Preparation and Resolution of Cr(III) Hydroxamate Complexes into their Geometrical and disstereoisomers (Part II)

MOHAMMAD RASUL JAN*, IMDADULLAH AND JASMIN SHAH
Department of Chemistry, University of Peshawar

(Received 30th April, 1988, revised 26th June, 1989)

Summary: Tris hydoxamate complexes of Cr(III) and Fe(III) have been prepared. As Fe(III) hydroxamates are kinetically labile, it was difficult to resolve them into its geometrical and diastereoisomers. The Cr(III) hydroxamates complexes were resolved into its geometrical and optical isomers based on their chromatographic behaviour and dipole moments. The results obtained by chromatographic and dipole moment studies confirm our finding based on U.V. visible and infrared studies (Part-I).

Introduction

Hydroxamic acids form metal complexes by chelation of metal ion between the two oxygen atom of the monoanion to give a five membered ring. They are well known to form both soluble and insoluble coloured complexes [1,2]. The ability of these hydroxamic acids to form stable complexes form the basis for their use as a transport medium for iron from the environment to the biological cell [3] and as a remover of excess iron from hyper transfused mice [4].

*Author to whom correspondence should be addressed.

Most of the microbial iron transport compounds contain three hydroxamate groups which coordinate ferric iron octahedrally and two important classes of these compounds are the ferrichromes and the ferrioxamines. Infact many of structure-function relationship of the ferrichromes (Siderochromes) cannot be answered, because of the kinetic lability of high-spin iron(III) complexes [5]. Substitution of chromic for ferric ion reduces kinetic inertness and increases the possibility of isolating coordination isomers of the biological iron transport compounds. X-ray crystallographic investigation have shown that ferrichrome A has the *-cis* configuration [6], while *tris* benzohydroxamate iron(III) crystalyses in a racemic cis form [7]. Detailed research has been carried out to investigate fully the coordination geometries of differrisiderchromes with some kinetically inert trivalent metal ions [8-11].

In this paper, the separation of the isomers have been reported, based mainly on their chromatographic behaviour and dipole moment studies.

Experimental

All the hydroxamic acid used in this work were synthesized in our own laboratory by the method already published [12], while $Cr(CO)_6$ were purchased commercially.

Physical method

U.V. visible spectra were recorded on a Perkin Elmer 552 Spectrophotometer, equipped with a PE 350 data station attachment.

Purification and Preparation of Materials:

Acetonitrile (Hopkins and Williams LTD) was dried over calcium sulphate and stored over molecular sieves, type 5A (Hopkins and Williams LTD). Chromium hexacarbonyl (Fluorochem LTD) was sublimed before use and stored at 0°C.

Preparation of tris hydroxamate Chromium(III) Complexes:

All the tris hydroxamate chromium(III) complexes were prepared by the same general procedure as discussed in Part-I.

Separation of Geometric Isomers of $Cr(AHA)_3$, $Cr(PHA)_3$ and $Cr(SHA)_3$

The *cis* and *trans* isomers were separated by column chromatography as follows. Kieselgel 60 (No. 7734, Merck Chemicals Ltd) in 20% CH_3-OH-$CHCl_3$ was packed under nitrogen pressure in a glass column (diameter = 20 mm, length = 500 mm). A solution of 100 mg of complex in 1 ml of eluent was applied to the column and eluted under nitrogen pressure. Two green fractions were collected within one hour at 0°C and stored in solution at 0°C in the absence of light until spectra and analysis were obtained. The purity of the *cis,* and *trans* isomers was ascertained by thin layer chromatography (tlc).

Separation of Diastereo Isomers:

The two *trans* isomers were separated by column chromatography. The complex (300 mg) was chromatographed on kieselgel 60 with 5% CH_3OH-$CHCl_3$ as the eluent on the column (diameter 35 nm length 500 nm). Three bluish green fractions were collected within 60 minutes at 0°C and stored in solution at 0°C in the absence of light until spectra and analysis were obtained. As before the purity of the isomers was ascertained by tlc.

