

# Molecular structures of metal complexes with mefenamic acid

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## Abstract

The infrared spectra of Na and Ca complexes of mefenamic acid were investigated in the region between 4000 and 400  $\text{cm}^{-1}$ . These spectra were compared with X-ray powder diffraction patterns of complexes. It is shown that the proposed structure for these complexes obtained from the infrared spectra was supported by X-ray powder diffraction measurements. Bands due to  $\nu_{\text{as}}(\text{COO})^-$  and  $\nu_{\text{s}}(\text{COO})^-$  stretching vibrations appear at about 1580  $\text{cm}^{-1}$  and in the range 1390–1400  $\text{cm}^{-1}$  in the infrared spectra of the samples, respectively. The values of NH deformation vibrations do not change in the spectra of mefenamic acid and its metal complexes. On the other hand, molecular mechanic calculations and conformational analysis of three compounds were also established in the present work. As a result of these theoretical studies, the atomic planes and the peak assignments of the powder diffraction patterns were determined. As a result of these experimental and theoretical investigations, it may be concluded that metal atoms are connected to the carboxyl group of the mefenamic acid. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* Mefenamic acid; Infrared spectra; X-Ray powder diffraction; Molecular mechanic calculation; Metal complexes

## 1. Introduction

Metal-binding substances, many of which function by chelation, form a class of substances which have provided many useful drugs and other substances of value in selective toxicity. They have found many uses in veterinary and human medicine. Humans require the lighter, and usually more abundant, metals: calcium (Ca) and sodium (Na) which are essential for all living cells [1].

Mefenamic acid is used as an agent against fever, ache and inflammation. Some drugs had been prepared on its basis [2,3]. It should be noted that infrared and X-ray powder diffraction data on its metal complexes are not plentiful in the literature. Brzyska and Ozga [4] had prepared some complexes of mefenamic acid with rare earth elements and studied their properties by using infrared spectra and diffraction patterns. As it is known, there is a possibility of interaction between the drug and many biologically important metal ions like Na, Ca, etc. present in body fluids. Hence we have extended this study and reported Na and Ca complexes of mefenamic

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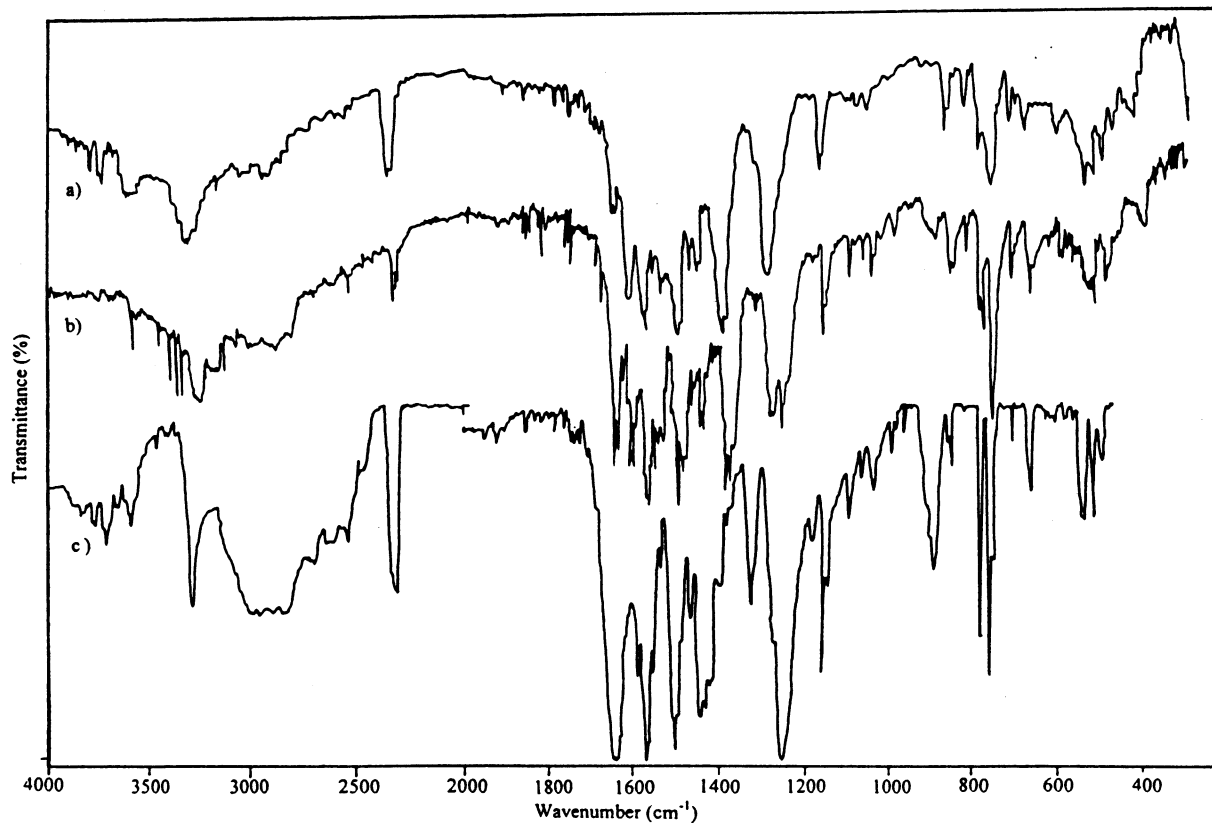


