Contribution from the Departments of Chemistry,
University College, Dublin, Ireland, and University College, Cork, Ireland

Design of Metal Chelates with Biological Activity. 5. Complexation Behavior of Dihydroxamic Acids with Metal Ions

David A. Brown,*† Ruth Geraty,† Jeremy D. Glennon,‡ and Nuala Ni Choileain‡

Received March 4, 1986

Analytical, NMR, and IR spectroscopic data on a series of aliphatic dihydroxamic acids of general formula RONR'CO-$(CH_2)_n$CONR'OR (R = H, CH_3; R' = H, CH_3; n = 3–8, 10) are reported. At low concentrations, the unsubstituted dihydroxamic acids show two sharp peaks in the 8–11-ppm region of the NMR spectrum while for the $(O\text{-Me})_2$-substituted acids the N–H peak appears at 10.9 ppm; with the $(N\text{-Me})_2$ acids the O–H peak occurs at 9.7 ppm. Strong intramolecular hydrogen bonding is apparent in the $(N\text{-Me})_2$-substituted acids from the solid-state infrared measurements. Species distribution analysis and stability constant data for complex species present in aqueous solution for the interaction of Fe(III) with glutarodihydroxamic acid (n = 3; R, R' = H) and for Ni(II) with pimelodihydroxamic acid (n = 5; R, R' = H) were obtained by analytical potentiometry. In the Fe(III) system, the major complex species at neutral pH is of Fe_2L_3 stoichiometry (log β_{pqr} = 48.6) analogous to the behavior of the naturally occurring dihydroxamic acid rhodotorulic acid. Spectroscopic data on isolated Ni(II) complexes of selected dihydroxamic acids confirm the presence of octahedral coordination and support the findings of the solution equilibria studies.

Introduction

In this series of papers[1-3] we have attempted to synthesize metal chelates with biological activity, either of the chelate itself or of the ligand presumed to be acting biologically via metal complexation. In previous papers[1-3] we have tested the ability of various iron(III) hydroxamates to raise the hemoglobin level of anemic rats as a preliminary indication of efficiency as an oral source of iron for the treatment of anemia. This biological test was used in conjunction with the following criteria for activity: (a) the chelate should be stable and remain monomeric or at least of low molecular weight at biological pH values for transfer to occur through cell membranes; (b) it should undergo rapid iron exchange with apotransferrin; (c) the free ligand should be able to extract iron fairly rapidly from ferric citrate polymer as a model for ferritin, the iron storage protein. Although there is no direct in vitro evidence for penetration of mammalian cells by simple hydroxamate ligands, previous studies on the absorption of tris(glycinohydroxamato)iron(III) by rat intestine support this criterion.[3] With these criteria, both iron(III) acetohydroxamate and iron(III) glycinohydroxamate showed reasonable but not sufficient activity compared with existing oral preparations[4] to justify their further exploitation. In view of this fact, we turned our attention to complexes of dihydroxamic acids of general formula

$$RONR'\text{-}CO\text{-}(CH_2)_n\text{-}CO\text{-}NR'OR$$

$$n = 3\text{-}8, 10$$

Although numerous complexes of monohydroxamic acids have been reported,[5-8] very few complexes of dihydroxamic acids have been prepared largely due to the difficulty of synthesizing even the simplest of unsubstituted dihydroxamic acids in which the two functional groups are separated by a straight-chain aliphatic group; for example, pimelodihydroxamic acid (n = 5) has never been reported. Recently, Raymond and co-workers reported[9] iron(III) complexes of the naturally occurring dihydroxamic acid rhodotorulic acid with a view to modeling its microbial iron-transport properties.

Recently, we have reported a method for the facile preparation of aliphatic dihydroxamic acids of general formula RONR'CO-$(CH_2)_n$CONR'OR ($n > 3$) that is also applicable to the synthesis of monohydroxamic acids.[10] Analytical and spectroscopic data are reported below for the above series with n = 3–10 (excluding n = 9). These acids complex readily with transition metals, and complexation behavior in aqueous solution of two transition-metal/dihydroxamic acid systems is discussed. Finally, the synthesis of complexes with Ni^{2+} and Cu^{2+} are described.

Experimental Section

All reagents and solvents were used as supplied. Infrared spectra were recorded as 1% KBr disks on a Perkin-Elmer 283B spectrophotometer linked to a 3600 data station. Proton NMR spectra were recorded in Me_2SO-d_6 on JEOL GX270, JEOL PS100, and Perkin-Elmer R12 60-MHz instruments. Solution and reflectance UV spectra were recorded on a PE 552 spectrophotometer. Microanalyses were determined by the Microanalytical Laboratory at UCD.

