Solution chemistry of vanadium-(IV) and -(V) with the bidentate ligand 1,2-dimethyl-3-hydroxy-4(1*H*)-pyridinone: relevance to the treatment of diabetes

Paul D. Taylor

Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, UK CO4 3SQ

1,2-Dimethyl-3-hydroxy-4(1*H*)-pyridinone (HL) forms an unusually wide range of oxo, hydroxy and non-oxo complexes with vanadium(IV) and vanadium(V) in aqueous solution; the tris non-oxo vanadium(IV) complex $[V^{IV}L_3]^+$ is the first such monocationic complex to be studied in aqueous solution and the monocationic tris hydroxyvanadium(V) complex $[V^{V}(OH)L_3]^+$ is the first such species to be reported; the neutral bis complex $[V^{V}(O)(OH)L_2]$ is of physiological significance in the treatment of diabetes.

While recent clinical studies in the treatment of diabetes with orally administered vanadyl sulfate or sodium metavanadate have given promising results,[1,2] recently reviewed,[3] specific vanadium complexes offer greater control of oral absorption.[4,5] The chelator 1,2-dimethyl-3-hydroxy-4(1*H*)-pyridinone HL, currently used in the treatment of iron-overload[6] under the name deferiprone, may also enhance absorption of orally administered vanadium. The species present in aqueous solution affect the oral activity of these complexes and are the subject of this study. Analysis of this speciation, from spectrophotometric equilibrium data, introduces a new computer program called STABOPT (ver. 1.3),[7] for the Microsoft Windows® environment, which optimizes stability constants by global non-linear regression analysis of multi-condition and multi-wavelength (MCAW) data or potentiometric data.

Due to its exceptional affinity for metal ions in high oxidation state, HL can displace oxo groups on both V^{IV} and V^{V}. Non-oxo vanadium complexes with other chelate ligands,[8,9,10] such as catechol, are intensely blue at concentrations at which oxo complexes are virtually colourless {*e.g.* for $[V^{IV}O(cat)_2]^{2-} \rightarrow [V^{IV}(cat)_3]^{2-}$, the molar absorptivity changes from 70 to 8500 $dm^3\ mol^{-1}\ cm^{-1}$ at 650 nm}. Chelate HL follows this pattern and four distinct, intensely coloured, complexes (**1d**, **1g–i**) have been detected. Non-linear regression analysis of MCAW equilibrium spectrophotometric data by STABOPT is shown in Fig. 1. The stoichiometry and optimized stability constants of the species are summarized in Table 1, the visible spectra are shown in Fig. 2.

Three molecules of the monoanion L^- are bound in the monocationic vanadium(IV) complex $[V^{IV}L_3]^+$ **1d**. The tendency for such cationic complexes to hydrolyse into hydroxy or oxo complexes is evidenced by the instability in water of $[V^{IV}(acac)_3]^+$ (acac = acetylacetonate), the only other cationic tris non-oxo complex to be reported.[13,14] The displacement of an oxo group by HL involves the loss of one proton from the ligand and the consumption of two protons by the oxo group to form water. This net uptake of one proton makes the reaction increasingly favourable as pH decreases. The formation of the oxo mono and bis complexes $[V^{IV}OL]^+$ and $[V^{IV}OL_2]$, from which the tris complex is formed, becomes *less* favourable as pH decreases, hence (for both V^{IV} and V^{V}) the tris non-oxo complex is formed only over a narrow, acidic, pH range. The lower affinity for vanadyl of related bidentate chelators,[15] 3-hydroxy-2(1*H*)-pyridinone (log K_1 = 8.79); 3-hydroxy-2-methyl-4(1*H*)-pyrone (maltol, log K_1 = 8.3); 5-hydroxy-2-hydroxymethyl-4-pyrone (kojic acid, log K_1 = 7.3) compared to HL (log K_1 = 11.75) means that much higher concentrations of ligand, in some cases higher than the ligand solubility in water, will be required to form the corresponding tris non-oxo complexes.