Fig. 1. The infrared spectra of (a) Ca complex (b) Na complex (c) mefenamic acid.

acid. Also, there is some disagreement regarding the assignments of the fundamental groups of mefenamic acid made by Brzyska and Ozga [4]. In our study, some revisions in the assignments have been made according to the literature. Furthermore, in the study of Brzyska and Ozga [4], the peak assignments of the X-ray diffraction patterns of the rare element complexes of mefenamic acid had not been given. In this work, the structures of these complexes were determined using infrared spectra and X-ray powder diffraction patterns with the peak assignments to provide a better understanding of the pharmacological studies.

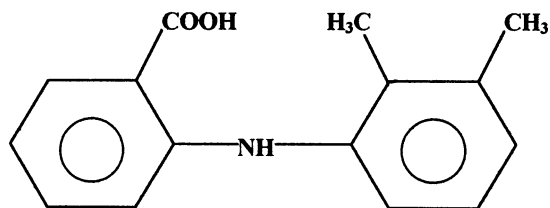
## 2. Material and methods

Light yellow crystals of mefenamic acid from Ponstan Forte tablets were grown by slow evapo-

ration of a solution of the compound in methanol at room temperature. The compounds were prepared in the following manner: Mefenamic acid (0.5 mmol) was dissolved in hot methanol by mixing. Then metal hydroxide solution (0.5 M) was added until pH 7.0 with constant stirring; the compound (light gray) was dried at room temperature for a few days.

The infrared spectra of the samples (Fig. 1) were recorded on a Perkin-Elmer 621 spectrometer using the KBr pellet technique in the region 4000–400  $\text{cm}^{-1}$  which is calibrated using polystyrene. The powder X-ray diffraction patterns (Fig. 2) were recorded using a General Electric XRD-700, SPG-2 manual spectrogoniometer employing Cu  $K_{\alpha}$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ) over the range  $2\theta$  ( $3 \leq 2\theta \leq 56^{\circ}$ ).

In order to optimize the geometries of the compounds, molecular mechanic calculation



Scheme 1.

methods were used [5]. This minimizer program performs a conjugate gradient minimization using a force field equation which is dependent on the conformation of the studied molecule and calculates the potential energy of a molecular conformation. The bond lengths, bond angles and torsion angles were fully optimized using the Alchemy 2000 program [6].

### 3. Results and discussion

As far as we know, few vibrational and structural studies have been reported for mefenamic acid molecule (Scheme 1). The infrared spectra and X-ray diffraction patterns of some complexes of mefenamic acid with rare earth elements had been reported by Brzyska and Ozga [4]. They determined the nature of the metal–organic ligand and coordination in the complexes and mentioned that in the rare earth element complexes of mefenamic acid, only carboxyl groups take part in the bonding of the metal–organic ligand by using infrared data. They gave only the shifts of absorption bands of the carboxyl group in the rare earth element complexes compared to similar bands in the sodium salt. But there is some serious disagreement regarding their assignments due to the fundamental groups of mefenamic acid. In their study, X-ray diffraction patterns of the rare element complexes of mefenamic acid had also been recorded. However, only relative intensities of the samples ( $J/J_0$ ) were given not their peak assignments.

In our study, we reported Na and Ca complexes of mefenamic acid. Some revisions in the assignments were made. The structures of these complexes were undertaken to see if any common

structural features exist between them and rare element complexes by using infrared spectra and X-ray powder diffraction patterns with the peak assignments.