In separation of both the geometric and diastereoisomers all the chromatographed fractions were stored in solution at 0°C in the dark as the isomers racemize and isomerize in solution even at room temperature.

Results and Discussion

Microanalytical results and physicochemical properties of the synthesised compounds are given in Table-1, and the results of the chromatographic studies are given in Table-2. In order to classify chelates in terms of their rearrangement rates, Holm *et al* [13-15] introduced the term "slow" and "fast". Slow complexes are those geometrical isomers which can be separated and at least partially resolved under ordinary conditions and are usually formed by nonlabile metal ions, such as Co(III), Cr(III), Rh(III) and Os(III). Fast or stereochemically nonrigid complexes are those whose rates are too large to permit isomer separation and resolution and are usually formed by labile

Table 1: Microanalytical data and physicochemical properties of Cr(III) hydroxamates

Compound	Analysis			Colour	M.P.°C	Magnetic moment B.M.
	C	H	N			
$Cr(AHA)_3$	24.82 (25.42)	4.82 (4.61)	14.38 (14.78)	blue/green	187-188	3.79
$Cr(PHA)_3H_2O$	32.33 (32.50)	5.99 (6.45)	12.57 12.76	blue/green	184-185	3.78
$Cr(SHA)_3$	67.21 (67.15)	11.41 (11.71)	4.35 3.51	green	180-181	3.82
$Cr(MAHA)_3.H_2O$	32.33 (32.47)	5.98 5.69	12.57 12.76	blue/green	189-190	3.78
$Cr(PBHA)_3$	68.03 67.72	4.36 4.67	6.10 5.96	blue/green	191-192	3.84

*Values in brackets are found values.
Values without brackets are theoretical values.

ions such as Ai(III), Ga(III), V(III) and high spin Fe(III).

Chromatographic behaviour of Cr(III) Hydroxamates:

With this classification of chelates Cr(III) and Fe(III) hydroxamates have been prepared and the geometrical isomers of Cr(III) have been resolved. The Fe(III) hydroxamates are "fast complexes" and separation of the geometric isomers was not possible, because the isomers are in rapid equilibrium in solution due to the lability caused by the high spin d^5 electronic configuration of the ferric ion. As a result the mixture of the two isomers *cis* and *trans* of the Fe(III) hydroxamates elute as one band with the R_f value, that is a weighed average of the R_f elution values of the *cis* and *trans* isomers of the Cr(III) hydroxamates. For our octahedral complexes formed with three equivalent optically active hydroxamate anions, there are two geometric isomers possible, *cis* and *trans*. Each of these geometric isomers consists of and optical isomers [16]. These are diastereoisomers because of the ligand optical activity and so there are four possible isomers that is *-cis, trans, -cis* and *-trans* as shown in Fig. 1.

The assignment of geometric isomers to the two green bands of $Cr(AHA)_3$, $Cr(PAA)_3$ and $Cr(SHA)_3$ is based on separation of these isomers by chromatographic techniques. The *trans* isomer is more abundant than the *cis* isomer. In the absence of any difference in energy, the *trans* isomer is always expected to be more abundant, since the probability of *trans* isomer is three times that of forming the cis isomer. For the Cr(III) hydroxamate prepared, the *trans* to *cis* ratio of 2.0 was obtained, which differ slightly from the statistical value of 3.0.

Separation of Diastereoisomers:

Four diastereoisomers may exist for the tris Cr(III) hydroxamate complexes of MAHA and PBHA as the ligand is chiral and the donor oxygen atoms are not equivalent. The properties of Cr(III) and Fe(III) complexes, $Fe(MAHA)_3$, $Cr(MAHA)_3$, $Fe(PBHA)_3$ and $Cr(PBHA)_3$ are summarized in Table-2. Due to the rapid equilibration of the kinetically labile ferric complex, thin layer chromatography results in one broad reddish brown band for which the R_f value is weighed average of the bluish green bands of the *cis* and *trans* isomers of the Cr(III) complexes.