Synthesis of Dihydroxamic Acids. A typical procedure is given for glutarodihydroxamic acid (n = 3). Glutaric acid (3.96 g, 0.03 mol) was stirred with *N,N'*-carbonyldiimidazole (9.73 g, 0.06 mol) in THF (150 mL) at room temperature for 24 h in a flask fitted with a gas outlet. After filtration and quick drying at the pump, the resulting diimidazolide (90% yield, 6.0 g, 0.02 mol) is stirred with hydroxylamine (1.72 g, 0.052 mol) in methanol (50 mL) at room temperature for 2 days to yield the desired product, glutarodihydroxamic acid (2.92 g, yield 59%) after filtration and drying. If necessary, the product may be recrystallized from 1:1 water/acetone mixtures. Note that after isolation of the intermediate diimidazolide, dissolution in methanol prior to its addition to the hydroxylamine dissolved in methanol is not recommended since this process tends to result in alcoholysis of the intermediate. Substituted dihydroxamic acids (at either the nitrogen or oxygen of the NHOH group) may be similarly prepared by starting from the appropriate substituted hydroxylamine. In certain cases the product may remain dissolved in methanol, when solvent removal and subsequent extraction with hot ethyl acetate is required.

Preparation of Metal Complexes. A typical procedure is given for nickel pimelodihydroxamate (n = 5). Pimelodihydroxamic acid (0.1 mM) dissolved in 20 mL of water is added to (0.09 mM) $NiCl_2 \cdot 6H_2O$ in 10 mL of water and the pH raised to 8.3 with NaOH. The resulting precipitate is filtered and washed with hot water and ethanol. Yield: 60%.

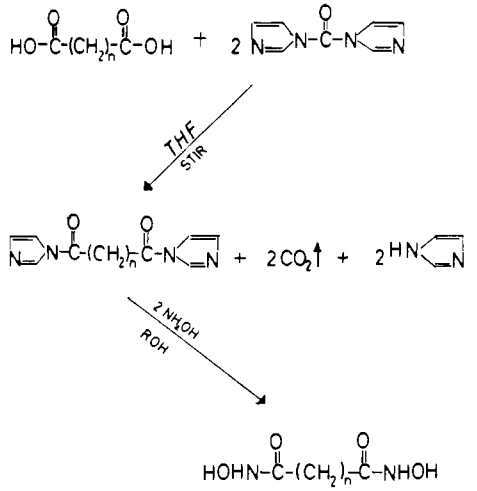
Potentiometric Titrations. Stock solutions were prepared from distilled and deionized water and stored over prepurified argon. All glassware used was metal-free. Prepurified argon was used to maintain an oxygen-free atmosphere throughout the titrations. The base used was carbonate-free 1.010 M NaOH standardized against weighed amounts of dried potassium hydrogen phthalate. This base was used to standardize a stock acid and salt solution, 0.024 M in 0.15 M $NaNO_3$, which was used directly for the titration analysis. A stock iron(III) solution, 0.515 M in 0.02 M HNO_3, was prepared from AnalaR $Fe(NO_3)_3 \cdot 9H_2O$ and

† University College, Dublin.
‡ University College, Cork.

(1) Part 4: Brown, D. A.; Sekhon, B. S. *Inorg. Chim. Acta* **1984**, *91*, 103.
(2) Brown, D. A.; Chidambaram, M. V. *Met. Ions Biol. Syst.* **1983**, *15*, 125.
(3) Brown, D. A.; Chidambaram, M. V.; Glennon, J. D. *Inorg. Chem.* **1980**, *19*, 3260.
(4) Pitt, C. G.; Gupta, A.; Estes, W. E.; Rosenkrantz, H.; Metterville, J. J.; Crumbliss, A. L.; Palmer, R. A.; Nordquest, K. A.; Sprinkle, Hardy, J. A.; Whitcomb, B. R.; Byer, B. R.; Arceneaux, J. E. X.; Gaines, C. G.; Sciortino, C. V. *J. Pharmacol. Exp. Ther.* **1979**, *208*, 12.
(5) (a) Brown, D. A.; Roche, A. L. *Inorg. Chem.* **1983**, *22*, 2199. (b) Brown, D. A.; Roche, A. L.; Pakkanen, T. A.; Pakkanen, T. T.; Smolander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 676.
(6) Brown, D. A.; Glass, W. K.; McGardle, S. J. C. *Inorg. Chim. Acta* **1983**, *80*, 13.
(7) Chatterjee, B. *J. Indian Chem. Soc.* **1973**, *50*, 758.
(8) Carrano, C. J.; Cooper, S. R.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 599.
(9) Carrano, C. J.; Raymond, K. *J. Am. Chem. Soc.* **1978**, *100*, 5371.
(10) Brown, D. A.; Geraty, R. A.; Glennon, J. D.; Ni Choileain, N. *Synth. Commun.* **1985**, *15*, 1159.

0020-1669/86/1325-3792$01.50/0 © 1986 American Chemical Society

Scheme I



standardized by atomic absorption spectrometry. In the case of Ni^{2+} studies, 0.098 M carbonate-free NaOH, 0.096 M HCl, 1.5 M NaCl, and 1.046×10^{-3} M Ni^{2+} solutions were used.

Titrations were performed with a Radiometer automatic titration apparatus consisting of a digital (PHM64) pH meter, an autoburette (ABU80), a titrator (TTA60), and an automatic recorder (REC61 Servograph). A computer interface link to a BBC microcomputer allowed automatic data collection at every 0.1 pH unit. The 50-mL titration vessel was thermostatically controlled at 25 ± 0.05 °C. The electrode pair consisted of a Radiometer G2040C glass electrode and a K4040 reference electrode.

