Spectral, Electrochemical and Molecular Modeling Studies of Some 3-(2-Hydroxy benzalhydrazino-4-thiazolyl)coumarins

N. RAJU and A. RAMACHANDRAIAH*

Department of Chemistry,
National Institute of Technology Warangal,
Warangal, 506004, Andhra Pradesh, India.
chandraiah@msn.com

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Abstract: Spectral, cyclic voltammetric and molecular modeling studies have been carried out on some 3-(2-hydroxybenzalhydrazino-4-thiozyl)coumarins (**1**), to understand their solution and electrochemical characteristics. These investigations reveal structural alterations in the conjugates of their acid-base equilibria as indicated by considerable bathochromic shift in electronic spectra and changes in electron transfer properties with rise in pH. The pK_a values and electrochemical data such as E_p , i_p , α_{na} , k^0_h , *etc.*, of **1** were evaluated. Further, the compound **1** is found to be good chelating ligands. Molecular modeling studies were also performed to correlate the spectral and electrochemical observations. Voltammetric analysis of **1** is also presented.

Keywords: Thiazolylcoumarins, Tautomerism, Wolff-Kishner reaction, Cyclic voltammetry, Isosbestic points, Molecular modeling.

Introduction

Schiff bases are known for their biological importance, especially in antimicrobial^{1,2} and antitumour³ activities and in the physiology of vision⁴. They are widely used as ligands for complexation⁵⁻⁹. They are also known to undergo hydrolysis readily in aqueous media^{10,11}. Some of the Schiff bases with OH group in *ortho* position to the imino group exhibit tautomerism^{5-9,12}. However, the electrochemical characterization of Schiff bases is not consummate to their other studies. In this paper, we present the spectral, electrochemical and preliminary molecular modeling studies of **1** which are Schiff bases arising from salicylaldehyde and hydrazinyl thiazocoumarins.

Experimental

All the three compounds, **1a–1c**, have been prepared based on the reported¹² procedure. A typical case is presented here.

Synthesis of **1a**

A mixture of 3-(2-bromoacetyl)coumarin (0.01 mol), thiosemicarbazide (0.01 mol) and salicylaldehyde (10 mL) was thoroughly stirred for 5 min at room temperature in a 50 mL RB flask at 60 °C. The solid mass was filtered and recrystallized from methanol.

A millimolar stock solution of **1** was prepared in methanol. 1 mL of the stock solution was made up to 25 mL by the Britton-Robinson buffer of the desired pH (ionic strength = 0.02 M) for the purpose of spectral or electrochemical run. An ATI Orion Model 902 Ion Meter was used for the pH-metry whereas an AnalytikJena Specord 205 Spectrophotometer for UV-vis spectral and a Metrohm 663 VA Stand for voltammetric and a BAS CV-27 Voltammograph for coulometric studies. Molecular modeling was carried out on a ChemOffice® Ultra Pro 10.0 platform.

Results and Discussion

Spectral studies

Even though salicylidinimine Schiff bases are known to undergo hydrolysis readily in aqueous buffers^{10,11,13,14}, no such instability has been observed for **1**. However, compounds, **1**, suffer structural change with pH. Figure 1 shows such time-independent but pH-dependent spectra for the case of **1a**. The compounds exhibit bathochromic shift from ~ 325 nm to ~ 370 nm with a well defined isosbestic point at ~350 nm. Many hydrazones are famous to undergo Wolff-Kishner reaction in alkaline media¹⁵ with a mechanism shown in Scheme 1 converting the azomethine carbon into a carbanion. In the present case of **1** too, we propose the generation of a carbanion upon deprotonation at elevated pH. Additional stability for this anion comes from the extended conjugation running from the phenyl group to the thiazolyl coumarin ring via the azo moiety besides Huckel's aromaticity encompassing all the three rings with $n=6$ in the $4n+2$ rule that includes the carbanion's lone pair. In other words, the azo moiety and the carbanion are stabilized at high pH. The acid-base equilibria for **1** as an extension of Scheme 1 are shown in Scheme 2.

Figure 1. Electronic spectra of **1a** ($5.2 \times 10^{-5} \text{ M}$) in aqueous buffers of pH (a) 1.2, (b) 2.8, (c) 5.8, (d) 6.8, (e) 7.75, (f) 8.5, (g) 9.7, (h) 10.8, (i) 11.4 and (j) 12.2.

Scheme 1

Scheme 2

The presence of isosbestic points at ~ 275 and ~ 350 nm is a strong evidence for the fact that there are only two absorbing species, **1** and **1⁻** in equilibrium. The pK_a of **1** were obtained by plotting absorbance vs. pH at the two λ_{max} as shown in Figure 2. It is worth comparing the spectral behaviour of **2** with that of **1**. Spectral variation with pH was observed¹⁶ to be negligible for **2**. This compound is analogous to **1** with phenolic group absent. Hence, we suggest the deprotonation at the phenolic group is more probable than that at the hydrazone. The bathochromic shift in the spectra of **1** is attributed to the involvement of tautomerism that is not possible in **2**.

