Chapter 4

Discussions

4.1 Syntheses of complexes

4.1.1 Finding the suitable solvent for curcumin

From Table 1, curcumin could dissolve in ethanol, dichloromrthane, methanol, ether, acetone, and acetyl acetate. In this work ethanol, methanol and acetone were selected because of different curcumin solubilities in these solvents which should have some effect on the crystallization of product. The results showed that among the three solvents, ethanol and methanol gave crystals of higher quality.

4.1.2 Varying mole ratio of reactants

From 2.3.2 (method 1), mixing metal salts ($NiCl_2.6H_2O$, $CuSO_4.5H_2O$, $FeSO_4.7H_2O$, and $FeCl_3.6H_2O$) with curcumin in 1:1 and 1:2 mole ratio were carried out. Results are given in Tables 2-3. From which it was shown that at the mole ratio of 1:2, more precipitate was obtained while other physical appearances were similar to the 1:1 mole ratio. The mole ratio 1:2 then was used in further experiment. The reactions between ferric chloride and curcumin were carried out both in the ratio of 1:1 and 1:2 and with two systems of solvents, water/methanol and water/acetone, which yielded dark brown (Fe-CU1) and red brown (Fe-CU2) precipitates, respectively. The products were characterized by XRF and IR techniques

From 2.3.2 (method 2), the complexes were prepared by adding metal salts (Cu(II), Hg(II), Cr(II) and Ni(II)) 0.05, 0.11, 0.22 mmol, respectively, to a solution of curcumin 0.08 mmol (in three different media in which curcumin

dissolved). These resulted in the mole ratio of curcumin : metal ion as 1.6 : 1, 1.6 : 2.2 , and 1.6 : 4.4. The results are given in Tables 4-6. The results showed that none of these ratios yielded any products or precipitates.

4.1.3 Varying the reaction temperatures

From 2.3.3, mixing curcumin with various metal salts ($NiCl_2.6H_2O$, $Ni(CH_3COO)_2.4H_2O$, $MnCl_2.4H_2O$, $Cd(NO_3)_2.4H_2O$, $CrCl_3.6H_2O$, $FeCl_3.6H_2O$, $LaCl_3.H_2O$, $Co(CH_3COO)_2.4H_2O$, $HgCl_2$) in the molar ratio 2:1 in ethanol. The resulting complexes were summarized in Table 7. The reactions with refluxing at 80 $^\circ$C gave good quality single crystals. The single crystals of complexes CUCr and CULa were studied by X-ray diffraction technique.

4.1.4 Addition of NaOH to promote the reaction

A solution of NaOH at different concentration (2.5, 5.0, 10, 20 and 50 mM) was added to solution of curcumin with metal salts. Results are given in Table 8. Addition of NaOH helps promote the reaction between curcumin and metal ion as shown in the following scheme (Jovanovic et al., 1999)
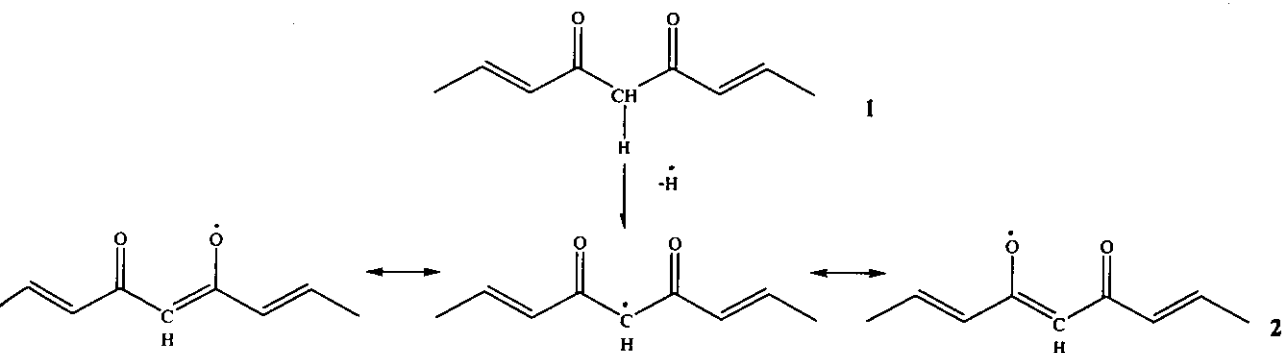
In methanol or other solvents with pH 3-7 curcumin exists in the keto form (1) but with pH > 8, such as the addition of NaOH, it changes to the enol