For the ligand concentration variation titrations, curves were obtained for $C_L = 4.183 \times 10^{-3}$, 5.108×10^{-3}, and 8.193×10^{-3} M with $C_{Fe} = 9.760 \times 10^{-4}$ M. In the metal concentration variation titrations $C_{Fe} = 4.880 \times 10^{-4}$ and 9.760×10^{-4} M with $C_L = 5.108 \times 10^{-3}$ M. For the Ni^{2+} system, the metal concentration variation curves had $C_{Ni} = 4.184 \times 10^{-4}$ and 2.092×10^{-4} M with $C_L = 1.212 \times 10^{-3}$. The ligand concentration variation used $C_L = 4.040 \times 10^{-4}$, 1.212×10^{-3}, and 2.020×10^{-3} with $C_{Ni} = 4.184 \times 10^{-4}$ M.

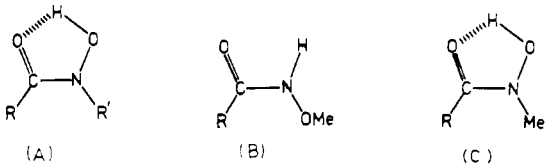
The titration data were treated by the program PLOT-3 to give values for the unbound portions of metal, the proton liberation term $\delta H^+/C_L$, and the free ligand concentrations. Further data processing through the use of the basic programs GUESS-3 and LEASK-4 yielded the species distribution and stability constant data, as previously described.[11] Titrations were repeated with a reproducibility of ±0.002 pH unit and ±0.002 μL in titration volumes. Stability constants are accurate to 0.001 log β unit.

Results and Discussion

Synthesis of Dihydroxamic Acids. At present, hydroxamic acids are generally synthesized by acylation of hydroxylamine,[12] which being a powerful nucleophile reacts readily with carboxylic esters. Acylation is usually carried out under basic conditions using potassium hydroxide in either alcohol or pyridine followed by acidification to release the hydroxamic acid. However, this method can present difficulties; for example, initial synthesis of the ester may result in an oil that has to be used directly in the acylation step; in addition, the reaction temperature is also often critical and the isolation of water soluble hydroxamic acids may require formation of their copper salts and subsequent treatment with H_2S.[13] Acid anhydrides and acyl halides are used less frequently due to their reactivity; often there is a loss of the desired product because significant diacylation occurs. More recently, a series of substituted and unsubstituted (n = 3, 6) dihydroxamic acids have been reported.[14]

A new method for the facile synthesis of aliphatic dihydroxamic acids (III) has recently been reported by reaction of free dicarboxylic acids with N,N'-carbonyldiimidazole at room temperature, which leads to the corresponding diimidazolide with evolution of CO_2 (Scheme I). Azolides have a high degree of reactivity in nucleophilic[15-17] reactions compared to that of acyl halides and anhydrides, and the isolated diimidazolides are readily acylated by reaction with hydroxylamine in MeOH. The method promises wide applicability not only in the synthesis of a series of substituted and unsubstituted dihydroxamic acids of varying chain length but also in the synthesis and design of new hydroxamic acids. Important practical advantages are the mild conditions used, the stability of the diimidazolide intermediate, and the direct precipitation of the desired dihydroxamic product from the reaction mixtures. Analytical data for these compounds are given in Table I.

Spectroscopic Results. In general, hydroxamic acids exist in the keto form (A) but can be subject to intramolecular hydrogen bonding,[18-20] causing a shift in the carbonyl stretching frequency $\nu(CO)_{st}$ from the normal ketone value of 1725 cm^{-1} to an intense broad band in the 1640–1620-cm^{-1} region and close to that in amides (1650 cm^{-1}). The unsubstituted dihydroxamic acids show



a strong $\nu(CO)_{st}$ at 1662 cm^{-1} except in the cases with n = 3 and 5, when the band appears at the lower values of 1646 and 1624 cm^{-1}, respectively.

The $\nu(NH)_{st}$ frequency in the region 3250–3265 cm^{-1} is easily identified by its position and intensity whereas the neighboring $\nu(OH)_{st}$ between 3050 and 3080 cm^{-1} is much broader and weaker.[20,21]

The $(O\text{-Me})_2$ compounds (B) have an NH stretching frequency similar to that of long-chain monohydroxamic acids at ca. 3240 cm^{-1} and an intense broad $\nu(C{=}O)_{st}$ at 1650 cm^{-1}. Since the oxygen-substituted dihydroxamic acids have no hydroxyl proton available for hydrogen bonding, the similarity in $\nu(CO)$ peak positions with those of the long-chain unsubstituted dihydroxamic acids (excluding n = 3, 5) indicates that the latter are at most subject to very weak intramolecular hydrogen bonding.

In contrast, the $(N\text{-Me})_2$ compounds (C) show significant differences in their IR spectra from those of the unsubstituted dihydroxamic acids. Thus, $\nu(O{-}H)_{st}$ is at 3143–3150 cm^{-1} and $\nu(C{=}O)_{st}$ lies at a very low value, 1600–1594 cm^{-1}, which indicates strong intramolecular hydrogen bonding as in structure A (R' = Me).

It should be stressed that these conclusions are based on solid-state infrared measurements.