Figure 2. Effect of pH on the absorbivities of **1a** at (a) 326 and (b) 370 nm. The solid lines are curv-fitted for $pK_a = 8.6$.

Electrochemical investigations

The cyclic voltammograms recorded for **1** on SMDE over a wide pH range are shown in Figure 3. The voltammograms indicate irreversible but pH-dependent reduction profiles. In the pH range, 1-6, the compounds exhibit a single irreversible reduction peak with an n value of 2. The plot of E_p vs. pH, in this range is used to evaluate the number of H^+ ions involved in the reduction process^{17, 18}.

Figure 3. Cyclic voltammograms of **1a** (6×10^{-5} M) at pH (a) 1.6, (b) 3.8, (c) 6.8, (d) 8.2, (e) 9.2, (f) 10.1 and (g) 11.5 on SMDE (6.25×10^{-6} m²) at 50 mVs^{-1} with KCl (0.05 M).

The 2-electron transfer is attributed to the reduction of the $-C=N-$ moiety of **1** or $1H^+$ as

Usually, the 2-electron reduction of Schiff bases intrinsically happens in a consecutive pair of single electron transfer processes as

giving two successive reduction current peaks¹⁹. If $k_2 \gg k_1$, one obtains a single two-electron reduction peak. The second consecutive reaction has a parallel dimerisation process²⁰ as

Usually, the k_d value is far slower than k_2 . If the potential scan rate is slow, there is a finite probability of the formation of the dimer which would undergo an easier electrochemical reduction as

In Figure 4 is shown the effect of scan rate on the cyclic voltammetric response of **1a** at a pH of 3. The electrochemical response for the reaction, (4), is observed, as expected, at low scan rate as a cathodic shoulder because of the finite life for product of **2a**. At faster scan rates the potential needed for **2b** is too quickly reached to allow any scope for (3). Hence, the response of (4) disappears with increased scan rate and the cyclic voltammograms manifest only the reaction, (2), a single 2-electron step.

Figure 4. Cyclic voltammograms of **1a** (6×10^{-5} M) at pH = 3.0 at scan rates of (a) 20, (b) 50, (c) 100, (d) 200 (e) 500, (f) 1000, (g) 2000, (h) 4000 and (i) 5000 mV s^{-1} .

The linearity of the plots of peak current, i_p , vs. $v^{1/2}$, the square root of the scan rate, suggests that the electrochemical reduction in the pH range, 1-6, is diffusion-controlled. The cathodic shift of peak potential, E_p , with increased scan rate also supports the irreversible nature of the electrode reaction. From plots of E_p vs. $\log v$, at different pH values, the transfer coefficients were evaluated. The cyclic voltammograms for **1** in the basic pH range are also shown in Figure 3. One gets an altogether different set of voltammograms showing a sharp and intense peak at ~ -0.7 V. Based on Scheme 2 one expects an electrochemical reduction mechanism characteristic to an azo group in this pH range. It is reported vastly in literature that stilbenes and azobenzenes exhibit reduction processes that are not diffusion controlled but adsorption complicated^{21,22}. The i_p vs. $v^{1/2}$ for the sharp peak at ~ -0.75 V are not linear but those of i_p vs. v are. Figure 5 shows the linear effect of scan rate on the current signal. Based on the plots of E_p vs. pH and coulometry, the electrochemical reduction of **1** in alkaline buffers is proposed as

A consolidated set of electron transfer processes shown in Scheme 3 is proposed for **1** while all their relevant electrochemical data are collected in Table 1.

Figure 5. Effect of scan rate on the peak current of **1a** (6×10^{-5} M) at pH=10.5.

Scheme 3.

Metal coordination of 1

Compounds, **1**, have several coordinating atoms that can bind to metal ions. Differential pulse polarography and electronic spectra have been used to elucidate complexation scheme for **1** with a few bivalent metal ions. The Job's plots give metal to ligand ratio as 1:2 for Cu(II) and Ni(II) and 1:3 for Co(II) ions. The plausible structures are shown in **3**. Detailed characterization of these complexes is underway.

Molecular modeling studies

Molecular modeling studies were done on **1** using CambridgeSoft ChemOffice. The global energy-minimized structure of **1a** is shown in Figure 6. The dihedral angles about 4 relevant bonds are given in Table 1. Torsional energy plots of **1a** over a few dihedrals are presented in Figure 7. It is evident from this figure that the phenol prefers hydrogen bond engagement with the azomethine nitrogen than with the distant hydrazine nitrogen.

Figure 6. Stereographic view of **1a** after global minimization along with the numbering scheme of the atoms.

Table 1. Electrochemical data of **1**.

