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Structures and Stabilities of Tungstate Complexes of α-Hydroxy Acids. ^{183}W NMR Study of the Influence of Ligand Substitution

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α-Hydroxy acids ($H_2L = R^1R^2C(OH)COOH$) react with tungstate ions in aqueous acidic solution to form mononuclear complexes $[WO_2L_2]^{2-}$ and 2:2 species that may be either mononuclear bis chelates (the tartrate compound) or dinuclear complexes (the isocitrate and mandelate compounds). Ligands with $R^1 \neq R^2$ afford a pair of 1:2 diastereoisomers. The formation constants of the colorless complexes were determined by indirect photometry, using a ligand−ligand exchange reaction. The stabilities of the 1:2 complexes depend on the nature of the substituents R^1 and R^2, whereas the acidity constants of the ligands are practically identical. Further structural characterization was achieved using ^{13}C and ^{183}W NMR data. All ligands chelate tungstate through the C(OH)−COOH system. The dinuclear 2:2 complexes are characterized by a single tungsten signal with δ_W close to −120 ppm. In the 1:2 complexes, substitution of the ligand by alkyl groups has a large shielding effect on the chemical shift of the tungsten nucleus (δ_W +81.2 to −13.9 ppm), which is correlated with the magnitude of the formation constant (log K_{122} 16.85 to 18.75).

Introduction

It was recently discovered that, in living organisms, tungsten competes with molybdenum for the binding site of molybdoenzymes[1] and is present in microbial enzymes like the formate dehydrogenase from *Clostridium thermoaceticum*.[2,3] This finding warrants a renewed interest in the reactions of this element with ligands of biological origin relevant to the field of bioinorganic chemistry. Monomeric chelates of tungsten(VI) with diols were also found to possess useful catalytic activity.[4,5]

We recently extended our studies of the tungstate complexes of carbohydrates[6−9] to acidic ligands derived from sugars, like gluconic acid, which were found effective in the chromatographic separation of tungsten and molybdenum, together with glycolic, malic, and citric acids.[10] They all possess one hydroxyl group in position α to a carboxyl group, and possibly other hydroxyl and carboxyl groups (Figure 1). These ligands appear to form a large variety of complexes, using several possible sites of chelation in which the donating oxygen atoms may belong to either hydroxyl or carboxylic groups.[11,12] Their complexes are generally poorly known, except those of citric acid that were recently studied by potentiometry[13] and crystallography.[14,15] The dinuclear tungstate complexes formed with polyols, which cannot involve carboxyl groups, were characterized by ^{183}W NMR spectroscopy[7−9] and are now fairly well-known. Thus we inferred that a preliminary study by the same technique of a series of α-hydroxy acids ($H_2L = R^1R^2C(OH)$-COOH), in which the site of chelation involves only two vicinal hydroxyl and carboxyl groups, would help to simplify the further identification of mixtures of complexes formed with acids related to carbohydrates.

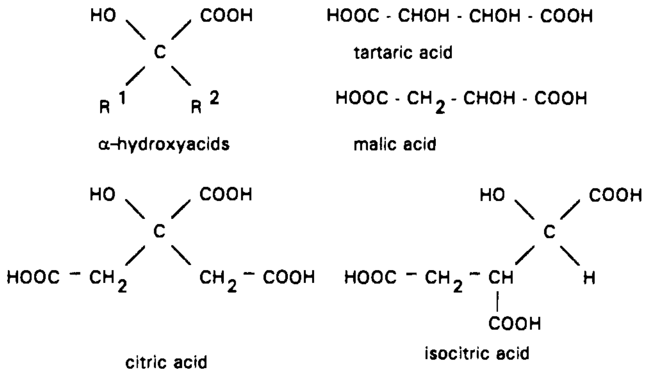

Figure 1. Formulas of the α-hydroxy acids considered in this work: $R^1 = R^2 = H$, glycolic acid; $R^1 = CH_3$, $R^2 = H$, lactic acid; $R^1 = C_2H_5$, $R^2 = H$, 2-hydroxybutanoic acid (HBA); $R^1 = C_6H_5$, $R^2 = H$, mandelic acid; $R^1 = R^2 = CH_3$, 2-hydroxy-2-methylpropanoic acid (HIBA, hydroxyisobutyric acid). In this work, DL acids were used, except for L-lactic acid.

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The relevant chemistry of the corresponding vanadate complexes of α-hydroxy acids[16] and monosaccharides[17] has been reviewed in relation to the biological significance of vanadium,[18] but tungstate complexes are more generally compared with the corresponding molybdate complexes, which are often isostructural.[19a] It is in particular the case for the complexes of α-hydroxy acids, for which (although earlier literature reports many conflicting results on the stoichiometries) it is now recognized that the major complexes of both elements are 1:2 species.[20,21] The structures of the complexed ligands have been investigated by ^{13}C NMR spectroscopy.[21,22] In contrast with studies made on vanadate complexes, the equilibrium constants were seldom determined, with the noticeable exception of a recent potentiometric study[23] of the molybdate and tungstate complexes of lactic acid at pH 2−6. The major species were found to be the (1,2,2) chelates, formulated as $[MO_2L_2]^{2-}$ with M = Mo or W and $L^{2-} = CH_3-CH(O^-)-CO_2^-$. The purpose of this work was to obtain a consistent larger set of data for the stability of a series of tungstate complexes of related structures, in relation to the NMR chemical shifts of the ^{13}C and ^{183}W nuclei.

Experimental Section

All chemicals were commercial products of the purest commercial available grade and were used as received. Water was deionized in a Millipore apparatus.