The comparison between the mefenamic acid wavenumbers observed in the infrared spectra of the Na and Ca complexes and our measurement on crystalline mefenamic acid helped in defining the structure of metal complexes. The main group frequencies of mefenamic acid observed in the infrared spectra of the metal complexes, together with our measurement on crystalline mefenamic acid are given in Table 1. Some vibrational assignments of mefenamic acid taken from Brzyska and Ozga [4] are included for comparison. There is some disagreement regarding the description of some group vibrations of mefenamic acid made by Brzyska and Ozga [4]. It is well known that the presence of an aromatic-type structure is best recognised by the presence of the C–H stretching vibrations in the region  $3120\text{--}3000\text{ cm}^{-1}$  [7,8]. In our study, the bands observed at  $3102$  and  $3033\text{ cm}^{-1}$  in the infrared spectrum of mefenamic acid are assigned to the C–H stretching vibrations arising from the ring. Brzyska and Ozga [4] had described these vibrations in the range  $1060\text{--}630\text{ cm}^{-1}$ . The bands appear in the region  $1265\text{--}1000$  and  $1000\text{--}620\text{ cm}^{-1}$  in the IR spectra of aromatic structure due to the in-plane bending and out-of-plane deformation vibrations of the hydrogen atoms remaining on the ring [7,8]. As seen from Table 1, we assigned two bands at  $1060$  and  $1033\text{ cm}^{-1}$  to in-plane CH bending and also observed two bands at  $887$  and  $776\text{ cm}^{-1}$  as out-of-plane CH deformation vibrations.

In addition, Brzyska and Ozga [4] had assigned the bands at  $750$ ,  $1160$ ,  $1255$  and  $1450\text{ cm}^{-1}$  to  $-\text{CH}_3$  stretching vibrations. We have also made some revisions in their assignments according to the correlation tables [7,8]. Methyl groups on aromatic rings usually has a prominent band in the region  $2895\text{--}2800\text{ cm}^{-1}$  due to symmetric stretching mode of  $-\text{CH}_3$  group [7,8]. In our study, this band was observed at  $2809\text{ cm}^{-1}$ . In addition, the  $\text{CH}_3$  degenerate deformation vibration is also found around  $1465\text{ cm}^{-1}$ . The symmetric deformation vibrations of the  $-\text{CH}_3$  group are observed in the region  $1300\text{--}1100\text{ cm}^{-1}$  [7,8].