NMR Spectra. There is very little NMR information available on unsubstituted dihydroxamic acids with no specific assignments of NH and OH chemical shifts.[23-26] The assignments given in Table I are based on a comparison of the ^1H NMR spectra of this series of unsubstituted, $(N\text{-Me})_2$- and $(O\text{-Me})_2$-substituted dihydroxamic acids. In each case the protons bonded to the carbon atoms are readily assigned. The unsubstituted dihydroxamic acids give two sharp peaks in the 8–11-ppm region, provided concentrations are less than 0.25 M, whereas the $(O\text{-Me})_2$-substituted acids give an N–H peak at 10.9 ppm and the $(N\text{-Me})_2$ acid an

(11) Sarkar, B.; Kruck, T. P. *Can. J. Chem.* **1973**, *51*, 3541.
(12) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209.
(13) Hurd, C. D.; Botteron, D. G. *J. Org. Chem.* **1946**, *11*, 207.
(14) Das, M. K.; Bose, P.; Roy, N. *J. Chem. Eng. Data* **1984**, *29*, 345.
(15) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *7*, 351.
(16) Staab, H. A.; Luking, M.; Durr, F. H.; *Chem. Ber.* **1962**, *95*, 1275.
(17) Anderson, G. W. *J. Am. Chem. Soc.* **1958**, *80*, 4423.
(18) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.
(19) Challis, B. C.; Challis, J. A. *Synthesis and Reactions of Organic Compounds*; Pergamon: Oxford, 1979; Chapter 9.
(20) Davies, M.; Spiers, N. A. *Spectrochim. Acta* **1959**, 487.
(21) Freeman, J. *J. Am. Chem. Soc.* **1958**, *80*, 5954.
(22) Johnson, J. *J. Org. Chem.* **1976**, *41*, 252.
(23) Feuer, H.; Pelle, D.; Braunstein, D. M.; Rao, C. N. R. *Spectrochim. Acta, Part A* **1969**, *25A*, 1393.
(24) Bell, C. L.; Nambury, C. N. V.; Bauer, L. *J. Org. Chem.* **1964**, *29*, 2873.
(25) Sohar, P. *Nuclear Magnetic Resonance Spectroscopy*; CRC Press: Boca Raton, FL, 1981.
(26) Sosnovsky, G.; Krogh, J. A. *Synthesis* **1980**, 654.

Table I. Analytical and Spectroscopic Data for Ligands and Properties of Metal Complexes

n	mp, °C	anal.,[a] %		NMR,[b] ppm		IR,[c] cm^{-1}
				R = CH_3, R′ = H		
3	154–155	C 36.8	(37.04)	1 1.93 (4 H) d		N—H 3199
		H 6.25	(6.22)	2 1.68 (2 H) m		O—H 3016
		N 17.0	(17.28)	3		C=O 1646
				4 8.69 (2 H) m		
				5 10.37 (2 H) s		
4	163–164	C 33.9	(33.96)	1 1.93 (4 H) d		N—H 3256
		H 7.76	(7.54)	2 1.44 (4 H) m		O-H 3063
		N 13.0	(13.20)	3		C=O 1662
				4 8.76 (2 H) m		
				5 10.41 (2 H) s		
5	162–164	C 44.0	(44.21)	1 1.92 (4 H) t		N—H 3203
		H 7.25	(7.37)	2 1.46 (4 H) q		O—H 3005
		N 14.6	(14.74)	3 1.20 (2 H) m		C=O 1624
				4 8.69 (2 H) m		
				5 10.35 (2 H) s		
6	162–163	C 46.9	(47.06)	1 1.92 (4 H) t		N—H 3252
		H 8.01	(7.84)	2 1.46 (4 H) m		O—H 3064
		N 13.5	(13.72)	3 1.21 (4 H) m		C=O 1662
				4 8.68 (2 H) m		
				5 10.34 (2 H) s		
7	155–156	C 49.3	(49.54)	1 1.92 (4 H) t		N—H 3257
		H 8.40	(8.26)	2 1.46 (4 H) m		O—H 3054
		N 13.2	(12.84)	3 1.21 (6 H) m		C=O 1664
				4 8.70 (2 H) m		
				5 10.34 (2 H) s		
8	164–166	C 51.9	(51.70)	1 1.93 (4 H) t		N—H 3264
		H 9.92	(8.68)	2 1.46 (4 H) m		O—H 3080
		N 11.8	(12.01)	3 1.22 (8 H) m		C=O 1662
				4 8.70 (2 H) m		
				5 10.36 (2 H) s		
10	159–161	C 55.4	(55.36)	1 1.93 (4 H) t		N—H 3256
		H 9.46	(9.29)	2 1.46 (4 H) m		O—H 3082
		N 10.3	(10.76)	3 1.22 (10 H) m		C=O 1662
				4 8.68 (2 H) m		
				5 10.34 (2 H) s		
2	78	C 53.7	(53.66)	1 2.32 (4 H) t		O—H 3150
		H 8.83	(8.96)	2 1.47 (4 H) m		C=O 1600
		N 11.4	(11.38)	3 1.27 (6 H) m		
				4 3.07 (6 H) s		
				5 9.74 (2 H) s		
8	102	C 55.1	(55.38)	1 2.33 (4 H) t		O—H 3150
		H 9.29	(9.23)	2 1.40 (4 H) m		C=O 1600
		N 10.6	(10.77)	3 1.26 (8 H) m		
				4 3.08 (6 H) s		
				5 9.71 (2 H) s		
10	104	C 58.7	(58.30)	1 2.25 (4 H) t		O—H 3143
		H 10.03	(9.72)	2 1.47 (4 H) m		C=O 1594
		N 9.4	(9.72)	3 1.25 (12 H) m		
				4 3.08 (6 H) s		
				5 9.76 (2 H) s		
				R′ = CH_3, R = H		
7	75	C 53.9	(53.66)	1 1.93 (4 H) t		N—H 3240
		H 8.68	(8.94)	2 1.47 (4 H) m		C=O 1650
		N 11.5	(11.38)	3 1.23 (6 H) m		
				4 10.94 (2 H) s		
				5 3.56 (6 H) s		
8	84	C 55.4	(55.38)	1 1.92 (4 H) t		N—H 3230
		H 9.54	(9.23)	2 1.47 (4 H) m		C=O 1650
		N 10.8	(10.77)	3 1.23 (8 H) m		
				4 10.92 (2 H) s		
				5 3.37 (6 H) s		

