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METAL COMPLEXES OF THE ANTI-INFLAMMATORY DRUG SODIUM [2-[(2,6-DICHLOROPHENYL)AMINO]PHENYL]ACETATE (DICLOFENAC SODIUM). MOLECULAR AND CRYSTAL STRUCTURE OF CADMIUM DICLOFENAC

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Abstract—The reactions of $ZnCl_2$, $CdCl_2$ and $Hg(NO_3)_2 \cdot H_2O$ with deprotonated diclofenac (L) were studied in aqueous solutions. Complexes of the formulae $[Zn(L)_2(H_2O)]$, $[Cd(L)_2(H_2O)]$, $[HgL_2]$ and $[Cd_2(H_2O)(C_2H_5OH)_2(L)_4]_n$ were isolated and characterized as solid products by elemental analyses and spectral (IR, ^1H NMR) and thermal studies. The crystal structure of the complex $[Cd_2(H_2O)(C_2H_5OH)_2L_4]_n$ was also solved. The central feature of the macromolecule is a dinuclear moiety. Distorted octahedral coordination at Cd(1) is completed by oxygen atoms from one molecule of water, two molecules of C_2H_5OH, two oxygen atoms from one chelating ligand with a monoatomic bridging oxygen that bridges the atoms Cd(2)—Cd(I) = 4.490(1) Å and one oxygen from a bidentate bridging carboxylato group that bridges the atoms Cd(1)—Cd(2) = 4.300(1) Å. The geometry at Cd(2) is that of a distorted square pyramid with oxygen atoms from one chelating and one monodentate carboxylato group and the monoatomic bridging oxygen atom occupying equatorial positions. The apical site of the square pyramid is occupied by the oxygen atom of the bidentate bridging carboxylato group. The crystal structure of the diclofenac acid is also reported.

Diclofenac sodium [2-[(2,6-dichlorophenyl)amino]-phenyl]acetate is a potent non-steroidal anti-inflammatory drug (NSAID), therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of diclofenac and most of its other pharmacological effects are thought to be related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are the mediators of the inflammatory process.[1,2] Diclofenac is a potent inhibitor of cyclo-oxygenase *in vitro* and *in vivo*, thereby decreasing the synthesis of prostaglandins, prostacyclin and thromboxane products. Also diclofenac is a potent reversible inhibitor of the secondary phase of induced platelet aggregation. Like other NSAIDs, diclofenac is highly (> 95%) protein bound.[1]

The importance of zinc to biochemistry, biology, pathology and clinical and veterinary medicine is now generally recognized. In the cells it is incorporated into more than 200 metalloenzymes involved in nucleic acid, protein, carbohydrate and lipid metabolism. Although zinc belongs to the "essential" metal ions, it becomes hazardous when present in excess. As a result there are metabolic disorders connected with both deficiencies and excess amounts of the metal ion. Cadmium and mercury have been found to be environmental pollutants. The toxicity of metals such as cadmium and

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mercury on a biological system may result from blocking the essential functional group of the biomolecules and inhibiting or enhancing their enzymatic activities or from displacing the essential metal ion in biomolecules. Cadmium appears to compete with zinc at the active sites of enzymes; isolation in the kidney and liver of a cadmium-containing metalloprotein, metallothionein, suggest that the protein is involved in detoxification processes.[3]

The interaction of these metal ions with drugs administered for therapeutic reasons is a subject of considerable interest. It is known that the drugs act via chelation or by inhibiting the activity of metalloenzymes, but for most of the drugs such as diclofenac little is known about how metal binding influences their activity.

As part of our research on understanding drug–metal interactions[4] we have been studying the complexing ability of diclofenac with d^{10} metal ions and transition metal ions.[4c]

RESULTS AND DISCUSSION

The complexes $[Zn(L)_2(H_2O)]$ (**1**), $[Cd(L)_2(H_2O)]$ (**2**) and $[Hg(L)_2]$ (**3**) were formed according to eqs (1)–(3) in aqueous solution in the pH range 5.0–7.0. Diclofenac has a dissociation constant near 4; at a physiological pH of 7.4 the molecules dissociate to more than 99% and thus are essentially confined to plasma in intra- and extracellular water.[2]

$$ZnCl_2 + 2LNa + H_2O \longrightarrow [ZnL_2H_2O] + 2NaCl \quad (1)$$

$$CdCl_2 + 2LNa + H_2O \longrightarrow [CdL_2H_2O] + 2NaCl \quad (2)$$

$$Hg(NO_3)_2 \cdot H_2O + 2LNa + H_2O \longrightarrow [HgL_2] + 2NaNO_3 + 2H_2O \quad (3)$$

