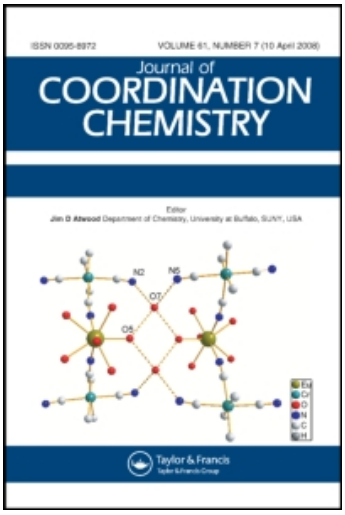

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Interaction of Naproxen with transition metals: synthesis, characterization, anti-inflammatory activity and kinetic studies

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Interaction of Naproxen with transition metals: synthesis, characterization, anti-inflammatory activity and kinetic studies

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Coordination complexes of transition metals (Co, Ni, Cu, Fe, Cr, Ru, Ir, Mn, and Zn) with 6-methoxy-α-methyl-2-naphthalene acetic acid (Naproxen) and triphenylphosphine have been synthesized and characterized by conductance, elemental analysis, UV-Vis, AAS, and FT-IR spectroscopy. The elemental analyses data reveal the presence of 1:1 (metal : ligand) stoichiometry and the IR data suggest that naproxen functions as a bidentate ligand in coordination with transition metals. The anti-inflammatory assays of these complexes have significant effect.

Keywords: Naproxen; Transition metal complexes; IR; UV-Vis; AAS

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed drugs in the treatment of pain and inflammation in diseases, including osteoarthritis and rheumatoid arthritis. A group of drugs inhibit both isoforms of cyclooxygenase enzyme (COX-1 and COX-2). Conventional NSAIDs are nonselective binding and inhibit both isoforms, but COX-1 is inhibited more avidly than COX-2. Inhibition of COX-1 is responsible for side effects and of COX-2 for therapeutic effects. This has resulted in the introduction of the COX-2 selective drugs [1]. These are a newer class of drugs, generally considered to be safer and at least equally efficacious. Using NSAIDs in most therapeutic situations is empirical, but certain principles help clinicians prescribe them safely and effectively [2].

During the last 10 years, a number of new drugs have been developed. One is Naproxen, 6-methoxy-α-methyl-2-naphthalene acetic acid (figure 1), a non-steroidal

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drug with antipyretic, anti-inflammatory and analgesic properties [3]. Naproxen has a relatively long plasma half-life, 13 to 14 h [4], and therefore has advantages over drugs like aspirin in that patients can take drugs less frequently for adequate analgesic effects. The longer duration of analgesia has been confirmed in a study in which 300–600 mg of naproxen statistically decreased pain intensity for 7 to 8 h [5]. Although naproxen has provided good, long-term analgesia, the need for a drug with even faster onset exists. Since alkali metal salts of weak organic acids dissolve rapidly as compared to the acid itself, the sodium salt of naproxen was developed to improve its bioavailability. Earlier studies of sodium naproxen demonstrated that significantly higher plasma levels were obtained with sodium salt as compared to naproxen. The properties that guide usage of triphenylphosphine are its nucleophilicity and its reducing character. The nucleophilicity of PPh_3 is indicated by its reactivity toward electrophilic alkenes, such as Michael-acceptors and alkyl halides. Triphenylphosphine binds well to most transition metals, especially those in groups 7–10 [6].

Most anti-inflammatory drugs are Na salts of carboxylic acids in which the carboxylate is available for metal–ligand interaction. In the present study, Na metal is replaced with Co, Ni, Cu, Fe, Cr, Ru, Ir, Mn and Zn to study the effectiveness of the drug. These transition metal compounds of naproxen were further reacted with triphenylphosphine to enhance their reactivity. The complexes were characterized by conductance, elemental analysis, UV-Vis, AAS, and FT-IR spectroscopy. The reported complexes were also checked for their anti-inflammatory activity.