n	color	anal., %		electronic spectrum, nm	IR, cm^{-1}
		$NiL \cdot H_2O$			
5	pale green	C 31.4	(31.73)	778 $^3T_{1g} \leftarrow {}^3A_{2g}$	N—H 3210
		H 5.04	(5.33)	398 $^3T_{1g}(P) \leftarrow {}^3A_{2g}$	C=O 1600
		N 10.5	(10.57)	283 n-π^*	
10	pale green	C 43.8	(43.02)		N—H 3205
		H 7.84	(7.17)		C=O 1600
		N 8.1	(8.37)		
		$CuL \cdot H_2O$			
5	dark green	C 31.1	(31.17)		N—H 3200
		H 4.44	(5.19)		C=O 1540
		N 10.0	(10.40)		

[a] For n = 4, two molecules of water of crystallization are present. [b] 1: C-CH_2*. 2: C-CH_2-CH_2*. 3: C-$(CH_2)_2$-(CH_2)*$_{n-4}$. 4: N-R′. 5: O-R. [c] 1% KBr.

O–H peak at 9.7 ppm. For the unsubstituted dihydroxamic acids (n = 3, 4, 5), increasing temperature results in the above two sharp peaks coalescing to form a broad resonance line that sharpens with further increase in temperature (Figure 1). An increase in concentration produces similar effects, and the upfield resonance line (8.68 ppm) broadens considerably and loses most of its structure at lower concentrations and temperatures compared to the case of the downfield peak; the upfield peak (8.68 ppm) is assigned to the N–H proton, its shape being attributed to quadrupole broadening by the nitrogen atom. The above temperature and concentration effects are consistent with the two protons being involved in a rapid exchange process.[25]

Solution Equilibria. The pK_a values of the two ionizable protons of most unsubstituted dihydroxamic acids (LH_2) have not previously been determined. For n = 3 and 5, the pK_a values were calculated and are given in Table II. The ligand concentrations employed were 1.008×10^{-2} and 1.010×10^{-3} M for n = 3 and 5, respectively. The values are as expected in comparison with other hydroxamic acids.[27,28]

Two systems were selected for study with transition metals, pimelodihydroxamic acid (n = 5) with Ni^{2+} and glutarodihydroxamic acid (n = 3) with Fe^{3+}. In each case titrations were performed in the presence of varying concentrations of metal and ligand. Stability constants of the complexes formed were calculated by using the method of Sarkar and Kruck.[11,29] Species distributions are plotted for each system in Figures 2 and 3.

Table II. Logarithms of the Stability Constants (log β_{pqr}) of Complex Species $M_pH_qL_r$

p	*q*	*r*	Ni^{2+} [a]	Fe^{3+} [b]	*p*	*q*	*r*	Ni^{2+} [a]	Fe^{3+} [b]
0	1	1	9.46	9.75	1	0	2	11.417	
0	2	1	18.40	18.42	3	0	4		69.950
1	2	1	21.357		2	0	3		48.640
1	1.5	1	18.792		2	−1	3		39.840
1	1	1		18.970	1	−2	1		−12.787
1	0	1	7.453	17.090	2	−2	3		30.150

[a] Data for Ni(II)–pimelodihydroxamic system. [b] Data for Fe(III)–glutarodihydroxamic system.

Ni(II)–Pimelodihydroxamic Acid System. There is little complexation at low pH; however, at pH 6.8, the rate of proton liberation increases rapidly allowing the formation of the ML species, which dominates a large area of the pH range (7.8–9.6),

(27) Adams, E. Q. *J. Am. Chem. Soc.* **1916**, *38*, 1503.
(28) Barclay, S. J.; Riley, P. E.; Raymond, K. N. *Inorg. Chem.* **1984**, *23*, 2003.
(29) Sarkar, B. *J. Indian Chem. Soc.* **1977**, *54*, 117.