form (2). In the presence of NaOH the acidic H-atom at the middle of the molecule is ionized as H^+ leaving the remaining of the entire curcumin molecule as the mono-negative anion. The negative charge located at one of the middle O atom but it can delocalize between the two O atoms. This helps attraction with the positive charge at the metal ion, hence, the reaction should take place more readily with the addtion of NaOH. Many reactions, with addition of NaOH, gave crystalline products as shown in Table 8. Among these, only A1, B1 and B2 were single crystals and could be studied further by X-ray technique.

4.1.5 Attempts to synthesize curcumin complex with lanthanide elements

A solution of metal oxide (Sm_2O_3, La_2O_3, Gd_2O_3, Nd_2O_3, Yb_2O_3, Dy_2O_3, Er_2O_3 and Pr_6O_{11} 0.10, 0.25, 0.50 and 1.00 ml) was added to a solution of curcumin in 10 mM NaOH/50%MeOH (30 ml). Results are given in Tables 9-10. For La_2O_3, Gd_2O_3, Nd_2O_3, Yb_2O_3, Dy_2O_3, Er_2O_3 and Pr_6O_{11} orange precipitates were obtained whereas for Sm_2O_3 yellow and orange precipitates resulted. The products were studied by XRF and IR techniques.

4.2 X-ray Fluorescence Spectrometry

This method was used to prove the presence or absence of the elemental composition of compounds, such as, the added metals (Fe, La, Yb, Er, Cu, Ni, *etc*). It was only fundamentally qualitative analysis. In this research, the complex of Fe-CU1, Fe-CU2 (in 2.3.2, method 1), and La-CU (in 2.3.5) were analyzed by XRF technique. For Fe-CU1 and Fe-CU2 complexes, the spectrum of Fe was detected which showed that Fe was present in the Fe-CU1 and Fe-CU2 complexes. For La-CU complex, the elements Fe, Si and Al were found in the complex, as the K_α lines of Fe, Si and Al

appeared at 6.40, 1.74 and 2.42 keV, respectively. In addition, trace amount of Mg, Ca, Ti, Ni and Cu were also found but the characteristic line of La did not appear in the La-CU complex. This indicated that the lanthanide elements were not present in the products or we can say that the lanthanide elements did not react with curcumin. The XRF spectra of all complexes are illustrated in Figures 12-20.

4.3 Single crystal X-ray diffraction

Four solid products of CULa, CUCr (in 2.3.3), A1 and B2 (in 2.3.4) were obtained as single crystals and subsequently were determined by X-ray diffraction method to investigate the coordination geometries including the interactions that affect their geometries and crystal packing.

The data of CULa, CUCr, A1 and B2 are shown in Tables 11-14. The single crystal structures of the four products (CULa, CUCr, A1 and B2) are similar. The results of X-ray data will be explained based on crystal of A1. The crystal consists of C, H and O atom. The crystal is monoclinic, and the space group is P2/n with Z = 4. The cell dimensions are a = 12.7013(10) Å, b = 7.2174(6) Å, c = 19.9093(16) Å, α = 90°, β = 95.2520(10)°, γ = 90°. The labeling of the atoms is indicated in Figures 19-20. Figure20 illustrates the molecule as it appears in crystal as well as the molecular packing and the hydrogen bonding system.

Since the vast majority of X-ray crystallography is conducted to elucidate the molecular structures and it still be a major tool for studying hydrogen bonding interactions despite the well-known limitation of this technique in the past for locating hydrogen atoms. Indeed, the relative strength of individual hydrogen bond can be inferred from the molecular arrangement in crystal structure.