2. Experimental

All chemicals were analytical grade of Merck and Fluka origin and used without purification. Melting points were determined in capillary tubes on an electrothermal melting point apparatus Mitamura Rikero Kogyo (Japan) and are uncorrected. Infrared spectra were recorded as KBr discs from 4000–250 cm^{-1} on a Perkin-Elmer Spectrum 1000 FT-IR Spectrophotometer. Atomic absorption data were recorded on an Analyst 300 of Perkin-Elmer. Conductances of the complexes were noted from a 712 conductometer of Metrohm. Thermogravimetric analysis was carried out on Perkin-Elmer, TGA-7 with computer interface. UV-Vis spectra were recorded on Lambda 2S of Perkin-Elmer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-250 spectrometer using $CDCl_3$ as an internal reference. Anti-inflammatory assay was conducted on Plathysmometer.

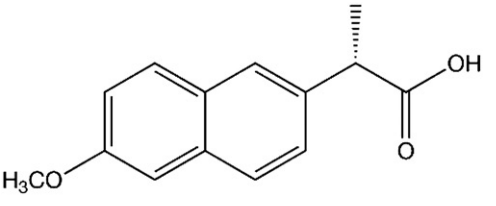

Figure 1. Chemical structure of 6-methoxy-α-methyl–2-naphthalene acetic acid (Naproxen) (**HL**).

2.1. *Synthesis of sodium salt of naproxene (HL)*

0.5 g (1 mmol) of Naproxen (ligand) was dissolved in dried ethanol with constant stirring until the solid was dissolved completely. 0.183 g (1 mmol) of $NaHCO_3$ dissolved in deionized water was added dropwise to the solution. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated on rotary evaporator under reduced pressure and the sodium salt was dried in air.

2.2. *General procedure for synthesis of transition metal complexes*

The sodium salt of Naproxen (1 mmol) was dissolved in ethanol in a round bottomed flask and stirred for 15 min. Equimolar $MClx \cdot nH_2O$ (where M = Co, Ni, Cu, Fe, Cr, Ru, Ir, Mn, Zn; $x = 2$, 3 and $n = 2$, 4, and 6) dissolved in ethanol was added to the above mixture and refluxed for 3 h. The sodium chloride formed was filtered off and solvent was evaporated at room temperature.

The solid product obtained was dissolved with an equimolar amount of triphenylphosphine (TPP) in ethanol and the reaction mixture was refluxed for 3 h. The product was filtered and dried at room temperature.

3. Results and discussion

The compounds were obtained by the reactions given in equations (1)–(3). The melting points, percentage yields, molecular weights, and molecular formulas are given in "Supplementary material". Elemental analyses data given in table 1 show good agreement with the calculated and found values.

$$\text{Nap} + \text{NaHCO}_3 \rightarrow \text{Na Nap} + \text{H}_2\text{O} + \text{CO}_2 \quad (1)$$

$$\text{NaNap} + \text{MCl}x \cdot n\text{H}_2\text{O} \rightarrow (\text{Nap})\text{Cl}x \cdot n\text{H}_2\text{O} + \text{NaCl} \quad (2)$$

$$\text{M(Nap)Cl}x \cdot n\text{H}_2\text{O} + \text{PPh}_3 \rightarrow \text{M(Nap)Cl}x\text{PPh}_3 \cdot n\text{H}_2\text{O} \quad (3)$$

where M = Co, Ni, Cu, Fe, Cr, Ru, Ir, Mn, and Zn; $x = 2$, 3, and $n = 2$, 4, and 6.

3.1. *Atomic absorption spectroscopy*

Atomic absorption data of the reported complexes are given in table 1, which shows good agreement between the theoretical and experimental percentage of metals.