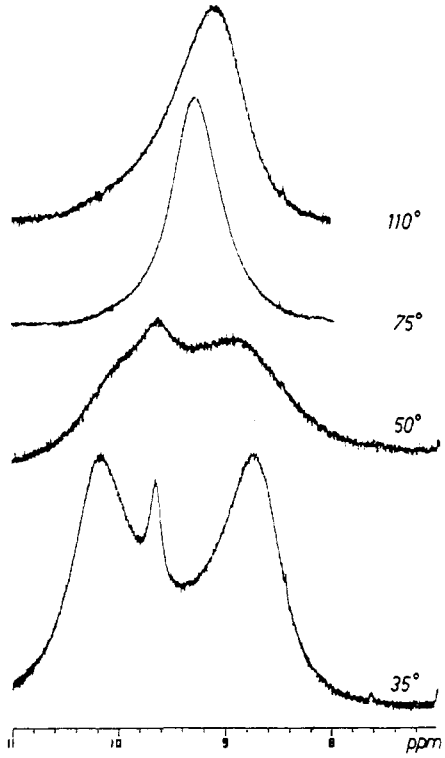


Figure 1. NMR ^1H temperature variation of pimelodihydroxamic acid (Me_2SO-d_6).

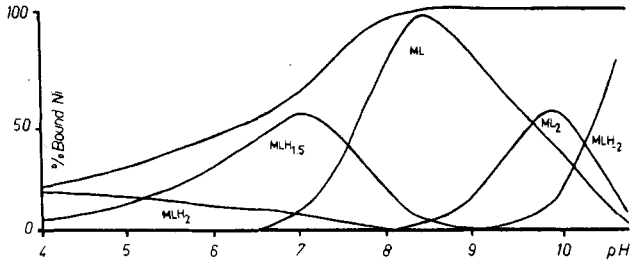


Figure 2. Species distribution diagram for the Ni(II)–pimelodihydroxamic acid system (C_{Ni} = 4.184 × 10^{-4} M, C_L = 1.212 × 10^{-3} M).

exhibiting a maximum concentration of 95% of total bound metal at pH 8.4. ML_2 and hydroxy or further deprotonated compounds are formed at higher pH values. The logarithms of the stability constants (log β_{pqr}) are given in Table II.

Fe(III)–Glutarodihydroxamic Acid System. The species distribution for the interaction of iron(III) with glutarodihydroxamic acid is dominated by the Fe_2L_3 complex species. It represents the major complex species between pH 5.8 and 8.8. A plot of $\bar{n}$ vs. pH shows a leveling off of $\bar{n}$ at a value of 1.5 in this pH range, supporting a formulation of Fe_2L_3. This is also consistent with the observed molar proton liberation ($\delta H^+/\delta C_{Fe}$) value of 3 and with the largely invariant visible absorption characteristics of the orange-red solution with λ_{max} 425 nm over this pH range. There is substantial complexation in the acidic region where the FeL complex is the major species, and an appreciable amount of a Fe_3L_4 complex is also formed. This is not inconsistent with the presence of an isosbestic point at 480 nm in the visible absorption spectra from pH 2.7 to 4.3, where the existence of the isosbestic point is taken to indicate the presence of at least two independent species.[30] In alkaline solutions, hydroxy or deprotonated $Fe_2H_{-1}L_3$ and $Fe_2H_{-2}L_3$ dimeric species are formed.

The formation of the Fe_2L_3 complex by glutarodihydroxamic acid is analogous to the behavior of the naturally occurring dihydroxamic acid rhodoturulic acid. The reported distribution

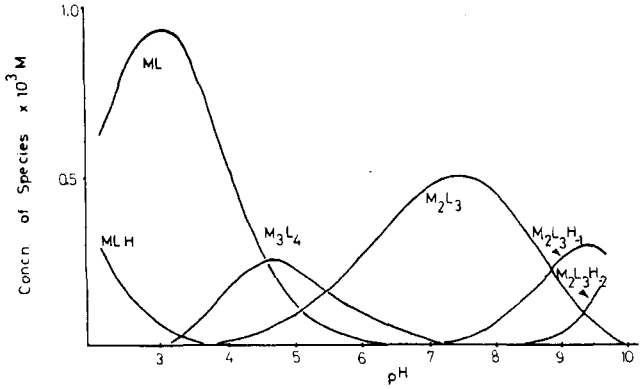


Figure 3. Species distribution diagram for the Fe(III)–glutarodihydroxamic acid system (C_{Fe} = 9.76 × 10^{-4} M, C_L = 5.11 × 10^{-3} M).

diagram represents the first clear mapping of a model Fe_2L_3 complex involving an unsubstituted dihydroxamic acid. Recent studies of N-substituted dihydroxamic acid models have suggested that complexation is dimeric in solution but possibly polymeric in the solid state.[28] There is, however, some indication of polymeric behavior in the Fe(III)–glutarodihydroxamic acid system in mildly acidic solution, a tendency that was also recorded in previous work on glutarobis(*N*-phenylhydroxamic acid).[31] The number of methylene groups separating the hydroxamic acid units may be the critical factor. Preliminary results on the Fe(III)–pimelodihydroxamic acid system indicate the existence of monomeric and dimeric species only.

The logarithms of the stability constants (log β_{pqr}) for the $Fe_pH_qL_r$ complex species are given in Table II together with those for the $Ni_pH_qL_r$ series. A comparison of the log β_{pqr} value of the Fe_2L_3 complex of glutarodihydroxamic acid (48.6) with those obtained for rhodoturulic acid (62.2) and *N*-isopropodihydroxamic acid analogues (62.1, n = 3) emphasizes the importance of N-substitution for thermodynamic stability.[32] Further investigations of the Fe(III) complexation by the synthesized *N*-methyl-substituted dihydroxamic acids are warranted.