In this structure, the molecules are aggregated inter-molecularly into infinite chains linked between the Ph (-OH) and the carbonyl O. The positions of the hydrogen

atoms at O1 and O18 were introduced from considerations of the hydrogen bond system. A final difference map suggested two possible positions for the last hydrogen atom supposed to be attached to the O10 or O12 atoms. The best result was obtained by placing a half hydrogen atom in each of the two positions indicating a statistical distribution of the hydrogen atom at the two positions. Such a network formation is attributed to intermolecular hydrogen bonds between terminal phenol moieties of curcumin assembling in a fibrous structure. Furthermore, it was found that the hydrogen bonding played an important role in the molecule packing of crystal curcumin.

Intra-molecular hydrogen bonding in the fragment – CO – HC = COH – indicated that the β-diketones prefer the *cis*-enol configuration stabilized by strong intra-molecular H-bond. This hydrogen bond appears moreover invariably to be asymmetrical, the hydrogen atom always found to be bonded to one unique oxygen atom.

The molecule may be described as consisting of three substituted planar groups interconnected through the two double bonds C8 – C9 and C13 – C14. The two terminal groups are identical but the inherent symmetry of the molecule is distorted in the crystal by a rotation of C12 – C13 bond.

All parameters are given in Tables 14-17. The bond lengths and angles are given in Table 18 and some torsion angles in Table 19. The study by this technique showed that CuCr, CULa, A1, and B2 were, in fact, the curcumin molecule. So the conclusion for this section is that no compounds between curcumin and metal ions have been produced from these reactions.

4.4 Infrared spectroscopy

Characterization of complexes was mainly based on X-ray diffraction studies.

Nevertheless, infrared spectroscopy is a good indicator of incorporation of metal ion and ligands into the complex systems. Studies of the effect of coordination on the infrared spectra of metallic complexes afford valuable information on the nature of the metal-ligand bond and the stability of the complex. The infrared spectrum of isolated molecule is determined by arrangement of atoms in space and by the force between atoms. When a ligand coordinated, all of these forces change. The changes are to be expected both in the vibrational spectral features associated with the free ligand and those systems to which it attached. IR spectra were recorded (KBr discs) in the region 4000-400 cm^{-1} on Perkin-Elmer Spectrum GX FT-IR spectrometer to obtain the information of the coordination mode of ligands.

Curcumin or diferuloylmethane having two *o*-methoxy phenolic OH groups attached to the α,β- unsaturated β-diketone (heptadiene-dione) moiety, which undergoes keto-enol tautomerism, where the diketone moiety can form metal chelates.


Keto form

Enol form
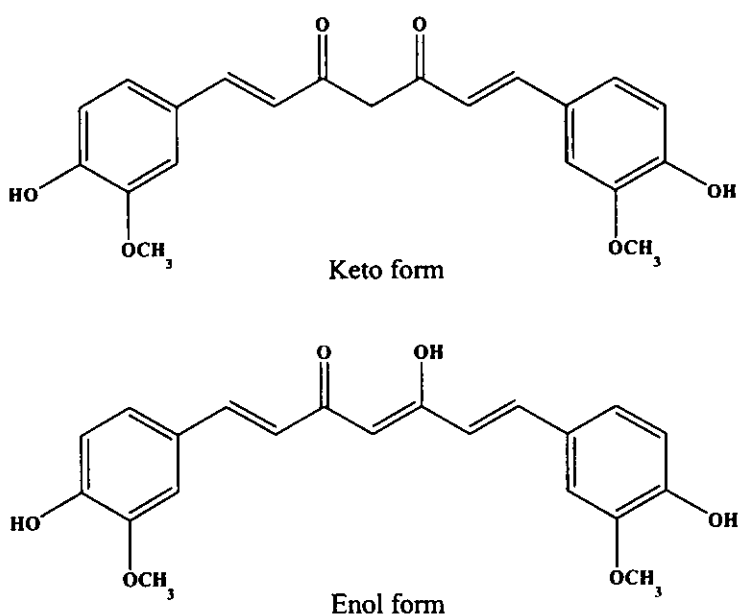
Recently there have been many reports in the literature on the metal-chelating properties of curcumin, employing techniques like potentiometry and absorption spectroscopy. Curcumin forms complexes of the type 1:1 and 1:2 with copper, iron and

other transition metals. This property of binding of curcumin to metals like iron and copper is considered as one of the useful requirements for the treatment of Alzheimer's disease.
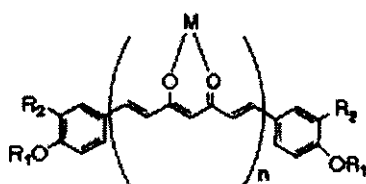
The previous studies of infrared absorption spectra for curcumin derivatives (or curcuminoids) and some metal curcumin complexes are summarized in Table 20 and as follows:

Sharma, et al. synthesized and studied the gold (I) complex, [AuL$_2$]Cl (L=curcumin) by infrared spectroscopic technique. The results showed that on complexation the position of the O-H band remained unaltered, which suggests that no coordination takes place through the OH group but the position of the C=O band is shifted towards lower wavenumbers, which suggests that the ligand coordinated with the central metal ion through the C=O group (Sharma et al., 1987).
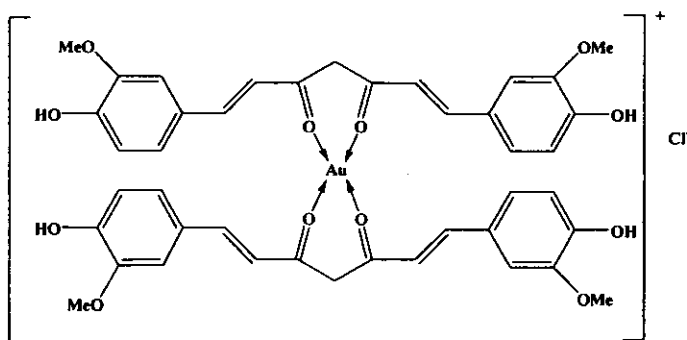
Barik, et al. synthesized and characterized a new copper(II)-curcumin complex. The result showed that the C=O frequency in curcumin which appeared at 1630 cm^{-1} was shifted by 10 cm^{-1} on copper complexation indicating its involvement in complexation (Barik et al., 2005).

Mohammadi, et al. synthesized and characterized various derivatives of vanadyl, gallium and indium curcumin complexes as follows (Mohammadi et al.,2005).

[VO(cur)₂], VO(DAC)₂]   n = 2; M=VO, R₁ = H, Ac; R₂ = OCH₃
[VO(BDC)₂], VO(DABC)₂]   n = 2; M=VO, R₁ = H, Ac; R₂ = H
Ga(cur)₃], [Ga(DAC)₃]   n = 3; M = Ga, R₁ = H, Ac; R₂ = OCH₃
[In(cur)₃], [In(DAC)₃]   n = 3; M = In, R₁ = H, Ac; R₂ = OCH₃

Table 20 is the compilation of vibrational modes of metal-curcumin complexes that have been reported.

Table 20 The previous studies of infrared absorption spectra for curcuminoids and some metal curcumin complexes.

References	Compounds	Vibrational modes	Region (cm^{-1})
Sharma et al.,1987	Gold(I)complex	ν_{O-H}	3350 (3350)
		$\nu_{C=O}$	<1730 (1730)
Barik et al.,2005	Cu(II) complex	ν_{O-H}	~3000
		$\nu_{C=O}$	1620 (1630)
		ν_{C-H} (in alkane)	1620
		ν_{C-O} (in phenol)	1280
		ν_{C-O} (in OCH$_3$)	1020
		ν_{C-H} (in aromatic)	980
Mohammadi et al.,2005	Vanadyl curcumin; [VO(cur)$_2$]	ν_{O-H}	~3495
		ν_{C-H}	3010-2935,1391
		$\nu_{C=O}$	1626
		$\nu_{C=C}$	1591,1489
		$\nu_{C-O,C-C-C}$	1261-1151
		ν_{C-H} (in aromatic)	847
		$\nu_{V=O}$	966

Table 20 (Continued)