3.2. *FT-IR studies*

Infrared spectra of transition metal derivatives of 6-methoxy-α-methyl-2-naphthalene acetic acid and triphenylphosphine from 4000–250 cm^{-1} as KBr disc are given in table 2. A new peak at 490–419 cm^{-1} is due to M–O stretching, confirming coordination through [O,O] donors. The Na salt shows a $\Delta\upsilon$ of 150 cm^{-1} and $\upsilon_{asym} = 1570\ cm^{-1}$ and

Table 1. Concentration of metal, carbon and hydrogen in transition metal complexes of Naproxen.

Compound No.	Compound	Metal (%)		Carbon (%)		Hydrogen (%)	
		Actual	Calc	Actual	Calc	Actual	Calc
HL	Na Nap	9.02	9.16	66.7	66.9	5.3	5.2
1	$[Cr_2(Nap)_2Cl_4]$	14.9	14.8	45.4	47.87	3.85	3.99
2	$[Cr(Nap)(PPh_3)]Cl_2$	8.61	8.48	61.49	62.6	4.44	4.73
3	$[Mn_2(Nap)_2Cl_2]$	16.4	17.22	53.35	52.68	4.43	4.39
4	$[Mn(Nap)(PPh_3)]Cl$	9.56	9.44	65.91	66.0	4.91	4.99
5	$[Fe_2(Nap)_2Cl_2]Cl_2$	14.22	15.7	47.01	47.34	3.86	3.95
6	$[Fe(Nap)(PPh_3)Cl_2]$	9.22	9.05	61.11	61.85	4.65	4.70
7	$[Co_2(Nap)_2Cl_2]Cl_2$	16.06	16.4	52.65	52.06	3.82	3.90
8	$[Co(Nap)(PPh_3)Cl_2]$	9.21	9.47	61.36	61.85	4.27	4.67
9	$[Ni_2(Nap)_2Cl_2]$	18.58	18.18	52.02	52.06	4.68	4.34
10	$[Ni(Nap)(PPh_3)CI]$	10.91	10.03	65.01	65.6	4.65	4.96
11	$[Cu_2(Nap)_2Cl_2]$	19.81	19.40	51.71	51.21	4.94	4.27
12	$[Cu(Nap)(PPh_3)Cl]$	10.13	10.77	65.12	65.08	4.45	4.91
13	$[Zn_2(Nap)_2Cl_2]$	19.85	19.85	51.2	51.0	4.79	4.25
14	$[Zn(Nap)(PPh_3)Cl]$	11.41	11.04	63.86	64.88	4.97	4.90
15	$[Ru_2(Nap)_2Cl_2]Cl_2$	25.52	25.26	41.05	41.99	3.72	3.50
16	$[Ru(Nap)(PPh_3)Cl_2]$	15.02	15.26	58.56	58.0	4.25	4.38
17	$Ir_2(Nap)_2Cl_4$	48.53	48.66	42.92	42.52	3.72	3.54

Nap = Naproxen.

Table 2. IR data (cm^{-1}) for transition metal complexes of Naproxen.

Compound No.	υ C=O	υCOO_{asym}	υCOO_{sym}	$\Delta\upsilon$	υ M–O
HL	1725	1554	1391	163	–
1	1730	1608	1421	187	477
2	1756	1567	1378	189	470
3	1726	1631	1455	176	481
4	1740	1572	1352	220	485
5	1713	1633	1455	178	475
6	1725	1580	1393	187	472
7	1728	1629	1457	172	481
8	1759	1545	1364	181	476
9	1728	1629	1456	173	481
10	1730	1608	1413	195	480
11	1728	1603	1404	199	422
12	1743	1603	1383	220	426
13	1727	1637	1459	178	480
14	1732	1554	1371	183	490
15	1730	1606	1430	176	476
16	1735	1584	1392	192	480
17	1726	1632	1456	176	419