For indirect photometry, the pH measurements were made at 25.0 °C using a Metrohm 632 pH-meter equipped with a combined glass electrode, standardized with commercial buffers of pH 4.00 and 7.00. No attempts were made to exclude carbon dioxide from the solutions, because the solutions were acidic (0.1 M sodium acetate buffers, pH 4.7 ± 0.7 adjusted with concentrated HCl). Acetate was chosen because it does not complex tungstate and does not interfere in the competing complexation reactions. The pK_a of the hydroxy acids were determined by classical titration with commercial standard solutions of sodium hydroxide.

The solutions of the sacrificial tungstate−dihydroxyquinone complex had equal initial concentrations of tungstate and ligand, $c_W = c_D = 6 \times 10^{-5}$ M. They were prepared by mixing in acetate buffer 1.50 cm^3 of stock solutions, both 4×10^{-3} M in disodium tungstate and dihydroxyquinone. Then aliquots ($V = 0.1-0.2$ cm^3) of a solution of the hydroxy acids (c = 5 or 10 g·L^{-1}) were added using a Gilson micropipet (total volume 0.2 cm^3).

UV−visible spectra were measured using a Perkin-Elmer Lambda 2 spectrophotometer. The temperature was fixed at 25.0 °C with a Lauda cryostat. The absorbance readings were made at λ = 320 nm, using quartz cells of optical path length l = 1.00 cm. The solutions were allowed to reach equilibrium during 5 min before reading of the absorbance.

The calculations of the formation constants of the complexes were performed with a microcomputer, using a laboratory-made routine written in QBasic, from a point-by-point analysis of the variations of absorbance vs the concentration of ligand c_L. The absorbances for the undissociated and the fully dissociated sacrificial complex, respectively A_2 and A_1, were measured at different acidities in independent experiments, using pure dihydroxyquinone for A_1 and an excess of tungstate for A_2. In the dissociation experiments, the concentrations of (x,y,z), free tungstate, and hydroxy acid were obtained as explained later in the text. For each run, 12 points at least were processed, corresponding to 10−70% dissociation of the sacrificial complex. The conditional formation constant K'_{xyz} was calculated by applying the law of mass action and assuming various integer values for x and y until a constant value was found. The results were rejected when there was a systematic variation of log K'_{xyz} with c_L or when individual values of log K'_{xyz} differed from the mean value by more than 1%. For the final refinement of the results, once the values of x and y were known, the values of A_1 and A_2 were adjusted (±0.03) until all individual values of log K'_{xyz} were within 0.2% of the calculated mean value. The values of z and log K_{xyz} were determined from the slope and intercept of a plot of log K'_{xyz} vs pH.

NMR spectra were obtained at 24 °C, using a Bruker ARX-400 spectrometer equipped with 5- and 10-mm multinuclear probes. Frequencies were respectively 100.62 and 16.65 MHz for the ^{13}C and ^{183}W nuclei. The references were respectively an aqueous solution of sodium 2,2,3,3-tetradeuterio-3-(dimethylsilyl)propionate (TMSP) and a 2 M solution of disodium tungstate in alkaline deuterium oxide. Experimental details for the recording of the ^{13}C spectra were described elsewhere.[7−9]

^{183}W NMR spectra were obtained using a sweeping range of 10 kHz, an acquisition time of 1 s, a relaxation delay of 1 s, and a digital resolution of 0.5 Hz/pt. The pulse width was 45 μs, corresponding to a 90° tip angle. Six left shifts were applied to the free induction decay before Fourier transform to minimize effects of probe acoustic ringing on the baseline. The sample concentrations were 2 M (disodium tungstate) and 1 M (hydroxy acid) in water containing deuterium hydroxide (10% v/v). The pH was adjusted by stepwise addition of concentrated HCl and was measured in the NMR tube with a Radiometer MI-412 combined micro glass electrode (external diameter 2 mm) and a Metrohm 632 pH-meter, calibrated as above. The samples were kept in stoppered NMR tubes and thus protected from atmospheric carbon dioxide.

Results

Formation Constants. Using the usual conventions, the complex formed between x tungstate ion(s), y ligand molecules, and z protons is written (x,y,z). In such equations, it is common practice in analytical chemistry to write the ligand in its fully deprotonated form. However, the pK_a value of the alcoholic hydroxyl group of α-hydroxy acids ($H_2L = R^1R^2C(OH)COOH$) is higher than 12, so that only the carboxylic group may ionize in aqueous solutions. Thus, in this paper, the deprotonated ligands are considered to be the carboxylate anions ($HL^- = R^1R^2C(OH)COO^-$) bearing an un-ionized hydroxyl group. The formation of a single complex (x,y,z) of tungstate ion(s), ligands in HL$^-$ form, and protons may be written as the general equation

$$x\mathrm{WO_4}^{2-} + y\mathrm{HL}^- + z\mathrm{H}^+ \rightleftharpoons (x,y,z)^{(2x+y-z)-} + n\mathrm{H_2O} \quad (1)$$

The formation constant K_{xyz} of the complex is defined as the equilibrium constant

$$K_{xyz} = [(x,y,z)][\mathrm{WO_4}^{2-}]^{-x}[\mathrm{HL}^-]^{-y}[\mathrm{H}^+]^{-z} \quad (2)$$