Colourless solutions of the oxovanadium(IV) complexes **1a–c** at pH 4.0, oxidized completely in air to the violet-blue $[V^{V}(O)(OH)L_2]$ species **1g** over a period of 5 h. Spectrophotometric titrations of V^{V} with HL at pH 2–5.5 indicate ionisation analagous to that of hydroxobis(8-quinolinato)oxovanadium(V),[16] a violet complex which is only sparingly soluble in water. Thus, the violet-blue colour of **1g** disappears at higher pH (**1g** $\rightleftharpoons$ **1f** + H^+, pK_a 5.4) and a green-blue complex **1h** is formed at lower pH (**1h** $\rightleftharpoons$ **1g** + H^+, pK_a 2.7). EPR spectra of these vanadium(V) solutions show traces of the vanadium(IV) complexes **1c** and **1d**, indicating that an internal redox reaction occurs. Since, as described above, the vanadium(IV) complexes are oxidized by air, a steady-state redox cycle is established with a low, constant concentration of V^{IV} determined by the pH and ligand concentration. The same amplitude EPR spectra can also

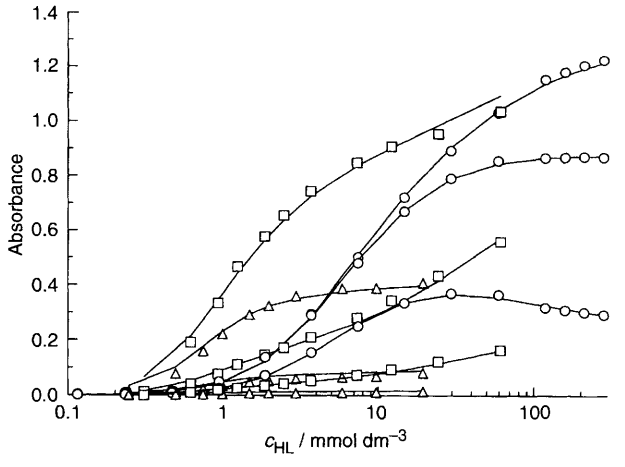
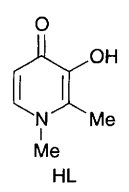


Fig. 1 Spectrophotometric titrations of 2.845×10^{-4} mol dm^{-3} V^{V} with HL at pH 2.07 (○), 4.162 (□), 5.522 (△) and at 560, 740 and 840 nm. The solid lines are simulated from parameters (Table 1) globally optimized with STABOPT from the entire nine-segment, multi-condition, multi-wavelength data set.



HL

Table 1 Logarithm of overall formation constants (25 °C, 0.5 mol dm^{-3} KCl) from the defined components (M = metal ion, L = chelator, H = proton) and molar absorptivity (optimized with STABOPT,[7] standard errors are in parentheses). Absorbance maxima and colour are also shown. The almost colourless vanadyl complexes **1a–c** were characterized by automated, simultaneous potentiometric/UV spectrophotometric titration (data not shown). Remaining complexes were characterized in half neutralized, 0.1 mol dm^{-3} buffer + 0.45 mol dm^{-3} KCl (pH 4.162, 5.522) or 0.01 mol dm^{-3} HCl + 0.49 mol dm^{-3} KCl (pH 2.07) to maintain constant ionic strength