Crystals of the complex $[Cd_2L_4Et_2H_2O]_n$ (**4**) suitable for X-ray analysis were formed by slow evaporation of an ethanolic solution of complex **2**. The

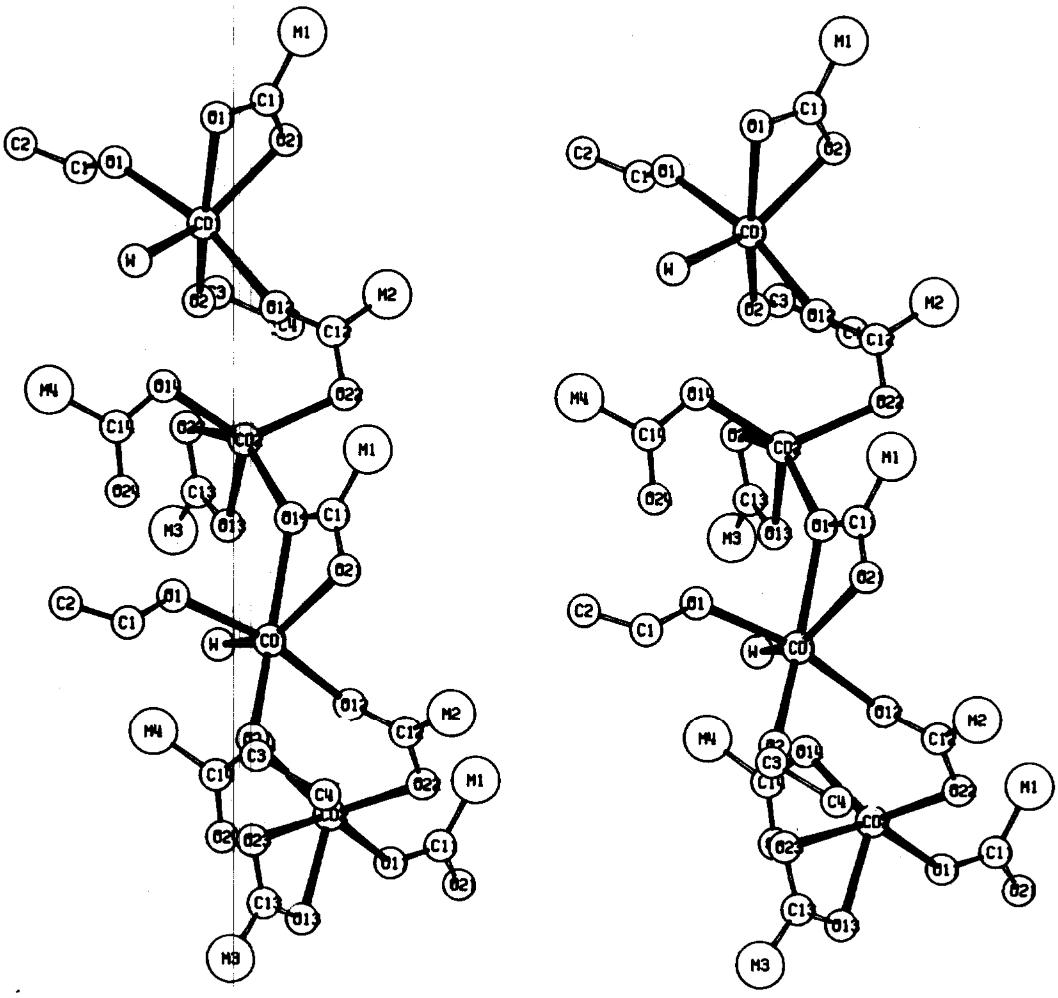

Fig. 1. Structure of compound **4**.

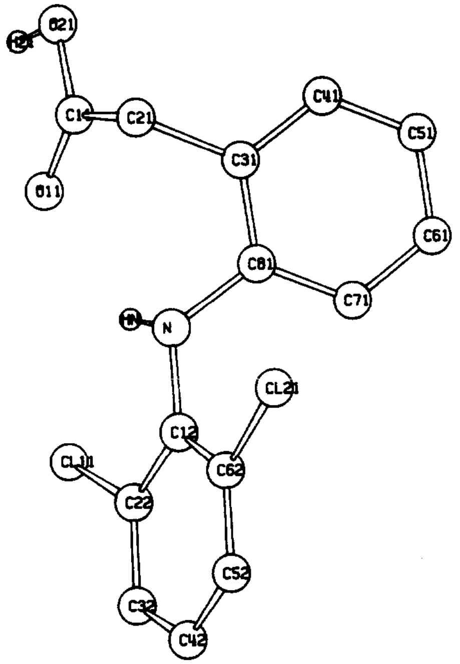

Fig. 2. Structure of diclofenac acid.

compounds are white, microcrystalline, diamagnetic solids that appear to be air- and moisture-stable. They are soluble in CH_3OH, C_2H_5OH, C_6H_{12} and are insoluble in water.