In a buffered solution of constant pH, one may define the conditional formation constant K'_{xyz} (which depends on the pH) by introducing the constant proton concentration into the formation constant and by replacing the concentration of the prevailing form of the ligand by the analytical concentration c_L of the ligand:

$$K'_{xyz} = [(x,y,z)][\mathrm{WO_4}^{2-}]^{-x}c_L^{\ -y} \quad (3)$$

The formation constants of all the complexes formed in a given system may be obtained by potentiometry, as was performed for lactic acid,[23] but the procedure is time-consuming. A spectrophotometric method would be faster but does not seem

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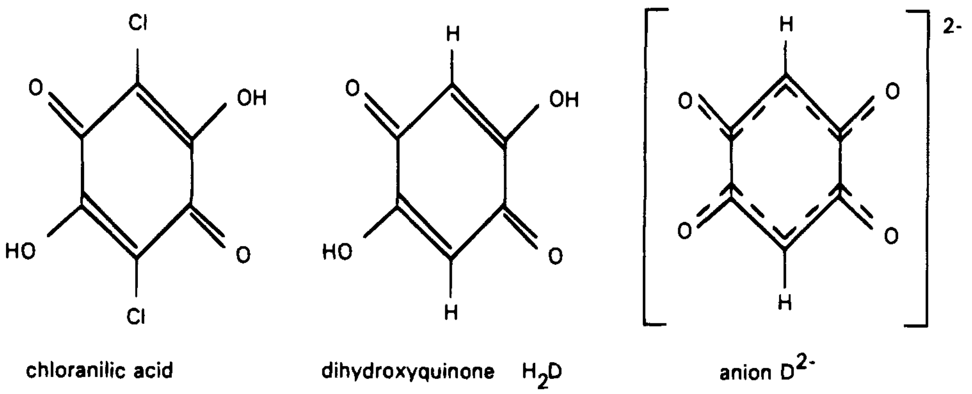

Figure 2. Structures of the auxiliary ligands used in ligand–ligand exchange reactions for the determination of the formation constants by indirect photometry.

suitable in the present case because the reagents and the complexes do not possess characteristic absorption bands in their electronic spectra. Therefore we used the photometric method in the indirect mode based on ligand–ligand displacement.[24–26] Basically, a single absorbing complex of low stability is prepared from tungstate and a suitable auxiliary ligand. This complex is dissociated when the ligand under study is introduced in the medium and reacts with tungstate, releasing the free auxiliary ligand. The overall ligand-exchange reaction produces large variations in the spectra that permit the calculation of the concentrations at equilibrium. Finally, knowing the formation constant of the sacrificial complex, one can obtain the unknown formation constant of the final complex.

With respect to potentiometry, indirect photometry presents some interesting features. First of all, it affords a second method based on a different principle, which allows an independent check of the results. Moreover, the effect of the self-condensation of tungstate[27] is minimized, because the monomeric tungstate ion participates in two complex-forming reactions and is present in uncomplexed form in a very low amount. Finally, when a single complex predominates, the treatment of data is much faster. Besides, the absence of mixed-ligand complexes must be verified by checking that the absorbance after complete dissociation of the sacrificial complex is equal to that of the free auxiliary ligand at the same pH.

In previous studies of molybdate complexes of carbohydrates, we used the 1:1 molybdate complex of chloranilic acid (3,6-dichloro-2,5-dihydroxy-1,4-benzoquinone, Figure 2) as the sacrificial species.[28] Unfortunately, this auxiliary ligand was unsuitable for use with tungstate, with which it forms a mixture of 1:1 and 1:2 complexes.[29] This is why we chose 2,5-dihydroxy-1,4-benzoquinone (DHQ = H_2D, Figure 2) which was shown[30] to form a single tungstate complex $(1,1,2)^{2-}$ in the pH range 3.5–6:

$$WO_4^{2-} + D^{2-} + 2H^+ \rightleftharpoons (1,1,2)^{2-} + 2H_2O \qquad (4)$$

A protonated complex $(1,1,3)^-$ is formed at pH < 3.20 and was not considered in this work. D^{2-} represents the anion of DHQ (Figure 2), in which the charges are highly delocalized. The thermodynamic formation constant of the (1,1,2) complex is

$$K_{112} = [(1,1,2)^{2-}][WO_4^{2-}]^{-1}[D^{2-}]^{-1}[H^+]^{-2} \qquad (5)$$

Experimentally, we determined the conditional formation constant K'_{112} by introducing the analytical concentration of DHQ, c_D, instead of the concentration of its dianion $[D^{2-}]$:

$$K'_{112} = [(1,1,2)^{2-}][WO_4^{2-}]^{-1}(c_D)^{-1} \qquad (6)$$

In a buffered solution, K'_{112} includes a term due to the constant concentration of protons. The value of the corresponding formation constant K_{112} is determined as follows. Knowing the acidity constants[30] for the HD^-/D^{2-} couple, pK_a = 4.87, and for the H_2D/HD^- couple, pK_a = 2.95, one may neglect the formation of H_2D in the considered pH range (4–5.5) and may write the analytical concentration of DHQ:

$$c_D = [D^{2-}] + [HD^-] = [D^{2-}](1 + ([H^+]/K_a) \qquad (7)$$

$$K_{112} = [(1,1,2)^{2-}][WO_4^{2-}]^{-1}[H^+]^{-2}(c_D)^{-1}(1 + ([H^+]/K_a) \qquad (8)$$

At pH $\gg$ 5, $[H^+]/K_a \ll 1$ and the free ligand is mainly in D^{2-} form ($c_D \approx [D^{2-}]$):

$$K_{112} = [(1,1,2)^{2-}][WO_4^{2-}]^{-1}[H^+]^{-2}(c_D)^{-1} = K'_{112}[H^+]^{-2} \qquad (9)$$