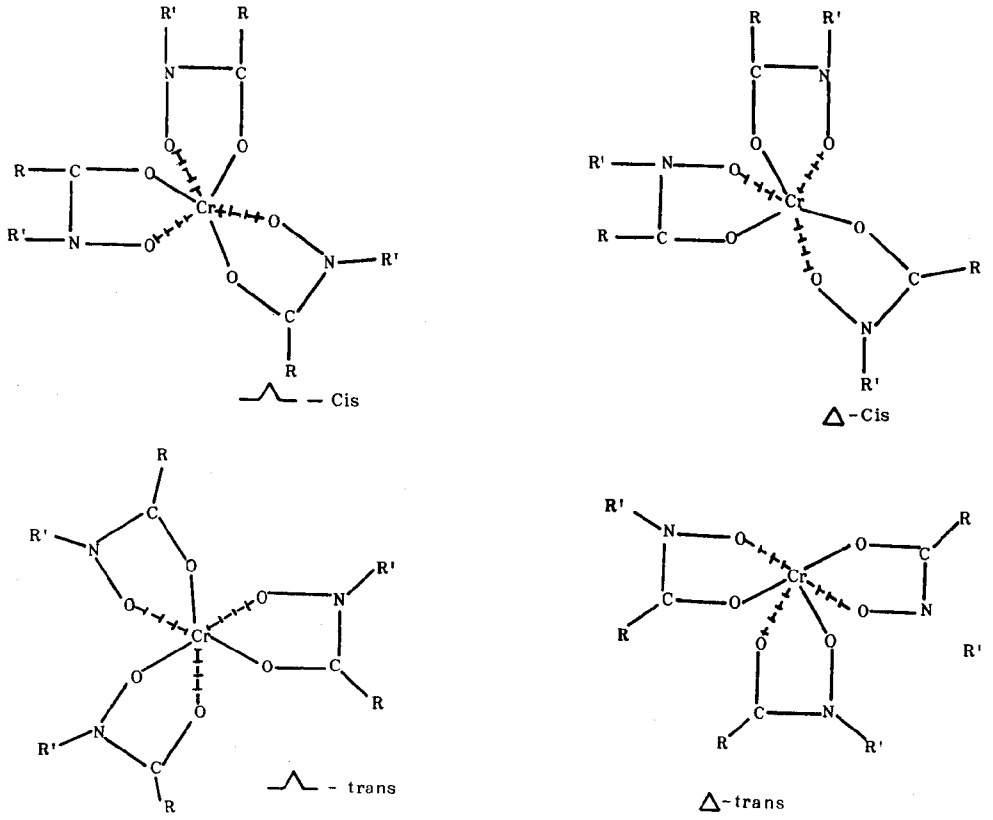

Fig. 1: Diastereoisomers of tris hydroxamate. Cr(III) complexes.

The presence of another free hydroxamic acid, MAHA or PBHA with the Cr(III) hydroxamate does not retard the racemization and isomerization of the tris hydroxamate complex. Therefore the Cr(III) hydroxamates are not sensitive to the substituent on the nitrogen as the non N-substituted [$Cr(AHA)_3$, $Cr(PHA)_3$ and $Cr(SHA)_3$] and N-substituted [$Cr(MAHA)_3$ and $Cr(PBHA)_3$] hydroxamate complexes isomerize with half lives of five hours.

Only three bluish green bands are separated by thin layer chromatography (tlc) of $Cr(MAHA)_3$. The same number of bands were separated for the other N-substituted Cr(III) hydroxamate complex [$Cr(PBHA)_3$]. As the examination of the molecular modes (Fig. 1) shows, all four diastereoisomers are possible, we conclude that two diastereoisomers are contained in one of the bluish green bands of the tlc.

For $Cr(MAHA)_3$, the isomer having an $R_f = 1.32$ was assigned as - *cis* isomer while that one with R_f value of 2.17 was assigned as a mixture of the *trans* and isomer in which the latter predominate. Similar assignments were made for $Cr(PBHA)_3$.

The assignment of geometric isomers were found to be consistent with their polarity, that is the more polar *cis* isomers elute slower than the *trans* in tlc. Thus the band in $Cr(MAHA)_3$ with R_f values of 1.32 and 0.98 were assigned as *cis* and the band with as R_f values of 2.17 must contain both *trans* isomers.

