMF and DMSO solvents.

Conclusion and comments

Trials to prepare mixed ligand complexes via the reaction of the phenolic hydrazone (H₂L) with VOSO₄·H₂O in presence of Oxine or Phen were unsuccessful. Instead, an Oxinato complex (in presence of Oxine or Phen were unsuccessful. These trials were successful in contrast, these trials were successful in case of the more flexible aliphatic base (Tmen) where a mixed ligand complex (4) was obtained. The obtained complexes have an octahedral arrangement except complex 2 which has a square pyramid arrangement. Also, they reflect the competency power towards the oxidovanadium (IV)- ion, and the following order holds; Oxine or Phen >> phenolic hydrazone (H₂L) > Tmen. This order reflects that the nucleophilicity of Oxine or Phen is stronger than that of phenolic hydrazone (H₂L).

Authors’ contributions

HSS designed the study, analyzed the data and drafted the manuscript. MAM prepared the organic ligand and its complexes. Both authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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