Description of the structures

An ORTEP plot of the inner coordination sphere about the Cd(1) and Cd(2) core for complex **4** is depicted in Fig. 1. The structure of diclofenac acid is shown in Fig. 2. A crystal packing diagram for the same complex (**4**) is shown in Fig. 3. Complete crystal data and parameters for data collection for diclofenac acid and complex **4** are reported in Table 1. Selected bond distances and angles are given in Table 2.

The formation of the compound only took place in ethanolic solution; during crystallization two molecules of EtOH are incorporated into the coordination sphere of Cd(1). The coordination geometry around each metal ion is severely distorted by the bulky ligand L. The compound is polymeric, consisting of hexa-coordinated Cd(1) atoms connected by oxygens O(12) and O(22) of a bridging carboxylato group to the Cd(2) atom, which is penta-coordinated and connected by the monoatomic bridging oxygen O(11) to Cd(1). The Cd(2) atom is, however, subjected to a sixth weaker interaction in the form of a carboxylato oxygen atom, O(12), approaching the Cd(2) atom. The distance Cd(2)—O(12) is 2.76(8) Å, long enough to be considered as a bond distance. When only the bonding interactions are considered Cd(2) is penta-coordinated. The Cd(1)—O(12)—O(22)—Cd(2) bridge is nearly symmetrical with bond distances Cd(1)—O(12) = 2.249(9) and Cd(2)—O(22) = 2.216(1) Å, $\Delta\delta = 0.031$ Å, while the Cd(2)—O(11)—Cd(1) bridge is asymmetrical with the two Cd—O distances, Cd(2)—O(11) = 2.278(8) and Cd(1)—O(11) = 2.407(7) Å, being significantly different. This bonding mode is probably responsible for the distortion of the coordination polyhedron.

In the complex molecule the ligands surround the Cd(1) atom in a propeller-like arrangement. The resulting coordination about the Cd(1) atom assumes distorted octahedral geometry with the

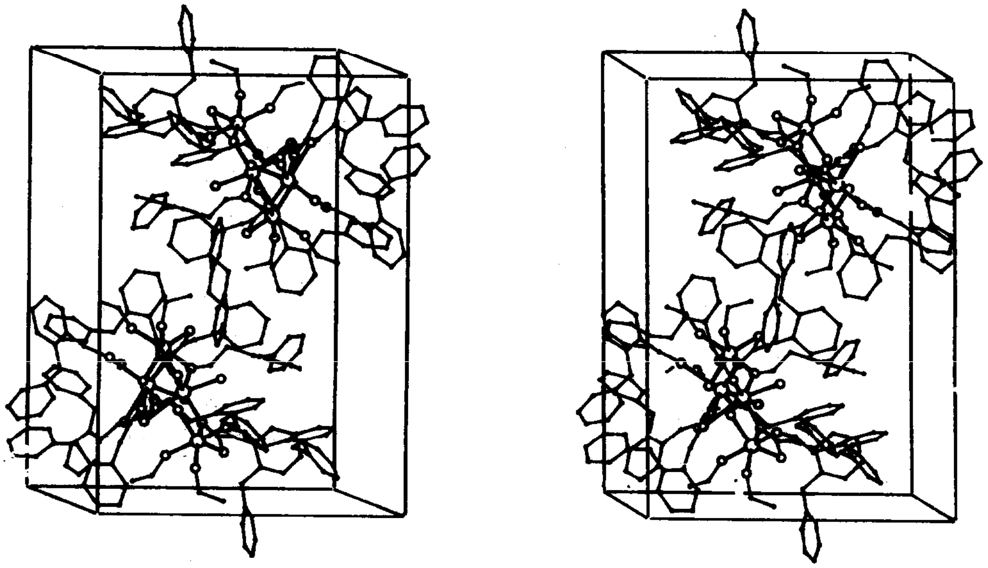

Fig. 3. Packing diagram of compound 4.