In logarithmic form, (9) becomes

$$\log K_{112} = \log K'_{112} + 2\,\text{pH} \qquad (10)$$

At pH $\ll$ 5, $[H^+]/K_a \gg 1$ and the free ligand is mainly present as the HD^- ion:

$$c_D = [HD^-] \approx [D^{2-}][H^+]/K_a \qquad (11)$$

The conditional formation constant is obtained from (8):

$$K_{112} = K'_{112}(K_a)^{-1}[H^+]^{-1} \qquad (12)$$

In logarithmic form, (12) becomes

$$\log K_{112} = \log K'_{112} + \text{p}K_a + \text{pH} \qquad (13)$$

We found log K_{112} = 15.98 ± 0.14, in agreement with the value given in a previous report, log K_{112} = 15.47.[30]

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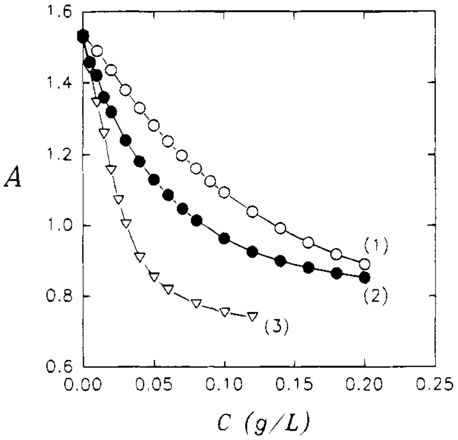

Figure 3. Plots of the variations of absorbance A (λ, 320 nm; l, 1 cm) of a solution of sacrificial complex (c, 6 10^{-5} M, pH 4.6) vs the concentration of ligands c_L: (1) glycolic acid; (2) HBA, 2-hydroxybutanoic acid; (3) HIBA, hydroxyisobutyric acid.

Initially, we defined the conditions which allow the largest dissociation of the sacrificial complex by addition of the α-hydroxy acids. The wavelength of maximal difference in absorbance between the uncomplexed dihydroxyquinone (mainly in D^{2-} form) and the complex is $\lambda = 320$ nm. The analytical concentrations of tungstate and dihydroxyquinone, $c_W = c_D = 6 \times 10^{-5}$ M, were fixed so that the initial absorbance was close to 1.6 and the final absorbance was 0.7 at pH 4.7, using cells of optical path length $l = 1$ cm. The final A_1 and initial A_2 absorbances, corresponding respectively to 100 and 0% dissociation of the dihydroxyquinone complex, depended on the acidity of the medium, and we independently recorded their variations with pH in preliminary experiments. In most experiments, the addition of hydroxy acid was continued until at least 70% dissociation of the sacrificial complex.

The experimental data are processed as a plot of the absorbance *versus* the analytical concentration c_L of the α-hydroxy acid (Figure 3). Each experimental value yields the concentrations of free and complexed DHQ:

$$[(1,1,2)^{2-}] = c_D(A - A_1)/(A_2 - A_1) \qquad (14)$$

$$[D^{2-}] = c_D(A_2 - A)/(A_2 - A_1) \qquad (15)$$

These give the concentration of free tungstate by use of relation (5):

$$[WO_4^{2-}] = [(1,1,2)^{2-}][H^+]^{-2}[D^{2-}]^{-1}(K_{112})^{-1} \qquad (16)$$

Then the concentration of the complex (x,y,z) is obtained from a mass-balance equation, using the total concentration of tungstate c_W:

$$x[(x,y,z)] = c_W - [(1,1,2)^{2-}] - [WO_4^{2-}] \qquad (17)$$

The concentration of free ligand (as the sum of its various protonated forms) is obtained from another mass-balance equation:

$$c_L\,(\text{free}) = c_L - y[(x,y,z)] \qquad (18)$$

First, the method was validated by studying the known $(2,1,2)^{2-}$ complex of D-glucitol, for which we obtained a formation constant (log $K_{212} = 19.50 \pm 0.20$) close to that determined by potentiometry (log $K_{212} = 19.15 \pm 0.20$).[6] The uncertainty was estimated from the standard deviation of the linear regression made on the plot of the variations of the conditional formation constant log K'_{212} vs pH. We also determined the formation constant of the $(1,2,2)^{2-}$ complex of lactic acid that was comparable to that determined by potentiometry by Cruywagen et al.[23] It may be concluded that the proposed method yields results in excellent agreement with those reported in literature and may be applied with confidence to unknown systems. The results for a series of α-hydroxy acids are displayed in Table 1. Like lactic acid, most of them were found to form a single complex of stoichiometry W:L = 1:2. The pH dependence of the conditional formation constant indicated that two protons were necessary for the formation of the complex from one tungstate ion and two monoprotonated ligands HL^-. The complex-forming equilibrium (19) is obtained from relation (1):

$$WO_4^{2-} + 2HL^- + 2H^+ \rightleftharpoons [WO_2L_2]^{2-} + 2H_2O \qquad (19)$$

where $HL^- = R^1R^2C(OH){-}COO^-$ and $L^{2-} = R^1R^2C(O^-){-}COO^-$.