	Component or complex	M	L	H	log β	ε/dm^3 mol^{-1} cm^{-1} [λ/nm]	λ_{max} /nm	Colour
	$[V^{IV}O]^{2+}$	1	0	0	0[a]			
	$[V^{IV}O(OH)]^{+}$	1	0	−1	−5.44[b]			
	$[L]^{-}$	0	1	0	—			
	[HL]	0	1	1	9.57			
	$[HL_2]^{+}$	0	1	2	13.22			
1a	$[V^{IV}OL]^{+}$	1	1	0	11.75 (0.02)	4,222 (25) [305]	288	
1b	$[V^{IV}O(OH)L]$	1	1	−1	6.65 (0.03)	5,718 (35) [305]		
1c	$[V^{IV}OL_2]$	1	2	0	22.01 (0.02)	10,330 (20) [305]	292	
1d	$[V^{IV}L_3]^{+}$	1	3	2	36.92 (0.04)	5,327 (96) [560]	526	royal blue
	$[V^{V}O_2]^{+}$	1	0	0	0[a]			
	$[V^{V}_pO_qH_r]^{+5p-2q+r}$	p	0	$r - 2q + 4p$	—[c]			
1e	$[V^{V}O_2L]$	1	1	0	11.9 (0.1)			
1f	$[V^{V}O_2L_2]^{-}$	1	2	0	19.2 (0.1)			
1g	$[V^{V}O(OH)L_2]$	1	2	1	24.6 (0.1)	3,257 (490) [560]	540	violet-blue
1h	$[V^{V}(OH)_2L_2]^{+}$	1	2	2	27.3 (0.2)	3,040 (88) [560]	638	green-blue
1i	$[V^{V}(OH)L_3]^{+}$	1	3	3	39.8 (0.2)	4,519 (212) [560]	619	royal blue

[a] Oxometal ions are defined as components rather than naked V^{4+} and V^{5+}. The log β of VO_2^{+} from V^{5+} adds a further 28.7.[11] [b] Ref. 12. [c] Thirteen mono and isopolyanions $[V^{V}_pO_qH_r]^{+5p-2q+r}$ were included in the model.[11]

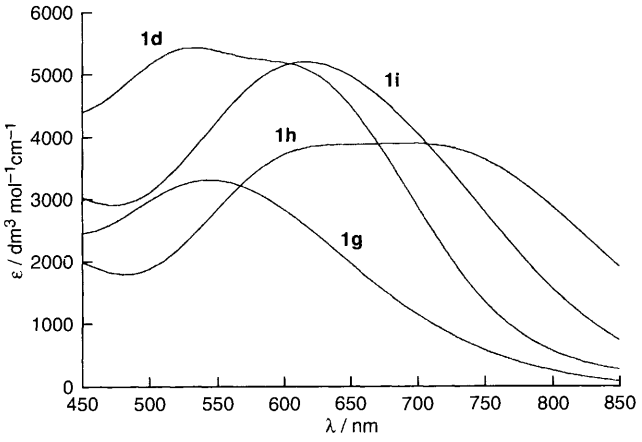


Fig. 2 Molar absorptivities of the four coloured complexes **1d** and **1g–i**. Full spectra of **1g–i** were reconstructed from regression analysis with STABOPT of the principal components obtained by factor analysis of the full spectra data.

be achieved starting from 100% vanadium(IV), under otherwise identical conditions, after several hours of exposure to air.

A royal blue complex with ligand stoichiometry >2 was formed from bis complexes **1g** or **1h** as ligand concentration increased at fixed pH. Global non-linear regression analysis of MCAW data was consistent with formation of the tris hydroxyvanadium(V) monocation $[V^{V}(OH)L_3]^{+}$ **1i**, rather than the dication $[VL_3]^{2+}$. While a seven-coordinate complex cannot be ruled out, a reasonable six-coordinate structure for the tris complex **1i** has two molecules of L^{-} coordinating *via* both oxygen atoms, a third molecule coordinating *via* a single oxygen, and the sixth site occupied by OH.

Chemical robustness, high affinity for metal ions, and high solubility of the complexes all contribute to making HL an ideal ligand for exemplifying the solution behaviour of unusual vanadium complexes. This is an area which has been largely overlooked in the existing literature which is mainly concerned with solid-phase work. A detailed description of solution chemistry is now essential in understanding the oral uptake and biological activity of the vanadium complexes of HL and related ligands. In the gastrointestinal tract, over the pH range 3–6, vanadium(IV) complexes **1a–d** would be oxidised to the neutral $[V^{V}(O)(OH)L_2]$ species **1g** which is potentially bio-available *via* passive membrane diffusion, in the manner proposed for the neutral bis(maltolato) oxovanadium(IV) species.[5]

I am grateful to Dr Dimitri Svistunenko for acquiring the EPR spectra and to Dr Gary Tilbrook for a sample of HL.

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Received, 29th September 1995; Com. 5/06431G