Some Transition Metal Complexes with Naproxen

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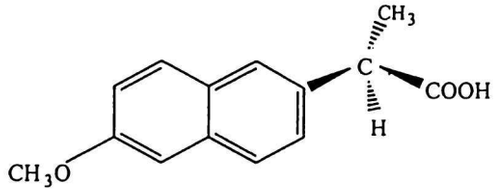
Several transition metal complexes of D-naproxen (HL) have been synthesized. Most of these complexes formed by the divalent metal ions have a 2:1 (ligand:metal) mole ratio and the carboxylate group of HL functions as a bridging ligand. Ni(II) and Cr(III) complexes exhibit a special composition and structure which possesses a free ligand coordinated to and bonded *via* hydrogen bonds, respectively. The inflammatory models by formaldehyde-induced rat paw edema and croton oil-induced mouse ear edema were used to examine the antiinflammatory action of the Cu(II) complex, which enhanced the antiinflammatory activity relative to the free ligand. The pharmaceutical synergy resulting from the coordination effect is discussed.

Naproxen (HL) is a nonsteroidal antiinflammatory analgesic extensively used in the clinical treatment of arthritis and chronic and acute pain states [1]. Many studies have shown that metal ions play a vital role in a vast number of widely different biological processes and some diseases are related to the lack of some metallic elements vital to life. It has been observed that a copper supplement is desirable in the treatment of rheumatoid arthritis [2]. Adjusting efficiently the concentration of copper ions in biological systems is an important part of the acting mechanism of nonsteroidal antiinflammatory agents. It is known that naproxen may function by releasing cupric ion from serum albumin either by a direct competitive complexing mechanism or through a remote mechanism whereby the drug becomes bonded to a site some distance from the copper ion and facilitates copper ion release through allosteric effects.



In order to enhance the understanding of drug—metal ion interaction, we report here on the results of an attempt to isolate some solid complexes of naproxen with the aim of obtaining materials for biological activity tests and of studying how naproxen binds to different transition metal ions.

Table 1 shows the results of elemental analyses of the complexes. Since HL is a monoprotic acid, for our study of the interaction of this drug with metal ions we decided to use the sodium salt as the starting ligand. Moreover, HL and NaOH were added to methanol in 1.5:1 mole ratio, so that there was contained some free HL in NaL and that there existed free HL in the complexes of Cr(III) and Ni(II). Most of the complexes are soluble in chloroform and coordination solvents like THF, DMF, and DMSO, but insoluble in ethanol and acetone, except for the Cr(III) and Ni(II) complexes. The values of molar conductances in DMF reveal the nonelectrolytic nature of all the complexes.

In the IR spectrum of HL the ν(C=O) stretching mode of the carboxylic acid group is observed as a band at $\tilde{\nu}$ = 1729 cm^{-1}. This disappears on deprotonation and in the sodium salt there are two new bands at 1545 cm^{-1} and 1409 cm^{-1}, the carboxylate antisymmetric (ν_{as}) and symmetric (ν_s) vibrations, respectively. The carboxylate ion usually coordinates to metal ions in one of the three main ways. Such differences are reflected in the relative position of the antisymmetric and symmetric stretching vibrations. The values of $\Delta\nu = \nu_{as}(COO) - \nu_s(COO)$ in unidentate complexes are expected to be much larger than that in the free ion. In bidentate complexes $\Delta\nu$ will be significantly smaller than in the free ion whereas $\Delta\nu$ of the bridging complexes is close to that of the free ion [3, 4]. The main IR bands in the spectra of the sodium salt and the complexes are listed in Ta-

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Table 1. Analytical Data, Molar Conductivities, and Thermal Data of the Complexes

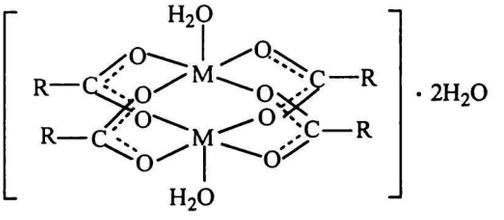
Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	$\theta_{dehyd.}$	$\theta_{decomp.}$	Λ	Colour
			C	H	M	%	°C	°C	$cm^2\ S\ mol^{-1}$	
$MnL_2 \cdot 2H_2O$	$C_{28}H_{30}O_8Mn$	549.5	61.15	5.46	10.00	91	111	238	7.9	White
			61.18	5.43	10.04					
$CoL_2 \cdot 2H_2O$	$C_{28}H_{30}O_8Co$	553.5	60.71	5.42	10.65	87	117	298	12.0	Light red
			60.67	5.35	10.71					
$CuL_2 \cdot 2H_2O$	$C_{28}H_{30}O_8Cu$	558.1	60.21	5.38	11.39	85	128	254	8.4	Green
			60.31	5.40	11.49					
$ZnL_2 \cdot 2H_2O$	$C_{28}H_{30}O_8Zn$	559.9	60.01	5.36	11.68	86	90	280	7.7	White
			60.10	5.38	11.73					
$FeL_3 \cdot 3H_2O$	$C_{42}H_{45}O_{12}Fe$	797.6	63.19	5.64	7.00	92	135	234	21.5	Yellow
			63.10	5.57	7.07					
$CrL_3(HL) \cdot 2H_2O$	$C_{56}H_{57}O_{14}Cr$	1006.0	66.80	5.67	5.17	68	110	150	16.2	Blue
			66.69	5.64	5.10					
NiL(HL)OH	$C_{28}H_{28}O_7Ni$	535.2	62.78	5.23	10.97	80		207	10.7	Light green
			62.68	5.21	10.93					
NaL	$C_{14}H_{13}O_3Na$	252.2	66.60	5.15		78				White
			66.65	5.13						

$L = C_{14}H_{13}O_3^-$; $HL = C_{14}H_{14}O_3$.