Two acids give major complexes of dimeric nature. The complex of tartaric acid H_4L has a 2:2:4 stoichiometry. Since the NMR data presented below prove that both tungsten atoms are surrounded by two chelating sites in the $CH(O^-){-}COO^-$ state and are not bridged, the ligand is in fully deprotonated form L^{4-} in the complex. Therefore, in the pH range 4.3–5, the formation equilibrium is

$$2WO_4^{2-} + 2H_2L^{2-} + 4H^+ \rightleftharpoons [(WO_2)_2L_2]^{4-} + 4H_2O \qquad (20)$$

The complex of isocitric acid H_4L also appears to possess a 2:2 stoichiometry, but its composition is (2,2,2). In the pH range 4.3–5, the reaction is formulated as

$$2WO_4^{2-} + 2H_2L^{2-} + 2H^+ \rightleftharpoons [(WO_2)_2O_2(HL)_2]^{6-} + 2H_2O \qquad (21)$$

Contrary to those for the tartrate complex, NMR data discussed below indicate that the tungsten atoms are presumably bridged. Considering the pK_a values given in Table 1, the free ligand is $H_2L^{2-} = {}^-OOC{-}CHOH{-}CH(COO^-){-}CH_2{-}COOH$, and in the complex, the chelating species is $HL^{3-} = {}^-OOC{-}CH(O^-){-}CH(COO^-){-}CH_2{-}COOH$.

Isocitric acid might have been expected to chelate tungstate by using its $CH_2{-}COOH$ arm. In order to check this hypothesis, we examined the reactions of tungstate with 3-hydroxybutanoic acid and butanedioic acid (succinic acid). Both were unable to dissociate the tungstate–DHQ complex in significant proportion and did not give rise to specific ^{13}C NMR signals, showing very weak complexing ability, if any, in agreement with results of a previous chromatographic study.[10] This indicates that, in all compounds, the likely site of chelation is always the C(OH)COOH system, even in the presence of additional hydroxyl or carboxyl groups β to the carboxyl group.

NMR Spectroscopy. The ^{13}C NMR spectra of aqueous solutions of the complexes show signals due to the free and complexed ligands. When the ligand is chelated, the carbon atoms of the COOH and C(OH) groups are deshielded and the variations of chemical shifts due to chelation, $\Delta\delta$, are defined as the coordination-induced shifts (CIS). In agreement with Gil et al.,[21] the $\Delta\delta$ values are close to 12 (C(OH)) and 5 ppm (COOH) for all complexes except that of tartrate (Table 2). For all other carbon atoms, the $\Delta\delta$ values are smaller than 2 ppm, confirming that the site of chelation only involves the $C(O^-){-}COO^-$ system.

Table 1. Acidity Constants of the α-Hydroxy Acids, Formation Constants of Their Major Tungstate Complexes, and 16.65-MHz ^{183}W NMR Chemical Shifts[a]

R^1	R^2	(x,y,z)	pK_a[b]	$\log K_{xyz}$[c]	δ_W, ppm (proportions)
H	H	(1,2,2)	3.90	16.85(±0.14)	81.2
				(15.7[d])	
CH_3	H	(1,2,2)	3.80	18.15(±0.14)	26.6 (75%)
		(1,2,2)		(17.47[e])	38.6 (25%)
CH_3-CH_2	H	(1,2,2)	3.80	18.25(±0.14)	31.8 (50%)
		(1,2,2)			38.3 (50%)
C_6H_5	H	(1,2,2)	3.50	18.15(±0.14)	34.8 (20%)
		(1,2,2)			41.8 (25%)
		(2,2,2)		ND	−120.4 (55%)
CH_3	CH_3	(1,2,2)	4.05	18.75(±0.14)	−13.9
CHOH−COOH	H	(2,2,4)	3.25	33.55(±0.25)	33.5
			4.25		
CH(COOH)−CH_2−COOH	H	(2,2,2)	3.05	25.7(±0.18)	−120.1
			4.30		
			5.75[f]		

[a] All NMR measurements were made at pH 4.8. ND: not determined. [b] Acidity constants determined by titration with sodium hydroxide; NaCl 0.10 M; 25 °C. [c] Formation constants, by indirect photometry; mean value for a pair of 1:2 isomers (acetate buffer 0.1 M; 25 °C). The uncertainty (standard error on triplicate runs) is given in parentheses. [d] Reference 21 (by NMR; NaCl 1.0 M). [e] Reference 23 (by potentiometry; NaCl 1.0 M). [f] Reference 35.

Table 2. 100.62-MHz ^{13}C NMR Chemical Shifts (δ, ppm) and Direct Coupling Constants $^1J_{C,H}$ (Hz) for the Tungstate Complexes of α-Hydroxy Acids[a]

	glycolic		tartaric	
	C-1	C-2	C-1/4	C-2/3
δ/*J*, u	182.6	63.9/143.3	176.0	73.4/143.0
δ/*J*, c	187.1	75.7/147.1	185.0	88.3/146.6
Δδ/Δ*J*	4.5	11.8/3.8	9.0	14.9/3.6

	lactic		
	C-1	C-2	C-3
δ/*J*, u	184.6	70.4/145.4	20.8/129.0
C_1 δ/*J*, c	189.3	81.5/145.2	22.4/127.9
Δδ/Δ*J*	4.7	11.1/−0.2	1.6/−1.1
C_2 δ/*J*, c	189.2	82.1/142.0	21.9/128.0
Δδ/Δ*J*	4.6	11.7/−3.4	1.1/−1.0