Table 1. Summary of crystal and intensity collection data

Compound	Ligand	Complex
Formula	$C_{14}H_{11}NO_2Cl_2$	$Cd_2(C_{14}H_{10}NO_2Cl_2)_4(C_2H_5O)_2H_2O$
fw	296.15	1513.52
a (Å)	20.263(1)	17.467(2)
b (Å)	7.0050(3)	25.187(3)
c (Å)	20.111(1)	15.000(2)
β (°)	109.578(2)	102.59(1)
V (Å^3)	2689.51(7)	6440(1)
Z	8	4
D_{calc} (Mg m^{-3})	1.462	1.560
D_{meas} (Mg m^{-3})	1.45	1.54
Space group	$C2/c$	$P2_1/c$
Radiation	Cu-K_α (λ = 1.5418)	
μ (cm^{-1})	41.65	87.94
Scan speed (° min^{-1})	3.0	5.0–18.0
Scan range (°)	1.7 plus α_1-α_2	
Background counting (s)	0.5 of scan time	
2θ limit (°)	130.0	100.0
Data unique	2267	6623
Data used	2087	6615
	$F_o > 4.0\sigma(F_o)$	All data
Range of *h*	−23–23	−17–17
Range of *k*	0–8	0–25
Range of *l*	−22–22	0–14
Weighting scheme	$1/w = \sigma^2(F_o)+gF^2_o$	
g	0.0003	0.0028
F(000)	1216	3040
Nr[a]	216	780
$\|\Delta/\sigma\|_{max}$	0.351	0.249
$(\Delta\rho)_{max}$ (e Å^{-3})	0.304	1.906
$(\Delta\rho)_{min}$ (e Å^{-3})	−0.321	−0.855
R_{obsd}[b]	0.0517	0.1000
$R_{all\ data}$[b]	0.0549	0.1007
$R_{w\,obsd}$[c]	0.0763	0.1119
$R_{w\,all\,data}$[c]	0.0771	0.1125

[a] *Nr* = number of refined parameters.

[b] $R = \Sigma|\Delta F|/\Sigma|F_o|$.

[c] $R_w = [\Sigma w(\Delta F)^2/\Sigma w|F_o|^2]^{1/2}$.

Cd(1)—O distances showing rather wide ranges of values. Cd(1) is surrounded by one water molecule, two EtOH molecules and three oxygen atoms from two carboxylato groups of the ligands M_1 and M_2. The penta-coordinate Cd(2) atom assumes square pyramidal geometry, with one apical bond, Cd(2)—O(22), from the bidentate bridging carboxylato group of the ligand M_2 and four equatorial bonds, two from the chelating carboxylate group O(13), O(23) of the ligand M_3, one from the monodentate carboxylate group O(14) of the ligand M_4 and one from the monoatomic bridging oxygen O(11) of the chelated carboxylato monoinion M_1. The cadmium-to-EtOH oxygen distances are Cd(1)—O(1) = 2.27(1) and Cd(1)—O(2) = 2.253(8) Å. The cadmium-to-H_2O oxygen distance is Cd(1)—O = 2.213(8) Å. One Cd—$O_{(carb.)}$ bond length, Cd(2)—O(23) = 2.5051(8) Å, is longer than the others. The Cd(2)—$O(14)_{(carb.monod.)}$ bond distance is 2.173(8) Å. The Cd—$O_{(carb.chel.)}$ bonds range from 2.282(8) to 2.505(8) Å. Although bidentate chelating carboxylates are known,[5–10] the formation of a four-membered M—O—C—O ring with the high angular strain involved is not expected to be energetically favourable. The distortion as well as the significant difference between Cd(2)—O(14) and Cd(2)—O(23) distances, 2.173 and 2.505 Å, respectively, could be due to intraligand steric interactions and a different coordination mode.

A comparison of the cadmium–oxygen bond distances in the present compound with those in other

Table 2. Coordination of the Cd atoms of the complex

Cd(1)—O(11)	2.407(7)	Cd(2)—O(11)	2.278(8)
Cd(1)—O(12)	2.249(9)	Cd(2)—O(12)	2.760(8)
Cd(1)—O(21)	2.321(7)	Cd(2)—O(22)	2.216(1)
Cd(1)—O(1)	2.27(1)	Cd(2)—O(13)	2.282(8)
Cd(1)—O(2)	2.253(8)	Cd(2)—O(23)	2.505(8)
Cd(1)—W	2.213(8)	Cd(2)—O(14)	2.173(8)
O(11)—Cd(1)—O(12)	109.5(3)	O(11)—Cd(2)—O(12)	133.8(3)
O(11)—Cd(1)—O(21)	54.6(3)	O(11)—Cd(2)—O(22)	93.6(3)
O(11)—Cd(1)—W	87.9(3)	O(11)—Cd(2)—O(13)	90.2(3)
O(11)—Cd(1)—O(1)	81.2(3)	O(11)—Cd(2)—O(14)	105.8(3)
O(11)—Cd(1)—O(2)	161.6(3)	O(11)—Cd(2)—O(23)	143.5(3)
O(12)—Cd(1)—O(21)	96.5(3)	O(13)—Cd(2)—O(23)	53.6(3)
O(12)—Cd(1)—O(2)	81.1(3)	O(13)—Cd(2)—O(14)	125.4(3)
O(12)—Cd(1)—W	83.0(3)	O(12)—Cd(2)—O(22)	51.4(3)
O(12)—Cd(1)—O(1)	167.8(3)	O(13)—Cd(2)—O(22)	105.6(3)
O(21)—Cd(1)—W	140.3(3)	O(22)—Cd(2)—O(23)	99.6(3)
O(21)—Cd(1)—O(1)	94.6(3)	O(23)—Cd(2)—O(14)	94.4(3)
O(21)—Cd(1)—O(2)	110.4(3)	O(22)—Cd(2)—O(14)	124.3(4)
O(1)—Cd(1)—O(2)	90.2(3)	O(12)—Cd(2)—O(23)	78.8(3)
W—Cd(1)—O(2)	108.7(3)	O(12)—Cd(2)—O(13)	124.5(3)
W—Cd(1)—O(1)	91.7(3)	O(12)—Cd(2)—O(14)	79.7(3)
		O(12)—Cd(2)—O(24)	127.7(3)