The abundance ratio of *trans* to *cis* as assigned to 2.6 for $Cr(MAHA)_3$ and 2.1 for $Cr(PBHA)_3$ is very similar to that observed for $Cr(AHA)_3$ of 2.0 and very near the statistical value of 3.0. As the *cis/ -cis* ratio is not very different for the $Cr(MAHA)_3$ and $Cr(PBHA)_3$ complexes.

Table 2: Characterization of Cr(III) Hydroxamate and Fe(III) Hydroxamate Complexes.

Assigned Configuration[a]	R_f[b]	Abundance % of total	Absorption Max, nm and Extinction coefficient (E)[c]	
			$^4T_{1g}$ $^4A_{2g}$	$^4T_{2g}$ $^4A_{2g}$
Fe(AHA)$_3$	1.23			
trans- Cr(AHA)$_3$	1.69	65	422.1(110.0),	593.4(80.1)
cis- Cr(AHA)$_3$	1.11	35	425.1(112.1),	595.8(80.7)
Fe(PHA)$_3$	1.30			
trans- Cr(PHA)$_3$	1.83	63	420.1(101.9),	591.6(85.2)
cis- Cr(PHA)$_3$	1.23	37	423.8(103.4),	594.3(82.3)
Fe(SHA)$_3$	1.21			
trans- Cr(SHA)$_3$	1.58	69	416.3(101.4),	590.1(82.1)
cis- Cr(SHA)$_3$	1.21	31	419.6(101.6),	592.3(82.3)
Fe(MAHA)$_3$	1.84			
trans- Cr(MAHA)$_3$	2.17	72	432.1(48.1),	589.1(68.9)
cis- Cr(MAHA)$_3$	1.32	8	435.1(63.4),	587.9(72.1)
cis- Cr(MAHA)$_3$	0.98	20	434.8(63.7),	588.6(72.2)
Fe(PBHA)$_3$	1.43			
trans- Cr(PBHA)$_3$	1.99	68	428.4(49.8),	590.1(70.3)
cis- Cr(PBHA)$_3$	1.23	12	429.9(66.2),	589.3(71.4)
cis- Cr(PBHA)$_3$	1.04	20	429.8(66.9),	589.5(71.5)
Fe(BHA)$_3$[d]	1.06			
trans- Cr(BHA)$_3$	1.48	68	400(117.1),	600 (83.1)
cis- Cr(BHA)$_3$	0.92	32	415(121.4),	596(82.3)

a. AHA = acetohydroxamic acid, PHA = Propionohydroxamic acid
SHA = stereohydroxamic acid, MAHA = N-Methyl acetohydroxamic acid
PBHA = N-Phenyl benzohydroxamic acid, BHA = Benzohydroxamic acid

b. R_f = (distance of complex from starting point)/(distance of the standard from the starting point). The standard is the appropriate hydroxamic acid e.g. AHA.

c. Data refer to visible region only, units are litre mol^{-1} cm^{-1}

d. of Ref. 4.

Therefore it must be concluded that some kinetic control of stereoselectivity occurs for the Cr(III) (N- substituted hydroxamate)$_3$ complexes.

Dipole moments:

In all cases the *cis* isomers should be strongly bound by the sorbent as the dipole moments of the *cis* Cr(III) hydroxamates are greater than those of the corresponding *trans* Cr(III) hydroxamates. Therefore the green band with the smaller R_f value was assigned as the *cis* isomer.

The expected molecular dipole moments of the six polar molecules of Cr(III) (AHA)$_3$ were calculated using the C-CH$_3$ and N-H group moments obtained from the aqueous mono-substituted benzene and ammonia, which are 0.37 and 1.33D, respectively. These moments were added vertically as indicated in Fig. 2. It was assumed that the C-C and N-H bonds make an angle of 12.5° with the Cartesian coordinate defined by the metal-oxygen framework as has been found in the crystal structure of Fe(OCOC)$_3$ [18].