	2-HBA[b]			
	C-1	C-2	C-3	C-4
δ/*J*, u	183.5	75.4/144.0	29.1/127.1	10.7/126.0
C_1 δ/*J*, c	188.2	86.0/148.4	29.4/128.4	10.5/126.5
Δδ/Δ*J*	4.7	10.6/4.4	0.3/1.3	−0.2/0.5
C_2 δ/*J*, c	187.9	87.4/145.5	29.5/127.1	11.4/126.0
Δδ/Δ*J*	4.4	12.0/1.5	0.4/0.0	0.7/0.0

	HIBA[b]			
	C-1	C-2	C-3	C-3′
δ/*J*, u	185.6	75.4	28.6/128.4	28.6/128.4
δ/*J*, c	190.4	87.3	27.4/127.7	28.3/127.7
Δδ/Δ*J*	4.8	11.9	−1.2/−0.7	-0.3/−0.7

	mandelic[c]					
	C-1	C-2	C-1′	C-2′/6′	C-3′/5′	C-4′
C_1 δ/*J*, c	185.7	86.7/149	141.5	130.2	128.3	129.2
C_2 δ/*J*, c	185.5	87.0/150	141.3	130.2	128.3	129.2
C_3 δ/*J*, c	185.5	87.7/145	141.8	130.2	128.3	129.2

[a] All measurements were made at pH 4.8. u: uncomplexed. c: complexed. Accuracy: δ, ±0.1 ppm; $^1J_{C,H}$, ±1 Hz. [b] 2-HBA is 2-hydroxybutanoic acid. HIBA is 2-hydroxy-2-methylpropanoic acid. [c] Free mandelic acid is not soluble in aqueous solution of pH 4.8. C_1 is the major 2:2 complex. C_2 and C_3 are the 1:2 diastereoisomers.

Table 3. 100.62-MHz ^{13}C NMR Chemical Shifts (δ, ppm) and Direct Coupling Constants $^1J_{C,H}$ (Hz) for the Tungstate Complex of Isocitric Acid[a]

	carbon			
	CHOH	CH	CH_2	COOH
δ/*J*, u	74.0/143	48.7/131	36.8/128	179.6 180.1; 180.3
δ/*J*, c	83.3/148.6	46.9/131	39.6/129	186.5 181.0; 181.0
Δδ/Δ*J*	9.3/5.6	−1.8/0	2.8/1	6.9 0.7; 0.9

[a] All measurements were performed at pH 4.8. u: uncomplexed. c: complexed. Accuracy : δ, ±0.1 ppm; $^1J_{C,H}$, ± 1Hz.

The ^{183}W NMR spectra of mixtures of sodium tungstate and the ligands show, in addition to the signals[31] of heptatungstate (when present), one or two signals that are attributed to the 1:2 complex(es). The chemical shifts are reported in Table 1. Two complexes are characterized by a ^{183}W NMR signal located near −120 ppm. The first one is the single isocitrate species, shown to be a (2,2,2) complex on the basis of the indirect photometric results. Its ^{13}C NMR spectrum (Table 3) shows that only one of the three carboxylic carbon atoms is deshielded, which was assumed to be the one in position α to the hydroxyl group. It follows that each tungsten atom must be chelated by one ligand and that the tungsten atoms must be bridged in order to account for the dimer stoichiometry. Another conclusion is that because a single tungsten signal is observed for this dimer, the tungsten atoms are magnetically equivalent and the structure of the complex must be symmetrical.

The case of mandelic acid is not so clear, because experiments using indirect photometry indicate the formation of 1:2 species only. Besides, the ^{183}W NMR spectrum shows three peaks with different intensities (Figure 4). Two of them (δ_W 34.8 and 41.8) are due to the minor 1:2 complexes, by analogy with the chemical shifts for the complexes of other α-hydroxy acids discussed below. The third signal (δ_W −120.4) is the major one (55%) and may be attributed to a 2:2 dimeric species on the basis of the similarity with the isocitrate complex (δ_W −120.1). Because mandelic acid is almost insoluble in aqueous solution of pH close to 5, we could not determine the CIS values for the carbon atoms. However, for the three complexes, the δ values of the CHOH (86.7−87.7 ppm) and of the COOH carbon atoms (185.5−185.7 ppm) are in the expected range for carbons that bear chelating oxygen atoms and show that the site of chelation of the mandelate ligand is similar in all its complexes, including the dimer. A possible reason for detecting only 1:2 monomeric species by indirect photometry may be the lower

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(31) Maksimovskaya, R. I.; Burtseva, K. G. *Polyhedron* **1985**, *4*, 1559.

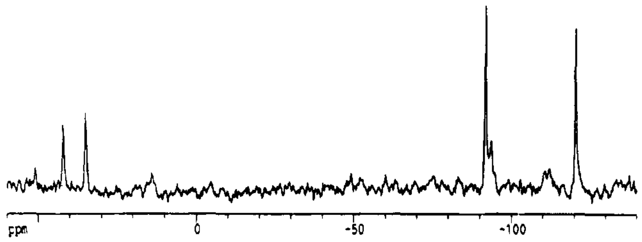

Figure 4. 16.65-MHz ^{183}W NMR spectrum of the tungstate complexes of DL-mandelic acid (38 000 scans, 24 h). The signal at δ −92 is due to free heptatungstate.[31] The signal at δ −120 is due to the (2,2,2) complex, and those at δ 30/40 are due to the pair of (1,2,2) diastereoisomers.

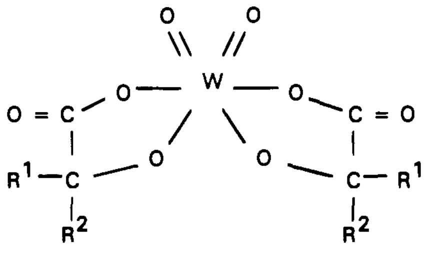

Figure 5. Proposed structure for the (1,2,2) tungstate complexes of α-hydroxy acids.

concentration used ($c_W = 6 \times 10^{-5}$ M versus 2 M for NMR measurements).