$\upsilon_{sym} = 1420\,cm^{-1}$ [7]. The υOH are broader and weaker than those for transition metal complexes of the corresponding Na salts, indicating that transition metal ions coordinate less water than Na^+. From 1650–1300 cm^{-1} stretching vibrations of the carboxylate (υ_{asym} and υ_{sym}) are present; their frequencies and $\Delta\upsilon$ give indications about the coordination. IR spectra of metal complexes with carboxylates have $\Delta\upsilon > 160\,cm^{-1}$ for bridging bidentate complexes and $\Delta\upsilon < 130\,cm^{-1}$ for chelating bidentate. Values of υ_{asym} and υ_{sym} frequencies are indicative with $\upsilon_{asym} < 1570\,cm^{-1}$ and $\upsilon_{sym} < 1450\,cm^{-1}$ for

bidentate chelate complexes and $\upsilon_{asym} > 1570\,cm^{-1}$ and $\upsilon_{sym} > 1400\,cm^{-1}$ for bridging bidentate complexes. For our complex υ_{as} is higher than the corresponding frequencies of the Na salt, in agreement with a binuclear dimeric structure. These findings suggest that carboxylate of Naproxen is a bridging bidentate ligand, in which each oxygen is bound to a transition metal ion in a dimeric structure [8–16]. Bands assigned to P–C modes shift to higher frequency $1095\,cm^{-1}$ from $1089\,cm^{-1}$ indicating coordination of triphenylphosphine. The 695–$705\,cm^{-1}$ absorption attributed to out-of-plane ring deformation is observed at 704–$708\,cm^{-1}$ in the complexes.

Coordination and protonation of the aromatic conjugated system affect the IR-spectroscopic patterns on the out-of-plane IR-characteristic bands within the region 900–$600\,cm^{-1}$, which has been studied in detail [17–26].

3.3. *Conductance*

The molar conductance values of the synthesized complexes **1**–**16** determined in ethanol at room temperature suggest the non-electrolytic nature of complexes. Data are given in Supplementary Material.

3.4. *Electronic spectra studies*

Electronic spectra for the ligand and its metal derivatives in absolute ethanol are given in table 3. Na Nap does not show bands in the 400–800 nm region. Triphenylphosphine shows three strong maxima at $35{,}714\,cm^{-1}$ (280 nm), $38{,}461\,cm^{-1}$ (260 nm) and $46{,}511\,cm^{-1}$ (215 nm). The maximum at $38{,}461\,cm^{-1}$ (260 nm) is a structureless band (in agreement with the literature). In the synthesized complexes broad band is observed at about $37{,}700\,cm^{-1}$.

UV–Vis spectra of the complexes (table 3) suggest octahedral complexes for Cr, Mn, Fe, Co, Ni, and Cu. Zn and Ru complexes show only the charge transfer bands. Iridium complexes show one band due to $^3T_{1g}(P) \rightarrow {}^3A_{2g}$ transition.

In almost all the complexes, some bands are derived from interligand and charge transfer or ($n \rightarrow \pi^*$) transitions at decreasing energies and intensities. The bands near $35{,}087\,cm^{-1}$ (285 nm), and $37{,}037\,cm^{-1}$ (270 nm) are assigned to interligand ($\pi \rightarrow \pi^*$) transitions for the aromatic moiety of the ligand. A few sharp absorption bands in the region $41{,}666\,cm^{-1}$ (240 nm) to $37{,}037\,cm^{-1}$ (270 nm) could be assigned as charge transfer ($L \rightarrow M$) or ($n \rightarrow \pi^*$) transitions.

3.5. *Thermogravimetric studies*

Thermogravimetric studies are provided in "Supplementary material".

3.6. *Anti-inflammatory assay*

Hind paw edema method. In the present study anti-inflammatory activity was determined in albino rats of either sex (180–220) according to Winter's method [27] using three animals in each group. The animals were injected carrageenan (1% w/v suspension in 0.9% saline) 0.05 mL in the right hind foot under the planter aponeurosis. The test groups of rats were given $25\,mg\,kg^{-1}$ of test sample suspended in 0.75% CMC

Table 3. UV–Visible spectral data of transition metal complexes of Naproxen.