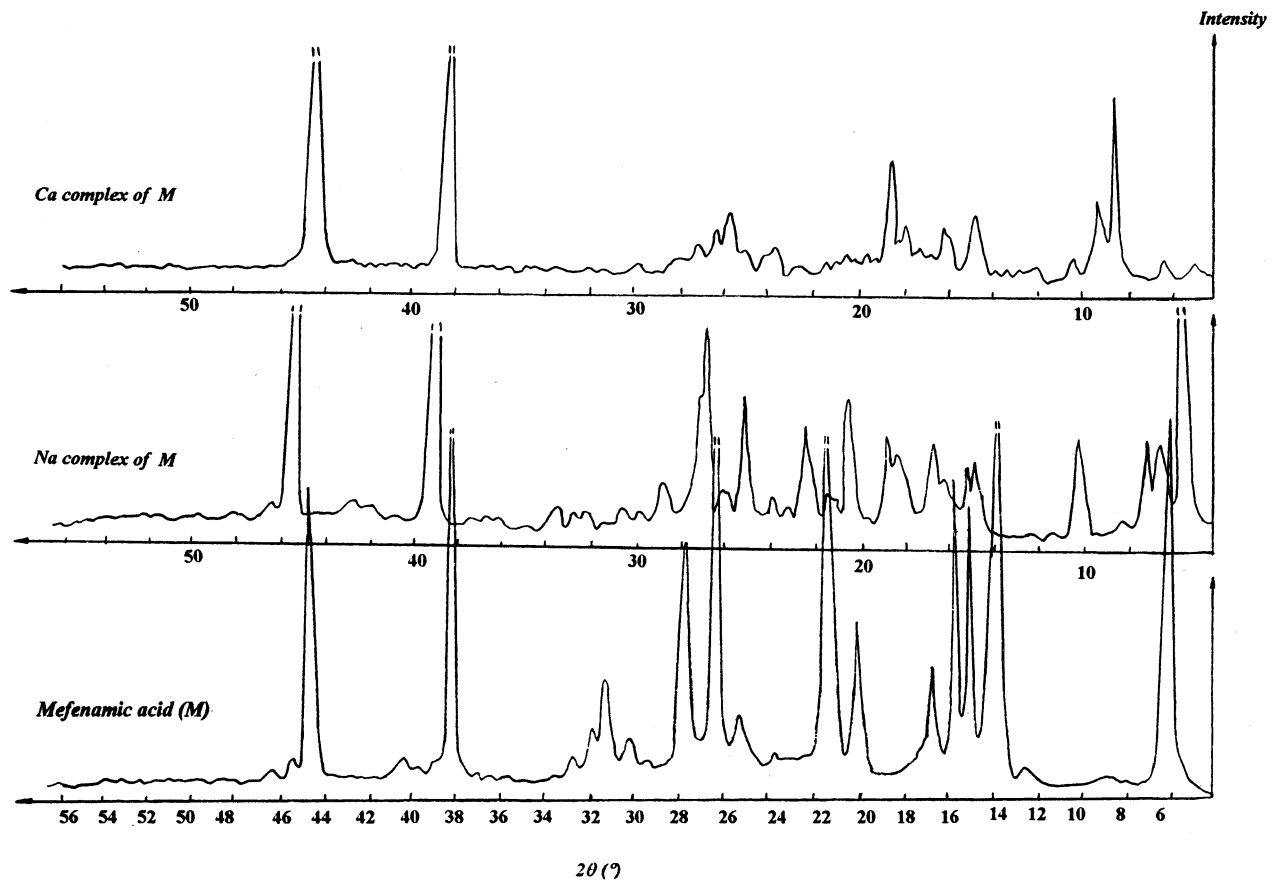


Fig. 2. X-Ray powder diffraction patterns of the samples.

As seen from Table 1, these vibrations were observed at 1450 and 1255, 1159  $\text{cm}^{-1}$  respectively. In Fig. 1, the absorption at about 1255  $\text{cm}^{-1}$  is found as a strong and broad band, so it can overlap with the OH deformation vibration in the COOH group. The band near 700–800  $\text{cm}^{-1}$  is assigned to  $-\text{CH}_3$  rocking vibration [7,8]. We observed this band at 755  $\text{cm}^{-1}$  in the IR spectrum of mefenamic acid.

In the infrared spectra of the rare earth element mefenamic acid, a broad water OH band with maximum at 3310–3350  $\text{cm}^{-1}$  had been observed by Brzyska and Ozga [4]. The NH absorptions appear near 3350 and 3250  $\text{cm}^{-1}$  [7,8]. As seen from Table 1, we assigned the observed wavenumber at 3290  $\text{cm}^{-1}$  to the stretching mode of the NH group of mefenamic acid. The band in the region 3500–3600  $\text{cm}^{-1}$  is assigned to OH stretching vibration [8]. In the infrared spectra of complexes (Fig. 1a,b), this vibration was observed about 3600  $\text{cm}^{-1}$ . In plane deformation modes of NH group in the regions 1650–

1660 and 1505–1510  $\text{cm}^{-1}$  do not have significant shifts in wavenumbers of metal complexes compared to the values in the free molecule (Fig. 1c). Brzyska and Ozga [4] had observed analogous effects in the rare earth element complexes of mefenamic acid. This conclusion is based on the fact that the coordination in the complexes should not occur through the nitrogen atom; hence the active binding site of mefenamic acid is not the nitrogen atom of the NH group. Brzyska and Ozga [4] also assigned a strong band at 1650  $\text{cm}^{-1}$  in the infrared spectrum of the mefenamic acid due to  $\nu(\text{CO})$  stretching band of COOH group. As seen from Table 1, we observed this band at 1645  $\text{cm}^{-1}$  in the infrared spectrum of free mefenamic acid. This band disappears and two new bands appear at about 1580 and 1380–1390  $\text{cm}^{-1}$ ; these are assigned to the  $\nu_{\text{as}}(\text{COO})^-$  and  $\nu_{\text{s}}(\text{COO})^-$  vibrations in the infrared spectra of metal complexes of mefenamic acid, respectively.