cadmium–carboxylate and cadmium–oxygen species are presented in Table 3.

The C—O bond lengths range from 1.22 to 1.30 Å and the C—C bonds of the C_6H_5 ring from 1.36 to 1.42 Å, while the $C_6H_3Cl_2$ ring ranges from 1.32 to 1.42 Å. The shorter C—O bond of each carboxylato group is held to the cadmium atom, indicating that the doubly-bonded oxygen is coordinated.

The relative orientation of the two phenyl rings depends upon the torsional angles. The observed values of the ligands M_1, M_2, M_3 and M_4 in the present crystal structure, compared with those of diclofenac acid are given in Table 4. The two torsion angles C(7j)—C(8j)—N(j)—C(1i) and C(8j)—N(j)—C(1i)—C(2i), between the two phenyl rings and the nitrogen, and the angle of twist C(8j)—N(j)—C(1i)—C(6i), between the planes of the phenyl rings, show that diclofenac acid and the ligands of complex **4**, M_1, M_3 and M_4, show very similar preferred conformations.

Moser *et al.*[2] studied for 36 congeners of diclofenac the inhibition of cyclooxygenase at the enzyme level and the *in vivo* inhibition of rat adjuvant arthritis and found that both activities can be explained by the lipophilicity and the twisting of the two aromatic rings (angle of twist = 58–69°). These findings allowed the rationalization of the high activity of diclofenac.

Spectral and thermal studies

Table 5 presents some diagnostic IR bands. In the $\nu(OH)_{water}$ region the spectra of complexes **1**, **2** and **4** show a broad absorption at 3500 cm^{-1}, attributed to the presence of coordinated water. As the carboxylic hydrogen is more acidic than the amino hydrogen the deprotonation occurs in the carboxylic group. This is confirmed by the IR spectra of the complexes, showing the characteristic bands for the secondary amino groups and for the coordinated carboxylate group.[11–13] The strong band at 3388 cm^{-1}, which appears in diclofenac, is assigned to the NH stretching motion and the broad band at 3260 cm^{-1} is taken to represent the $\nu(NH\text{---}O)$ mode, due to intramolecular hydrogen bonding.[2] The absence of large systematic shifts of the $\nu(NH)$ and $\delta(NH)$ bands in the spectra of the complexes compared with those of the ligand indicates that there is no interaction between the NH group and the metal ions, which is also confirmed by X-ray analysis. Assignment of the type of carboxylate group coordination was based on both the position of the ν_s and ν_{as} bands and the values of Δ_v.[11–13] The separations between ν_{as} and ν_s, Δ_v, in a bidentate (chelate) complex will be significantly smaller than in the free ion; in the bridging complex the Δ_v value is closer to the free ion, while in the monodentate complex it will be

Table 3. Comparison of cadmium–oxygen bond distances (Å) in various cadmium(II) derivatives