Isolation of Metal Complexes. On the basis of the above results of the potentiometric titrations, complexes of pimelo and other dihydroxamic acids with Fe^{3+}, Ni^{2+}, and Cu^{2+} were isolated (as described in the Experimental Section) from the appropriate metal chloride and dihydroxamic acid. All the complexes are extremely insoluble. Microanalytical and IR spectral data are given in Table I. Reaction of Ni^{2+} and Cu^{2+} with the dihydroxamic acids gave ML complexes whose stoichiometry agreed with the dominant complex observed in the nickel–pimelo species distribution in contrast to the reaction of iron(III) with glutarodihydroxamic acid.

The isolated Ni complexes are very similar in character and appearance to the bis(acetohydroxamato)- and bis(propiohydroxamato)nickel(II) complexes previously prepared.[5] The UV reflectance spectrum of nickel pimelodihydroxamate is typical of Ni(II) in an octahedral environment with two maxima in the 800–300-nm region (778 nm, $^3T_{1g} \leftarrow {}^3A_{2g}$; 398 nm, $^3T_{1g}(P) \leftarrow {}^3A_{2g}$).[33] The sharp absorption at 284 nm is attributed to the ($n \rightarrow \pi^*$) transition of the C=O group shifted from its free-ligand value of 217 nm. The absence of ν(O–H) at 3000 cm^{-1} and the broad carbonyl stretching band at 1600 cm^{-1} shifted by 25 cm^{-1} from that of the free ligand confirm normal oxygen coordination of the nickel atom and complexation with the dihydroxamic acid. Further studies of the biological activity of the iron complexes are in progress.

Registry No. $HONHCO(CH_2)_3CONHOH$, 7068-55-5; $HONHCO(CH_2)_4CONHOH$, 4726-83-4; $HONHCO(CH_2)_5CONHOH$, 38937-65-4; $HONHCO(CH_2)_6CONHOH$, 38937-66-5; $HONHCO(CH_2)_7CONHOH$, 18992-11-5; $HONHCO(CH_2)_8CONHOH$, 5578-84-7; HON-

(30) Hartley, F. R.; Burgess, C.; Alcock, R. M. *Solution Equilibria*; Wiley: New York, 1968; Chapter 2, p 35.

(31) Ghosh, N. M.; Sarkar, D. K. *J. Indian Chem. Soc.* **1970**, *47*, 562.
(32) Brink, C. P.; Crumbliss, A. L. *Inorg. Chem.* **1984**, *23*, 4708.
(33) Lever, A. B. P. *Inorganic Electron Spectroscopy*; Elsevier: Amsterdam, 1968.

$HCO(CH_2)_{10}CONHOH$, 103682-93-5; $MeONHCO(CH_2)_7CONHOMe$, 103682-96-8; $MeONHCO(CH_2)_8CONHOMe$, 103682-97-9; $MeONHCO(CH_2)_{10}CONHOMe$, 103835-51-4; $HONMeCO(CH_2)_7CONMeOH$, 103682-94-6; $HONMeCO(CH_2)_8CONMeOH$, 99102-77-9; $NiL\cdot H_2O$ (n = 5), 103835-53-6; $CuL\cdot H_2O$ (n = 5), 103835-54-7; $NiL\cdot H_2O$ (n = 10), 103835-55-8; glutaric acid, 110-94-1; *N,N'*-carbonyldiimidazole, 530-62-1; hydroxylamine, 7803-49-8; glutaric acid diimidazolide, 103835-52-5.

Contribution from the Institute of Inorganic Chemistry, University of Trondheim, N-7034 Trondheim-NTH, Norway

Successive High-Temperature Chlorine Substitution and Infrared Matrix-Isolation Spectroscopy of Methylaluminum Chlorides

Erling Rytter* and Steinar Kvisle[1]

Received June 12, 1985

Infrared spectra of the monomers $(CH_3)_2AlCl$ and $(CH_3)AlCl_2$ have been obtained by thermal dissociation of the corresponding dimers followed by isolation in argon matrices. The Al–C bond is found to be of similar stability for all monomers $(CH_3)_{3-n}AlCl_n$ (n = 0–2) while the strength of the Al–Cl bond decreases with higher alkyl contents. Several chlorine-bridged dimers, $(CH_3)_{6-n}Al_2Cl_n$ (n = 2–6), were identified in studies of dimeric dimethylaluminum chloride and methylaluminum dichloride. The experiments included elevated Knudsen cell temperatures, causing the following decompositions to occur: $(CH_3)_4Al_2Cl_2 \rightarrow (CH_3)_3AlCl_3 \rightarrow$ *trans*-$(CH_3)_2Al_2Cl_4$ (350–450 °C) and $(CH_3)_2Al_2Cl_4 \rightarrow (CH_3)Al_2Cl_5 \rightarrow Al_2Cl_6$ (550 °C). These cracking reactions are more prominent than the mere dissociations. On the basis of the valence force field of Al_2Cl_6 a good agreement between calculated and observed skeletal frequencies was achieved for the dimers. Frequencies were found to fall within narrow ranges for skeletal stretching modes involving the same atoms or groups.