References	Compounds	Vibrational modes	Region (cm^{-1})
	Tris(curcuminato)-gallium(III); [Ga(cur)$_3$]	ν_{O-H}	3500-3200
		ν_{C-H}	3150-2700,1391
		$\nu_{C=O}$	1624
		$\nu_{C=C}$	1600,1507
		$\nu_{C-O,C-C-C}$	1286-1125
		ν_{C-H}(in aromatic)	972
		$\nu_{V=O}$	847
		ν_{Ga-O}	469
	Tris(curcuminato)-indium(III); [In(cur)$_3$]	ν_{O-H}	3500-3200
		ν_{C-H}	3200-2700,1391
		$\nu_{C=O}$	1624
		$\nu_{C=C}$	1596,1511
		$\nu_{C-O,C-C-C}$	1286-1125
		$\nu_{H-C=C-H \text{ (trans)}}$	984
		ν_{C-H}(in aromatic)	815
		ν_{In-O}	465

In this work, curcumin and the products of 2.3.2(method 1, Fe-CU1 and Fe-CU2) and 2.3.5 (in Table 10) were recorded by IR technique. From the results in Table 10, yellow precipitate of Sm-CU(0.5) and orange precipitate of Sm-CU, La-CU, Gd-CU, Nd-CU, Yb-CU, Dy-CU, Er-CU, and Pr-CU were analyzed. The vibrational modes of these are summarized in Tables 21-22.

Table 21 IR data of curcumin, Fe-CU1 and Fe-CU2.

Vibrational modes	Frequencies (cm^{-1})		
	Curcumin	Fe-CU1	Fe-CU2
ν_{O-H}	3510	-	-
ν_{C-H}	3070-2942	3000-2900	3000-2900
$\nu_{C=O}$	1627	1594	1594
$\nu_{C=C}$	1510	1508	1509
ν_{C-O}(in phenol)	1280	1274	1270
ν_{C-O}(in OCH_3)	1029	1028	1025
ν_{C-H}(in aromatic)	962	973	975

Table 22 The vibrational modes of metal curcumin complexes

Vibrational modes	Frequencies (cm^{-1})									
	Curcumin	Sm-CU(0.5)	Sm-CU	La-CU	Gd-CU	Nd-CU	Yb-CU	Dy-CU	Er-CU	Pr-CU
ν_{O-H}	3510	3405,3265	3500	3400,3265	3400,3255	3400, 3260	3400,3260	3400,3260	3405,3265	3400,3260
ν_{C-H}	3070-2942	3035-2920	3040-2920	3000-2900	3040-2920	3040-2920	3000-2900	3040-2920	3000-2900	3000-2900
$\nu_{C=O}$	1627	1630	1630	1627	1627	1630	1630	1630	1627	1627
$\nu_{C=C}$	1510	1585,1510	1510	1590,1505	1590,1510	1590,1510	1585,1505	1580,1510	1590,1510	1590,1510
ν_{C-O}(in phenol)	1280	1270	1275	1265	1270	1275	1260	1260	1265	1270
ν_{C-O}(in OCH$_3$)	1029	1035	1030	1025	1030	1030	1030	1030	1025	1030
ν_{C-H} (in aromatic)	962	965	965	965	965	965	965	965	970	965

In order to clarify the mode of bonding the IR spectra of the complexes were compared with the spectra of the curcumin. The IR spectra of all compounds are similar. The salient feature of solid state IR spectra of the compounds exhibited by the presence of O-H stretching, C-H stretching, C=O stretching, C=C stretching, C-O stretching in OCH_3 and phenol, and C-H stretching in aromatic. IR spectroscopy provided direct information regarding the coordination of ligand.

A comparative study of the ligand and the complexes suggests that the important IR spectrum of the ligand exhibits band at 3510 cm^{-1} and 1630 cm^{-1}, due to the OH group (in enol form) and C=O group, respectively. On Fe-CU1 and Fe-CU2 (in 2.3.2, method 1), the positions of these bands are different from the ligand. The O-H stretching mode in complexes did not appear in the region 3500-3550 cm^{-1} and the C=O stretching are slightly shifted to lower frequencies, about 36 cm^{-1}, compared to free ligand. This suggests that the ligand coordinates with the central metal ion (Fe) through the C=O group. So the IR data correspond to XRF result. Furthermore, the IR spectra of all the lanthanide added products are similar to the ligand. The O-H and C=O stretching modes did not change in the complexes. This suggests that the ligand did not coordinate with the lanthanide elements. This also agrees with the XRF results which showed that the lanthanide elements were absence in all of these products. These precipitates were likely the unreacted curcumin.