As a result, the new bands observed in the IR

Table 1  
Observed wavenumbers ( $\text{cm}^{-1}$ ) of mefenamic acid and its metal complexes

Mefenamic acid	Mefenamic acid <sup>a</sup>	$\text{Na}(\text{C}_{15}\text{H}_{14}\text{NO}_2)$	$\text{Ca}(\text{C}_{15}\text{H}_{14}\text{NO}_2)$	Assignment
–	–	3603	3605	$\nu(\text{OH})$
3290	–	3291	3290	$\nu(\text{NH})$
3102	–	3082	–	$\nu(\text{CH})$
3033	–	–	–	$\nu(\text{CH})$
2809	–	–	–	$\nu(\text{CH}_3)$
1659	1660	1654	1653	$\delta(\text{NH})$
1645	1650	–	–	$\nu(\text{CO})$
–	–	1580	1583	$\nu_{\text{as}}(\text{COO})^-$
1509	1510	1508	1504	$\delta(\text{NH})$
1450	1450	1450	1450	$\delta(\text{CH}_3)$
–	–	1390	1384	$\nu_{\text{s}}(\text{COO})^-$
1255	1255	1258	1260	$\delta_{\text{s}}(\text{CH}_3)$
1159	1160	1163	1161	$\delta_{\text{s}}(\text{CH}_3)$
1060	1060–630	1060	1058	$\delta(\text{CH})$
1033	–	1036	1033	$\delta(\text{CH})$
887	–	852	858	$\gamma(\text{CH})$
776	–	776	778	$\gamma(\text{CH})$
755	750	754	750	$\delta_{\text{r}}(\text{CH}_3)$
–	–	470	470	$\nu(\text{M-O})$

<sup>a</sup> Taken from Ref. [4].

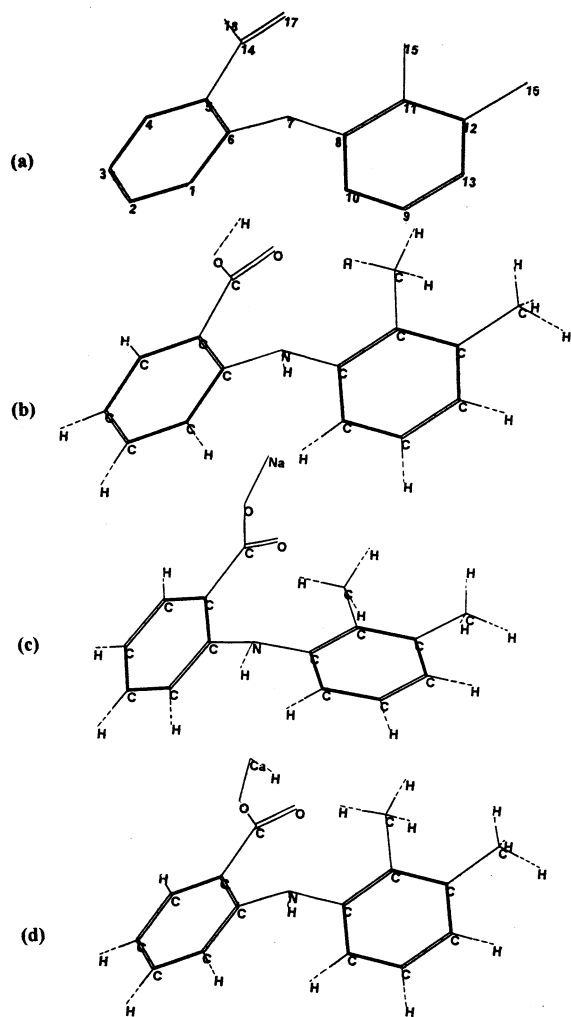


Fig. 3. (a) Numbering scheme for molecules. Molecular conformations of (b) mefenamic acid (c) Na complex (d) Ca complex.

spectra (Fig. 1) of the metal complexes for the stretching modes of  $\text{COO}^-$  allow us to hypothesize that the hydrogen atom in the  $\text{COOH}$  group is substituted by a metal atom, so the active binding site of mefenamic acid is the oxygen atom of the carboxyl group.

Molecular mechanic calculations predict the total steric energies of 19.54, 17.94 and 19.53 (kcal/mol) for mefenamic acid and Na and Ca complexes of mefenamic acid, respectively. The predicted molecular conformations of these

molecules are given in Fig. 3. All moieties have similar shapes, while their conformations slightly differ due to some different senses of torsion about the  $-\text{C6}-\text{N7}-\text{C8}-$  linkage. As a result of these studies, torsion angles which indicate the atomic planes are given in Table 2. Examinations of these torsion angles showed that the conformations of three molecules have two main planes. These are two methyl groups, the N-membered phenyl ring (I), and carboxyl group or metal binding phenyl ring (II). When the powder diffraction pattern was examined, the effects of these planes were seen.