Compound	Coordination number	Geometry	Coordination site	Distance ν(Cd—O) (Å)	Ref.
$Cd[C_6H_4(COO)_2] \cdot H_2O$	7		$O_{(H_2O)}$	2.338(4)	5
			$O_{(carb.chel.)}$	2.368(4)–2.436(4)	
			$O_{(carb.bridg.)}$	2.254(3)	
			$O_{(C=O.\ ketonic)}$	2.489.9–2.571(8)	
$Sr[Cd(EGTA)] \cdot 7H_2O$	8	Dodecahedral	$O_{(ether)}$	2.580(8)	6
			$O_{(carb.chel.)}$	2.325(3)–2.585(3)	
$K[Cd(ClC_6H_4SO_2NCONH_nPr)_3]$	6	Trigonal prismatic	$O_{(C=O,\ ketonic)}$	2.489(9)–2.581(8)	7
$[(C_6H_4OHCOO)_2Cd \cdot H_2O]_2$	7	Pentagonal bipyramid	$O_{(H_2O)}$	2.300(2), 2.243(2)	8
			$O_{(carb.chel.)}$	2.322(2), 2.429(1); 2.314(1), 2.535(2)	
			$O_{(carb.monoatom.bridg,)}$	2.271(2), 2.535(2)	
$[(C_6H_5N)_3(C_6H_4OHCOO)_2Cd]$	7	Pentagonal bipyramid	$O_{(carb.chel.)}$	2.375(2), 2.497(2); 2.424(2), 2.481(2)	8
$[(H_2O)_6Mg(EDTA)H_2OCd]_n \cdot 3nH_2O$	7	Pentagonal bipyramid	$O_{(H_2o}$	2.246(9)	9
			$O_{(carb.chel.)}$	2.336(6)–2.457(7)	
$2CdO(CH_2COO)_2 \cdot 7H_2O$	7	Pentagonal bipyramid	$O_{(carb.chel.)}$	2.278(15)–2.491(14)	10
$[Cd_2C_{14}H_{10}NC_2Cl_2)_4(C_2H_5OH)_2H_2O]_n$	6 5	Cd(1) distorted-octahedral Cd(2) tetragonal-pyramid	$O_{(H_2O)}$	2.213(8)	Present work
			$O_{(C_2H_5OH)}$	2.253(8), 2.27(1)	
			$O_{(carb.chel.)}$	2.321(7)–2.505(8)	
			$O_{(carb.bridg.)}$	2.216(1), 2.249(9)	
			$O_{(carb.monod.)}$	2.173(8)	
			$O_{(carb.oxyg.monoat.bridg.)}$	2.278(8), 2.407(7)	

Table 4. Torsion angles of the ligands

Angles	Ligand[a] $j = 1, i = 2$	Complex[b] $j = 1, i = 5$	Complex[c] $j = 2, i = 6$	Complex[d] $j = 3, i = 7$	Complex[e] $j = 4, i = 8$
O(1j)—C(1j)—C(2j)—C(3j)	70	−151	−136	−162	−172
O(2j)—C(1j)—C(2j)—C(3j)	−109	33	49	22	13
C(1j)—C(2j)—C(3j)—C(4j)	98	103	111	105	116
C(1j)—C(2j)—C(3j)—C(8j)	−82	−75	−72	−76	−67
C(2j)—C(3j)—C(8j)—N(j)	2	2	1	2	3
C(3j)—C(8j)—N(j)—C(1i)	−166	−166	−166	−174	−162
C(7j)—C(8j)—N(j)—C(1i)	15	10	12	6	14
C(8j)—N(j)—C(1i)—C(2i)	−123	−118	62	−122	−125
C(8j)—N(j)—C(1i)—C(6i)	62	60	−127	62	60

[a] See fig. 2; *j* is referred to the phenyl acetate ring and *i* is referred to the 2,6-dichloro-phenyl-amino ring.

[b,c,d,e] Referred to the ligand molecules M_1, M_2, M_3 and M_4, respectively.

Table 5. Diagnostic IR and far-IR bands (cm^{-1}) of dichlofenac and its complexes

Assignments	Diclofenac	1	2	3	4
ν(OH)		3550br	3550br		3550–32000br
ν(NH)	3388s 3260br	3380s 3314s	3300br	3330br	
ν(CH)	3085m 3040m	3070w 3040w	3078w 3030w	3070m 3030m	
ν(CH$_2$)	2980m 2920w	2980w 2915vw	2990vw 2930vw	2970w 2920vw	2980w 2920w
ν_s(COO$^-$)	1572vs	1630vs 1545vs	1545vs 1565vs	1707s 1565vs	1610m 1580s 1540vs
δ(OH)		1610mw	1610mw		1620sh
δ(NH) + ring stretch	1590s	1592s	1590mw	1590s	1592ms
Ring stretch	1558s 1510sh	1580s 1568s 1510sh 1508s	1580s 1570ms 1508s	1577s 1500s	1577s 1560sh 1500sh
δ(CH$_2$)	1456vs	1458vs	1453vs	1452vs	1458vs
ν_{as}(COO$^-$)	1402s	1436s 1395s	1410s	1350ms	1420s 1400vs 1320m
δ(CH)	767vs 748vs	766vs 742vs	768vs 745vs	769vs 742vs	761s 741vs
ν(M—O)$_{(HO)}$		405mw	390mw		390m
ν(M—O)$_{(carb.monod.)}$		392m		402m	400m
ν(M—O)$_{(carb.bid.chel.)}$		312w 299ms 280m	315w 305m 250m		312w 291m 279mw