Compound No.	$\upsilon(cm^{-1})$	Absorbance	Transition
1	16,011	1.44	$^4A_{2g} \rightarrow {}^4T_{2g}$
	21,190	1.00	$^4A_{2g} \rightarrow {}^4T_{1g}$
	35,214	1.22	$^4A_{2g} \rightarrow {}^4T_{1g}$
2	15,711	1.2	$^4A_{2g} \rightarrow {}^4T_{2g}$
	22,051	1.3	$^4A_{2g} \rightarrow {}^4T_{1g}$
	34,912	1.23	$^4A_{2g} \rightarrow {}^4T_{1g}$
3	16,595	1.8	$^6A_{1g} \rightarrow {}^4T_{1g}$
	24,566	2.3	$^6A_{1g} \rightarrow {}^4E_g{}^4T_{1g}$
	30,189	1.54	$^6A_{1g} \rightarrow {}^4E_g$
4	16,502	1.6	$^6A_{1g} \rightarrow {}^4T_{1g}$
	24,570	2.3	$^6A_{1g} \rightarrow {}^4E_g{}^4T_{1g}$
	30,166	2.86	$^6A_{1g} \rightarrow {}^4E_g$
5	16,666	1.92	$^6A_{1g} \rightarrow {}^5T_{1g}$
	20,152	1.2	$^6A_{1g} \rightarrow {}^4T_{2g}$
6	16,528	2.09	$^6A_{1g} \rightarrow {}^5T_{1g}$
	20,000	1.92	$^6A_{1g} \rightarrow {}^4T_{2g}$
7	8546	1.23	$^4T_{1g} \rightarrow {}^4T_{2g}$
	16,440	1.56	$^4T_{1g} \rightarrow {}^4A_{2g}$
	22,002	1.45	$^4T_{1g} \rightarrow {}^4T_{1g}$
8	8560	1.35	$^4T_{1g} \rightarrow {}^4T_{2g}$
	16,459	1.0	$^4T_{1g} \rightarrow {}^4A_{2g}$
	21,750	1.22	$^4T_{1g} \rightarrow {}^4T_{1g}$
9	9786	1.44	$^3A_{2g} \rightarrow {}^3T_{2g}$
	16,250	1.36	$^3A_{2g} \rightarrow {}^3T_{1g}$
	25,113	1.11	$^3A_{2g} \rightarrow {}^3T_{1g}$
10	9582	1.51	$^3A_{2g} \rightarrow {}^3T_{2g}$
	17,282	1.29	$^3A_{2g} \rightarrow {}^3T_{1g}$
	25,021	1.32	$^3A_{2g} \rightarrow {}^3T_{1g}$
11	14,598	0.0535	$^2Eg_2 \rightarrow {}^2T_{2g}$
	30,165.9	1.88	$^2B_2 \rightarrow {}^2A_1$
	31,546	1.70	$^2B_2 \rightarrow {}^2A_1$
12	14,492	0.069	$^2Eg_2 \rightarrow {}^2T_{2g}$
	30,211	3.22	$^2B_2 \rightarrow {}^2A_1$
	31,543	3.01	$^2B_2 \rightarrow {}^2A_1$
13	43,165	1.92	CT
14	44,166	1.26	$^2B_2 \rightarrow {}^2A_1$
15	43,496	2.18	CT
16	44,092	2.56	CT
17	28,902	1.25	$^3T_{1g}(P) \rightarrow {}^3A_{2g}$

Sodium ($5\,mL\,kg^{-1}$ body weight) orally, 1 h before the carrageenan injection. The controls were given the same volume ($5\,mL\,kg^{-1}$ body weight) of 0.75% CMC Sodium as in the test group. Another group of rats was treated with $10\,mg\,kg^{-1}$ of Diclofenac Potassium as standard drug suspended in the 0.75% CMC Sodium ($5\,mL\,kg^{-1}$ body weight) orally 1 h before the injection of carrageenan. The inflammation was quantitated by using plethysmometer (Ugo Basile) immediately before carrageenan injection and then 1, 2, 3, and 4 h after carrageenan injection. The percent inhibition of edema was calculated for each group with respect to its vehicle-treated control group by using the relation

$$\frac{A-B}{A} \times 100$$

Table 4. Anti-inflammatory assay of transition metal complexes of Naproxen.