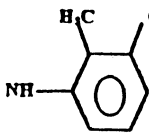
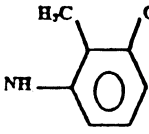
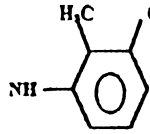

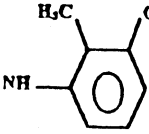
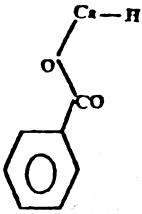

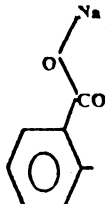
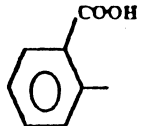
Table 3 shows the Bragg angles ( $2\theta$ ), interplanar spacing ( $d$ ) and relative intensities ( $I/I_0$ ) of the samples, together with their peak assignments. When the results of the molecular mechanic calculations were investigated it could be seen that metal binding phenyl rings (plane II) in metal complexes are more planar than the same phenyl ring including a carboxyl group in mefenamic acid. On the other hand, the opposite of this result for the other phenyl ring including methyl groups and N atom (plane I) was determined in the same research. It means that when metal atoms were bound to the mefenamic acid, two methyl groups and the N-membered phenyl ring deviate from planarity. If we examine the peak assignments of powder diffraction patterns the

Table 2  
Some torsion angles of three molecules ( $^\circ$ )<sup>a</sup>

Torsion angles	Mefenamic acid	Na complex	Ca complex
C6–N7–C8–C10	–28.35	30.11	–31.38
C5–C6–N7–C8	–73.99	–72.36	–71.43
C15–C11–C12–C16	0.36	1.46	1.89
N7–C8–C11–C15	–1.42	–1.23	–1.77
O17–C14–C5–C6	–13.96	–7.37	–7.16
O18–C14–C5–C6	168.16	172.67	172.92
C14–C5–C4–C3	–177.92	–178.55	–178.72
C4–C5–C6–N7	177.58	175.59	176.01

<sup>a</sup> The numbering scheme for molecules is given in Fig. 3a.

Table 3  
X-Ray powder diffraction analysis and peak assignments for mefenamic acid and its metal complexes

Mefenamic acid				Na complex				Ca complex			
$2\theta$ (°)	$d$ (Å)	$I/I_0$	Assignment	$2\theta$ (°)	$d$ (Å)	$I/I_0$	Assignment	$2\theta$ (°)	$d$ (Å)	$I/I_0$	Assignment
6.2	14.26	83.7		4.5	19.63	82.2		8.5	10.40	52.9	
13.7	6.46	100.0		5.6	15.78	19.5		9.2	9.61	25.9	
14.3	6.19	38.1		6.2	14.26	20.0		14.7	6.03	20.7	
15.1	5.87	58.7		9.1	9.72	26.0		16.2	5.47	17.2	
15.8	5.61	56.0		13.8	6.42	18.6		17.7	5.01	18.4	
16.8	5.28	24.1		14.2	6.24	19.0		18.4	4.82	36.2	
20.1	4.42	31.5		15.7	5.64	24.1		23.5	3.79	11.5	
21.4	4.15	85.6		17.3	5.13	21.8		25.6	3.48	21.8	
25.4	3.51	14.0		17.8	4.98	24.5		25.9	3.44	18.4	
26.4	3.38	91.4		19.4	4.58	33.2		26.3	3.39	15.5	
27.8	3.21	45.5		21.3	4.17	28.6		27.2	3.28	12.1	
30.6	2.92	9.3		24.0	3.71	35.5		38.4	2.34	100.0	
31.4	2.85	21.0		25.7	3.47	48.6		44.6	2.03	79.9	
32.0	2.80	11.3		25.9	3.44	34.5					
38.2	2.36	74.0		38.2	2.36	100.0					
44.6	2.03	58.0		44.5	2.04	86.4					

same results may also be obtained. The increased value of the relative intensity peak of plane II and the decreased value of the relative intensity peak of plane I can be seen in the diffraction patterns of metal complexes. At the end of X-ray studies, it may be said that, some atomic groups are planar or nearly planar. These atoms located in the same planes, have diffracted X-rays strongly and some sharp peaks were seen in the powder diffraction pattern. This means that sharp peaks are assigned to large atom numbers in the diffraction planes if an atom (for example Ni, Co, etc.) was bound to the planar atom group. This peak may

be glide the low  $2\theta$  range. With the help of this knowledge, molecular mechanic calculations and unit cell knowledge of some sulfanomides, the assignments in Table 3 may be given. According to these theoretical and X-ray studies, it may be concluded that metal atoms are bound to the carboxyl group of mefenamic acid.

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