Table 6. Chemical shifts and coupling constants obtained from ^1H NMR spectra of diclofenac and its complexes

	NH	N—C(3i) H—C(5i)	H—C(4i)	H—C(4*j*)	H—C(6*j*)	H—C(5*j*)	H—C(7*j*)	CH_2	$H_2O_{coor.}$
Diclofenac	10.24s	7.43; 7.46 $^3J = 8.0$	7.03; 7.06; 7.09 $^3J = 8.0$	7.05; 7.08 $^3J = 7.8$ $^4J = 1.5$	6.89; 6.92; 6.95 $^3J = 7.8$ $^4J = 1.6$	6.70; 6.73; 6.76 $^3J = 7.3$ $^4J = 1.2$	6.23; 6.26 $^3J = 8.0$ $^4J = 0.8$	3.44s	
1	8.29s	7.42; 7.45 $^3J = 8.0$ $\Delta\delta = -0.01$	7.06; 7.09; 7.12 $^3J = 7.8$ $\Delta\delta = +0.03$	7.15; 7.18 $^3J = 6.4$ $^4J = 1.5$ $\Delta\delta = +0.10$	6.99; 7.01; 7.04 $^3J = 7.3$ $^4J = 1.2$ $\Delta\delta = +0.10$	6.79; 6.82; 6.85 $^3J = 6.49$ $^4J = 1.4$ $\Delta\delta = +0.09$	6.29; 6.32 $^3J = 7.5$ $^4J = 0.9$ $\Delta\delta = +0.06$	3.59s	3.36s
2	8.61s	7.42; 7.45 $^3J = 8.0$ $\Delta\delta = -0.1$	7.05; 7.08; 7.11 $^3J = 8.0$ $\Delta\delta = +0.02$	7.15; 7.18 $^3J = 7.5$ $\Delta\delta = +0.10$	6.98; 7.01; 7.04 $^3J = 7.5$ $^3J = 7.9$ $^4J = 1.5$ $\Delta\delta = +0.11$	6.79; 6.82; 6.85 $^3J = 7.5$ $^3J = 7.9$ $^4J = 1.5$ $\Delta\delta = +0.09$	6.28; 6.31 $^3J = 7.9$ $^4J = 0.7$ $\Delta\delta = +0.05$	3.59s	3.37
3	7.66br	7.49; 7.52 $^3J = 8.1$ $\Delta\delta = +0.04$	7.13; 7.15; 7.18 $^3J = 8.1$ $\Delta\delta = +0.10$	7.21; 7.24 $^3J = 8.3$ $^4J = 1.4$ $\Delta\delta = +0.16$	7.03; 7.06; 7.09 $^3J = 7.4$ $^4J = 1.2$ $\Delta\delta = 0.14$	6.84; 6.87; 6.89 $^3J = 7.10$ $\Delta\delta = +0.14$	6.28; 6.30; 6.33 $^3J = 8.2$ $\Delta\delta = +0.05$	3.71	

higher.[11,12] The $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ bands of complex **2** are observed at 1545 and 1410 cm^{-1}, respectively; the difference, $\Delta_v = 135$ cm^{-1}, is less than that of the free ion (sodium salt diclofenac), $\Delta_v = 1572–1402 = 170$ cm^{-1}, as expected for bidentate coordination. Two $\nu_{as}(COO^-)$ bands at 1630 and 1545 cm^{1} and two $\nu_s(COO^-)$ bands at 1436 and 1395 cm^{-1} are observed for complex **1**. The bands at 1630 and 1395 cm^{-1}, $\Delta_v = 235$ cm^{-1}, are assigned to the stretching mode for monodentate carboxylate ligation, while the bands at 1545 and 1436 cm^{-1}, $\Delta_v = 109$ cm^{-1}, are assigned to the stretching mode for bidentate chelate carboxylate ligation. The $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ bands are observed at 1577 and 1350 cm^{-1} for complex **3**; the difference, $\Delta_v = 227$ cm^{-1}, is consistent with monodentate coordination. The new bands in the region 400–200 cm^{-1} are assigned to ν(M—O)(H_2O) and ν(M—O)(COO^-) modes.[11–14] The metal–ligand vibrations are important in determining the structures of the complexes and are included in Table 5.