Compound	pH 6.00					pH 11.00				
	$i_p^{\#}$, μA	E_p , (V)	α_{na}	$D_o \times 10^6$, $\text{cm}^2 \text{s}^{-1}$	$k_h^o \times 10^{10}$, cm s^{-1}	$i_p^{\#}$, μA	E_p , V	α_{na}	$D_o \times 10^6$, $\text{cm}^2 \text{s}^{-1}$	$k_h^o \times 10^{10}$, cm s^{-1}
1a	0.47	1.092	0.72	6.4	3.8	0.19	0.716	0.63	2.1	7.4
1b	0.39	1.106	0.71	6.8	4.7	0.24	0.753	0.65	2.6	9.3
1c	0.45	1.021	0.68	7.5	5.9	0.24	0.730	0.59	3.8	10.0

*# with **1** at $2.75 \times 10^{-5} \text{ M}$ on SMDE of $2.75 \times 10^{-6} \text{ m}^2$ surface area at $v = 100 \text{ mVs}^{-1}$*

The quantum mechanical HOMO-LUMO energy calculations have been used for computing the expected gas-phase electronic transitions. These values are collected in Table 2 along with the experimental spectral data whose trends are in good agreement. The thermodynamic and electrical dipole moment data obtained by modeling are also collected in Table 2 for the conjugate acid-base forms of **1**. It is noteworthy that the standard heats of formation of IH^+ and I^- are lower than that of **1**.

Figure 7. Torsional energy plots (a) over (●)C(8)-C(11), (■) C(14)-N(16), (◆)N(16)-N(17) and (▲) C(18-C(19) bonds from -180 to $+180^\circ$ and (b) double dihedral plot over C(14)-N(15)-N(16) bonds (*c.f.* Figure 6 for numbering scheme for atoms)

Table 2. Molecular modeled thermodynamic, dipole moment, dihedral angle (ϕ) and spectral data of **1**.

System/ Property	1a			1b			1c		
	1H⁺	1	1⁻	1H⁺	1	1⁻	1H⁺	1	1⁻
ΔH_f° , kJ mol ⁻¹	5.01	5.20	0.74	2.16	7.01	1.56	5.01	9.20	3.14
μ (DB)	4.22	1.50	6.57	4.25	1.67	6.93	3.27	0.80	6.59
$\phi_{7-8-11-15}$, deg	13.3	10.0	14.6	13.8	10.5	14.9	12.9	9.3	13.7
$\phi_{15-14-16-17}$, deg	39.9	2.1	4.7	41.9	3.6	5.8	42.9	4.1	5.7
$\phi_{14-16-17-18}$, deg	51.6	0.1	3.3	52.6	0.5	4.2	50.8	0.8	2.9
$\phi_{7-8-11-12}$, deg	15.2	4.3	18.8	18.2	5.5	19.3	16.8	5.1	16.9
$\Delta_{\text{(LUMO-HOMO)}}$, eV	4.10	4.01	2.65	4.41	4.38	2.95	4.39	4.32	2.87
λ_{max} , nm	301.9	308.7	467.1	280.7	282.6	419.6	281.9	286.5	431.3
λ_{max}^* , nm	327.8	328.0	372.1	320.3	319.0	368.4	323.4	324.5	371.2

ΔH_f° are MM2-wise energy-minimized standard heats of formation; $\phi_{a-b-c-d}$ is angle between abc and bcd planes of the contiguous a-b-c-d atomic chain; λ_{max}^* are experimental values (mostly from Table 3).

Table 3. Spectral and thermodynamic data[#] of **1**.

Compound	λ_{const} (ε)	λ_{low} (ε)	λ_{high} (ε)	λ_{iso} (ε)	pK _a	K _a × 10 ⁹	ΔG°
1a	301.0	328.0	372.1	347.0	8.6	2.512	49.10
	(80263)	(77632)	(57895)	(40790)			
1b	298.4	319.0	368.4	345.3	8.4	3.981	47.96
	(78290)	(75000)	(55921)	(39399)			
1c	296.7	324.5	371.2	349.6	8.3	5.012	47.39
	(76974)	(73026)	(54606)	(38472)			

[#] λ in nm; ϵ (in lt mol⁻¹ cm⁻¹); K_a and ΔG° (in kJ mol⁻¹) are for the process, $1 \rightarrow 1^-$; λ_{const} is unchanging high energy wavelength while λ_{low} and λ_{high} are wave lengths below and above the isosbestic wave length, λ_{iso} , respectively.

Photometric and voltammetric assaying of 1

The spectral and cyclic voltammetric features of **1** suggest photometric and/or voltammetric analysis of **1**. In Figure 8 is shown a typical medium range calibration plot obtained for **1a**.

Figure 8. Differential pulse polarographic calibration plot of **1a** in neutral buffers (pH = 6.5) on SMDE ($6.25 \times 10^{-6} \text{ m}^2$) at 5 mVs^{-1} and a pulse height of 50 mV with KCl (0.05 M).

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