Comp. No.	First hour	Second hour	Third hour	Fourth hour
Standard	30 ± 5	67 ± 3	64 ± 4	63 ± 6
HL	37 ± 3	64 ± 2	66 ± 5	65 ± 3
1	39 ± 2	60 ± 3	65 ± 5	71 ± 4
2	31 ± 1	34 ± 2	53 ± 2	34 ± 2
3	51 ± 2	30 ± 3	49 ± 4	37 ± 4
4	59 ± 1	39 ± 1	67 ± 1	60 ± 3
5	33 ± 9	62 ± 5	65 ± 1	68 ± 7
6	38 ± 2	41 ± 1	56 ± 2	52 ± 3
7	37 ± 5	63 ± 7	65 ± 1	69 ± 5
8	30 ± 3	37 ± 1	48 ± 6	38 ± 4
9	31 ± 1	62 ± 3	60 ± 1	56 ± 2
10	24 ± 6	56 ± 5	51 ± 5	47 ± 8
11	29 ± 5	61 ± 3	52 ± 8	52 ± 8
12	40 ± 0.0	43 ± 2	56 ± 2	52 ± 7
13	34 ± 1	36 ± 2	62 ± 0.4	64 ± 6
14	54 ± 1	67 ± 1	68 ± 0.9	40 ± 2
15	24 ± 5	64 ± 8	37 ± 4	70 ± 1
16	41 ± 3	38 ± 1	58 ± 2	33 ± 2
17	38 ± 5	65 ± 2	62 ± 3	53 ± 3

Data represent the mean of triplicate.

where A and B denote mean increase in paw volume of control and drug-treated animals, respectively. The anti-inflammatory effects, table 4, are minimal in the first hour, double in the second hour, and remain almost constant in the third and fourth hours of injection, as shown by the results of standard (Diclofenac Potassium) and Sodium salt of Naproxen (drug usually available in the market). The behavior of almost all the complexes is similar in the first hour, but Naproxen complexes of Ni, Cu, and Ir have slightly less anti-inflammatory effect, whereas in Co, Fe, and Cr complexes the effect is more than that of the standard used. $[Zn_2(Nap)_2Cl_2]$ did not activate in the first two hours. From the third hour onwards the effect increases. $[Mn_2(Nap)_2Cl_2]$ activates immediately after its injection and then decreases from the second hour. $[Ru_2(Nap)_2Cl_2]Cl_2$ has less effect in the first hour, maximum in second, less in third and again shows maximum effect in the fourth hour. Co, Fe, and Cr complexes of Naproxen have better anti-inflammatory effects than the Na salt of naproxen. When the triphenylphosphine is attached, the activities of Cr, Fe, and Co complexes increase, but only activate in the third hour of injection. The activity of the Mn and Zn complexes is enhanced compared to $[Mn_2(Nap)_2Cl_2]$ and $[Zn_2(Nap)_2Cl_2]$. The activity of Mn is high in the first hour, decreases in the second hour and goes to a maximum in the third and fourth hours. The trend of $[Ni(Nap)(PPh_3)CI]$ is the same as that of the $[Ni_2(Nap)_2Cl_2]$. $[Cu(Nap)(PPh_3)Cl]$ activates slowly compared with $[Cu_2(Nap)_2Cl_2]$. $[Ru(Nap)(PPh_3)Cl_2]$ activates only in the third hour.

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