Table 6 gives the ^{1}H NMR chemical shifts of diclofenac and its complexes in DMSO-d$_6$. The study was based on comparisons with a number of related ligands and complexes.[2,15,16]

Coordination of a metal centre to NH or a carboxylato group causes a downfield shift in the proton resonances. These metal ions deshield the CH_2 protons attracting electron density; the CH_2 protons are affected more, while the phenyl ring protons, away from the coordination site, are less affected. The above data show that all the δ values move to lower fields on complex formation. The $\Delta\delta$ values ($\delta_{complex}$-$\delta_{free\ ligand}$) depend on the proximity of the proton in question to the metal centres. The H—C(7j) signal of diclofenac appears at the rather high field 6.26 ppm, due to the shielding effect of the aryl ring (2,6-dichlorophenyl).[2] The proton on the nitrogen atom undergoes rapid exchange and is decoupled from the nitrogen atom and from protons on adjacent carbon atoms. The NH peak is, therefore, a sharp singlet. A deshielding effect is exerted on this NH proton via intramolecular or intermolecular hydrogen bonding, with the resonance occurring at low fields[15,16] from 7.66 to 10.24 ppm.

Complexes **1** and **2** show that a similar decomposition occurs in two steps. The complex CdL_2H_2O was decomposed at 194°C. This reaction appears to be completed at 265°C. Two endothermic and one exothermic effect are observed at 199, 229 and 240°C, respectively. The first inflection in the mass loss curve corresponds to a loss of $H_2O \cdot 1\frac{1}{2}L$ molecules. The thermal decomposition of the complex is completed in the 465–605°C temperature range. The final residue of pyrolysis was the corresponding carbonate salt and metallic oxide.

From the overall study presented above it is concluded that in all the new complexes prepared diclofenac behaves as a monodentate or bidentate ligand, bonding through the carboxylate oxygen atoms. Several stereochemistries are assigned for the diclofenac complexes in the solid state. Synthetic and spectroscopic data suggests that **1** consists of the pseudo-tetrahedral ZnO_4 entity, formed by one bidentate chelate ligand, one monodentate ligand and one coordinated water molecule. For complex **2** two ligands are coordinated to one cadmium(II) atom in a bidentate chelate mode, with both the oxygens of the carobylato group bound to the metal centre. Complex **2** consists of the $CdO_{2(carb.chel.)}O_{2(carb.chel.)}O_{(H_2O)}$ coordination sphere. In complex **3** the coordination environment around the Hg^{2+} atom is linear and the ligands are bound in a monodentate fashion. Complex **4** has a polymeric structure with both the monodentate and bidentate ligands chelating and bridging. One M_2 ligand is in the familiar bidentate bridging mode and another M_1 ligand is in the rare monoatomic bridging mode.

EXPERIMENTAL

All the solvents and chemicals used were of high purity and purchased from Fluka. Diclofenac was a gift from "HELP EPE". Physicochemical measurements and spectroscopic techniques were performed using published methods.[4,17,18] Proton NMR spectra were obtained on a Bruker AC 250 MH FT-NMR spectrophotometer with Me_4Si as an internal standard. Chemical shifts are reported in parts per million (ppm).

Preparation of the complexes

The complexes were prepared by mixing aqueous solutions of the ligand diclofenac (sodium salt) and aqueous solutions of the metal salts (4 : 2 ligand-to-metal molar ratio). The pH of the reaction mixture was adjusted to 5.5–7.5 by the addition of small quantities of 0.1 N KOH. The reaction mixture was stirred for 4–6 h at room temperature. The resulting powders were filtered, washed with water and dried *in vacuo* over silica gel. They were further dried at 90°C *in vacuo* over P_4O_{10}. The yields of the products were 82% for complex **3** and *ca* 100% for complexes **1** and **2**. The elemental analyses agreed very well with the assigned formulae.

X-ray analysis

The crystal system and space group (Table 1) were determined from preliminary oscillation and

Weissenberg photographs. Unit cell dimensions were derived from least-squares refinement of the setting angles of 15 automatically centred reflections in the range $50° < 2\theta < 52°$ on a Syntex $P2_1$ diffractometer using nickel filtered Cu-K_α radiation. The crystal was of very low quality. The intensities of three standard reflections monitored after every 67 reflections showed $<3\%$ intensity fluctuation. Lorentz, polarization and ψ-scan absorption corrections were applied.

The structure was solved by direct methods using the SHELX86 program.[19] Refinement was performed by blocked full-matrix least-squares, in which $\Sigma w\Delta^2$ was minimized with SHELX76.[20] All hydrogen atoms were calculated as riding on carbon atoms at 0.96 Å. All non-hydrogen atoms were refined using anisotropic and hydrogen atoms using isotropic temperature factors. Atomic scattering factors were taken from the International Tables of X-ray Crystallography.[21]

Supplementary material. Tables of positional parameters and anisotropic temperatures factors, observed and calculated structure factors and a list of bond distances and angles of the ligand have been deposited.

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