Introduction

Aluminum alkyls and the related chlorides are essential components in Ziegler–Natta catalysts for the polymerization of propene.[2] Although these alkyls are important industrial chemicals, the knowledge on their structure and reactivity is relatively scarce. In this context, spectroscopic characterization is important, particularly if it is possible to prepare compounds with successive substitution of chlorine for alkyls. Group frequencies, relative bond strengths, and inductive effects then may be evaluated.

The most feasible possibility seems to be to produce the desired new compounds by high-temperature gas-phase experiments. Cracking reactions, dissociation of dimers and redistribution among alkyls and chlorine atoms may take place under these conditions. The products may be unstable and difficult to identify at high temperature, but immediate condensation with an inert material at cryogenic temperature allows the species to be studied carefully.

In a previous paper we reported the first infrared (IR) spectra of trimethyl- and triethylaluminum isolated in solid argon.[3] Matrices containing the monomers of these aluminum trialkyls were prepared by thermal dissociation of the dimers via the Knudsen cell technique. The dissociations were obtained without significant side reactions.

The chlorine-bridged dimeric structure of $(CH_3)_2AlCl$ and CH_3AlCl_2 has been confirmed by various spectroscopic methods,[4] including IR spectroscopy.[5-9] Vibrational data have, however, not been reported for the monomeric compounds and spectroscopic data are incomplete even for the dimers. This deficiency probably is due to experimental problems as the compounds are very reactive and hence difficult to handle. Furthermore, thermal dissociation of the dimers might be expected to be more difficult for the chlorides than for the pure aluminum alkyls as the chlorine bridge is stronger than the alkyl bridge.[10,11]

Here, we discuss the reactions of dimethylaluminum chloride (DMAC) and methylaluminum dichloride (MADC) at temperatures up to 550 °C. By the use of the Knudsen cell technique in conjunction with matrix isolation, reaction products could be isolated and characterized by IR spectroscopy. Interpretation of the vast amount of data gathered for different reaction temperatures and matrix-annealing times benefitted from normal coordinate analyses of the skeletal modes. A single dynamic model for alkyl groups and accurate force constants transferred from similar molecules constitute an effective tool in the identification and vibrational assignment of halogen-bridged compounds.

Experimental Section

The matrix-isolation apparatus has been described in detail elsewhere.[3,12] It consists of a closed-cycle helium cryostat (Cryodyne Cryocooler Model 21, CTI), a Pfeiffer TSU 110 turbomolecular pump, a stainless-steel deposition chamber equipped with CsI windows, a furnace, and a gas-mixing system. The inner stainless-steel tube of the furnace is sealed to the deposition chamber. Knudsen effusion cells of Graph-I-Tite G with an orifice diameter of 0.3 mm were employed. The temperature was measured with a Chromel/Alumel thermocouple connected to a Eurotherm proportional controller.

To avoid water and oxygen in the system, all parts were heated during evacuation, cooled and exposed in trimethylaluminum, and evacuated to 5×10^{-6} Torr before the deposition chamber was closed off from the pump.

Matrices were prepared by mixing the species leaving the Knudsen cell with argon gas immediately before the deposition window. The alkylaluminum chlorides were let into the Knudsen cell through a stainless-steel tube from a glass bulb attached to the furnace. The vapor pressure of the compound in the bulb was controlled by the temperature. Applied temperatures were 0 and 25 °C for DMAC and MADC, respectively, giving estimated vapor pressures of ca. 2–3 Torr.[13] Argon deposition rates were in the range 2–15 mmol/h, deposition times were 45 min, and

(1) Present address: Center for Industrial Research, 0314 Oslo 3, Norway.
(2) Boor, J. *Ziegler-Natta Catalysts and Polymerizations*; Academic: New York, 1979.
(3) Kvisle, S.; Rytter, E. *Spectrochim. Acta, Part A* **1984**, *40A*, 939.
(4) Mole, T.; Jeffery, E. A. *Organoaluminium Compounds*; Elsevier: Amsterdam, 1972, and references therein.
(5) Hoffmann, E. G. *Z. Elektrochem.* **1960**, *64*, 616.
(6) Groenewege, M. P. *Z. Phys. Chem. (Munich)* **1958**, *18*, 147.
(7) Gray, A. P. *Can. J. Chem.* **1963**, *41*, 1511.
(8) Onishi, T.; Shimanouchi, T. *Spectrochim. Acta* **1964**, *20*, 325.
(9) Weidlein, J. *J. Organomet. Chem.* **1969**, *17*, 213.
(10) *JANAF Thermochemical Tables*, 2nd ed.; NSRDS-NBS 37; U.S. Department of Commerce: Washington, D.C., 1971.
(11) Smith, M. B. *J. Organometal. Chem.* **1972**, *46*, 31.
(12) Kvisle, S.; Rytter, E. *J. Mol. Struct.* **1984**, *117*, 51.
(13) (a) *Aluminum Alkyls*; Texas Alkyls: Westport, TX, 1976. (b) Ufnalski, W.; Sporzynski, A. *J. Organomet. Chem.* **1983**, *244*, 1.

0020-1669/86/1325-3796$01.50/0 © 1986 American Chemical Society