All other complexes, but the tartrate compounds, are 1:2 species from the results of the photometric study. NMR data show that glycolic acid and 2-hydroxy-2-methylpropanoic acid (2-hydroxyisobutyric acid, HIBA) give single complexes. Both of them possess $R^1 = R^2$. On the contrary, the chelates of other ligands with $R^1 \neq R^2$ and R^2 = H give two tungsten signals (δ_w 34 ± 7 ppm) separated by about 7−12 ppm and thus probably exist as pairs of diastereoisomers. Only two sets of ^{13}C NMR signals are observed for each pair, demonstrating that, in a given diastereoisomer, both molecules of ligand are perfectly equivalent and display the same ^{13}C NMR spectrum.

A surprising finding is that the signals of the tungsten atoms of the various 1:2 complexes occupy a wide range of chemical shifts (δ_W −13.9 to +81.2). The data in Table 1 show that the variations occur stepwise with increasing the substitution of the ligands. The lower value corresponds to $R^1 = R^2 = CH_3$ and the higher value to $R^1 = R^2$ = H.

The single dimeric (2,2,4) complex of DL-tartaric acid displays only one tungsten signal (δ_W 33.5), the chemical shift of which differs from that for the signal of the dimeric complexes (δ_W ca. −120) of isocitrate and mandelate and lies instead in the range expected for a 1:2 complex. It indicates that both tungsten atoms have the same environment and suggests that the tartrate complex should be considered as a dimer of the 1:2 complexes of α-hydroxy acids.

Discussion

The 1:2 Complexes. Since succinic acid, $HOOCCH_2CH_2COOH$, and 3-hydroxypropanoic acid, $HOCH_2CH_2COOH$, do not complex tungstate under our experimental conditions, the presence of a hydroxyl group α to the carboxyl group is essential for the chelating efficiency of the ligands. ^{13}C NMR data also confirm that both the C(OH) and COOH groups of the ligands are involved in the site of chelation, supporting a structure of the bis-chelate type proposed by many authors (Figure 5).

The 2:2 Complexes. A potentiometric study of the tungstate−lactate system showed that at pH 4−5, where the major species is (1,2,2), the formation of a minor species formulated (2,2,3) must be taken into account in order to obtain a model that fits satisfactorily the experimental data.[23] Several minor dimers (2,2,*n*) with *n* = 2−4 were also detected in the lactate−molybdate system. These results may indicate that dimeric 2:2 complexes are formed, even in small amounts, by all α-hydroxy acids concurrently with the prevailing (1,2,2) species. However, NMR spectroscopy cannot detect species in amounts lower than 10%.

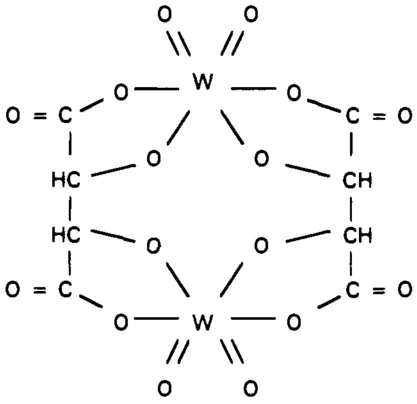

Figure 6. Proposed structure for the (2,2,4) tungstate complex of tartaric acid.

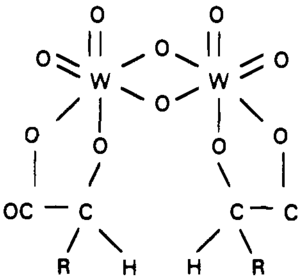

Figure 7. Proposed structure for the (2,2,2) tungstate complex of isocitric acid. R = $CH(COOH)-CH_2-COOH$. The same structure is assumed to hold for the 2:2 mandelate species.

The (2,2,4) tartrate complex is shown from NMR evidence to possess tungsten atoms in similar environments, analogous to those found in the 1:2 complexes. A possible structure is represented in Figure 6, in which the tungsten atoms are independent; i.e., they are not bridged by oxygen atoms, but are bridged through the tetradentate ligands.

On the contrary, the (2,2,2) isocitrate complex (and the similar mandelate species) must possess bridged tungsten atoms, the characteristic δ_W value (−120 ppm) of which does not lie in the range observed for monomeric 1:2 species, because bridging by the ligands is not possible. The number of oxygen bridges cannot be specified using the available data. However, the bis chelates of α-hydroxy acids resemble the MoO_2L_2 species formed by molybdate with catechol and tropolone (Htrop),[32] suggesting that the ligands possess similar complexing abilities. In the case of tungstate compounds, a 2:2 tropolonate complex has been reported,[32] whereas a $[(trop)MoO_2(\mu\text{-}O)_2MoO_2(trop)]^{2-}$ ion has been structurally characterized.[33] A possible structure for a bis(μ-oxo) complex is represented in Figure 7.

Influence of the Substitution on the Stabilities of the 1:2 Complexes. The evolution of the properties of the complexes within the series presents several noteworthy features. First, the acidity constants of the ligands are remarkably independent of the substituents R^1 and R^2 (Table 1). It contrasts with the well-known observation of electronic effects in the $R-CH_2-COOH$ series and indicates that the C(OH)−COOH system is

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(32) Griffith, W. P.; Pumphrey, C. A.; Skapski, A. C. *Polyhedron* **1987**, *6*, 891.

(33) Liu, S.; Zubieta, J. *Polyhedron* **1988**, *7*, 1129.

strongly insulated from such effects. On the other hand, the formation constants of the 1:2 complexes vary when the substituents are changed, suggesting that the electronic effects mentioned above are restored in the complexes. A steric influence is likely, because the stabilization observed when H is exchanged for R is much higher than that observed when R is exchanged for R′. The increasing stabilization of the complex due to the substitution of the ligand by a larger number of alkyl groups is accompanied by a shielding effect on the tungsten atom (Table 1). A rough correlation seems to exist between the formation constants and the δ_W values. Such variations of the shielding effects on the metal atom have already been reported for a series of iron complexes with ligands of increasing strength.[34] The stronger complex is that formed with HIBA ($R^1 = R^2 = CH_3$). This ligand is recognized as an efficient chelating agent and is widely used for the separation of metals.[19b]

A practical consequence is that the tungstate complexes of α-hydroxy acids cannot be characterized by a single, typical value of the chemical shift of their tungsten atoms, but rather by a set of three values depending on the nature of the carbon that bears the hydroxyl group (primary, δ_W 81.2; secondary, ca. 34 ± 7 ppm; tertiary, −13.9 ppm). Such variations did not occur in the series of tungstate complexes of polyols previously investigated, in which the range of chemical shifts for tungsten atoms was very narrow in a given series and could be used for the identification of the type of complex.[7−9]

Relevance to Complexes of Biological Ligands. Citric and malic acid are biological compounds that possess a C(OH)−COOH system and additional carboxyl groups. The tungstate complexes of citrate[13] appear to differ from those characterized in the present study, since they mainly occur as 1:1:*n* species ($n = 1-4$), accompanied by two dimers 2:2:*n* ($n = 4-5$), and the (1,2,6) and (2,1,4) species. At pH 5, the prevailing species are formulated (1,1,2) and (2,2,4). In the proposed structures, it is postulated that the site of chelation is always the C(OH)−COOH group and does not involve the CH_2-COOH groups. The 1:2 and 2:2 complexes have formulas compatible with this assumption, but the formation of 1:1 species has no equivalent in the series of α-hydroxy acids and may indicate the formation of a different structural type of complex. No monomeric tungstate complexes have been structurally characterized, but the crystal structure of the sodium salt of the (2,2,4) tungstate−citrate complex revealed the presence of a $[(WO_2)_2O(cit)_2]^{6-}$ anion, in which the tungsten atoms are bridged by a single oxygen atom.[14,15]

It is noteworthy to remark that, in contrast, isocitric acid forms a single (2,2,2) tungstate complex. The comparison of the structures of citric and isocitric acids (Figure 1) does not show obvious differences that could justify such different behaviors as ligands.

The tungstate complexes of malic acid were studied earlier by ^1H NMR.[36] Four complexes were reported, including two 1:2 and one 2:1 species, together with a major 1:1 (possibly 2:2) species. We made a preliminary ^{183}W NMR investigation of this system which showed, among several other as yet unidentified signals, the presence of two minor peaks at δ_W 31.3−38.8 (28% of total intensity) that exactly corresponded to those expected for a pair of isomeric 1:2 complexes involving the CHOH−COOH site. It confirms that the study of polyhydroxy acids that afford mixtures of complexes may indeed be simplified by ^{183}W NMR, which allows the fast identification of the chelates formed by the C(OH)−COOH system.

Although tungstate affords mixtures of complexes with α-hydroxy acids, the situation is simpler than for species of vanadate, which possesses a remarkable versatility as it adapts its coordination geometry to a variety of structures. For example, in the presence of lactate, vanadate forms many derivatives,[16] including a tetrahedrally coordinated ester, two trigonal bipyramidally coordinated products, both mononuclear in vanadium but containing either one or two lactate ligands, and two dinuclear complexes, one with octahedral coordination about each vanadium nucleus and the other with one octahedral and one tetrahedral vanadium atom.

Conclusion

This study provided new information on the 1:2 and 2:2 tungstate complexes of α-hydroxy acids that all involve the C(OH)−COOH site of chelation. The stoichiometries and formation constants of the major complexes were determined by a photometric indirect method, using the (1,1,2) tungstate complex of 2,5-dihydroxy-1,4-benzoquinone as the sacrificial species. ^{183}W NMR data were used for further structural characterization. All the 1:2 species are of the $[WO_2L_2]^{2-}$ type, whereas the dimeric complexes may be either dinuclear (2,2,2) complexes (mandelate and isocitrate) or mononuclear (2,2,4) (tartrate) bis chelates. The dimers in which tungsten atoms are bridged are characterized by δ_W values close to −120 ppm. The ^{13}C NMR spectra of all the chelated ligands are very similar and cannot be used for their characterization. On the contrary, ^{183}W NMR is a powerful tool for distinguishing the different types.

A large effect of the substitution of the ligands by alkyl groups is observed on the formation constant of the 1:2 complexes (but not on their basicity) and on the chemical shift of the tungsten atom. This must be taken into account for the identification of the various species in mixtures of tungstate complexes formed by polyhydroxy acids.

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(35) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum: New York, 1989; Vol. 6, 2nd Suppl., p 355.

(36) Gil, V. M. S.; Saraiva, M. E. T. L.; Caldeira, M. M.; Pereira, A. M. D. *J. Inorg. Nucl. Chem.* **1980**, *42*, 389.