Table 2. IR Spectral Data ($\tilde{\nu}/cm^{-1}$) of Complexes

Compound	$\nu(COO^-)$			$\nu(H_2O)$
	ν_{as}	ν_s	$\Delta\nu$	
NaL	1545	1409	136	
$MnL_2 \cdot 2H_2O$	1560	1410	150	3394
	1519		109	
$CoL_2 \cdot 2H_2O$	1522	1393	126	3433
$CuL_2 \cdot 2H_2O$	1567	1407	160	3421
$ZnL_2 \cdot 2H_2O$	1561	1411	150	3445
$FeL_3 \cdot 3H_2O$	1533	1411	122	3334
$CrL_3(HL) \cdot 2H_2O$	1536	1418	118	3190, 3600[a]
NiL(HL)OH	1567	1410	157	3574[a]

a) ν(O—H) in HL.



ble 2. A strong broad band observed in the region 3190—3450 cm^{-1} is certainly due to the absorption of crystal or coordination water. Assignment of the type of carboxylate group coordination is based on both the position of ν_{as} and ν_s bands and the values of $\Delta\nu$ [5—9]. The values of $\Delta\nu$ for all complexes lie in the range of 109—160 cm^{-1} which is close to that of NaL indicating that the carboxylate group functions as a bridging ligand. Since the synthesized complexes containing M(II) all have the general formula $ML_2 \cdot 2H_2O$, the naproxen acts as a bridging ligand. The formula is dimeric at least, $[M_2L_4(OH_2)_2] \cdot 2H_2O$, where M = Mn(II), Co(II), Cu(II), and Zn(II); L = $C_{14}H_{13}O_3^-$, with a structure as shown in the formula (R = $C_{13}H_{13}O$). The same argument may be applied to the Fe(III) complex with the formula $[Fe_2L_6(OH_2)_4] \cdot 2H_2O$.

The IR spectrum of the Cr(III) complex exhibits a strong band at 1728 cm^{-1}, due to the ν(C=O) stretching mode of the carboxylic acid with hardly any shift, and the band at 3600 cm^{-1} assigned to ν(O—H) of the carboxylic group in HL is also unaffected on coordination and this free carboxylic group may bind to other carboxylate groups *via* intensive inter- or intramolecular H-bonds. The IR spectrum of the Ni(II) complex shows a band at 1678 cm^{-1} due to ν(C=O) of the carboxylic group, which shifts to lower frequency by 51 cm^{-1} relative to the free ligand. The shift to a lower frequency for ν(C=O) in HL suggests that the carboxylic group in free HL is taking part in coordination with the nickel ion. Two other bands at 3422 cm^{-1} and 3574 cm^{-1} appear and are ascribed to the OH group of the carboxylic group in the free ligand and the OH group bonding to the Ni(II) ion.

In the ^1H NMR spectrum of HL, the methyl (CH_3) protons give a sharp doublet centred at δ = 1.6, the methenyl (—CH) proton occurs as a triplet around δ = 3.63—3.84, the methoxy (CH_3O) protons exhibit a sharp singlet at δ = 3.92, and the naphthyl protons appear at δ = 7.10—7.76 as a multiplet while the carboxyl proton peak is unobserved. All these protons shift upfield in complexes, the methenyl proton displaying the highest shift (δ = 0.20—0.30) whereas the

methoxy protons shift the least ($\delta \approx 0.05$). This is due to the lesser electron-withdrawing capacity of metal ions in the complexes relative to that of the carboxy proton in the ligand.

The thermogram of the Cr(III) complex exhibits a mass fraction loss (5.41 %) at 110—120 °C, corresponding to the loss of two molecules of water and the observed percentage of dehydration is quite close to the theoretical value (3.85 %). Then the TG curve shows a mass fraction loss (22.96 %) at 140—160 °C and in the relevant DTA curve a sharp endothermic peak appears at 153 °C, which suggests that on heating one free ligand molecule bonded by hydrogen bonding is first removed from the metal coordination sphere. This further supports the discussion from the IR spectra. The TG curve for the Ni(II) complex has a mass fraction loss (43.13 %) at 180—230 °C, corresponding to one free ligand molecule eliminated on heating, and the observed mass fraction loss coincides very well with the theoretically calculated value (43.02 %), while a sharp endothermic peak is observed at 207 °C in the relevant DTA curve. The higher temperature for the loss of the free ligand in the Ni(II) complex than that in the Cr(III) complex reveals the fact that the HL binds more strongly in the former than in the latter case, so the HL may be bonded *via* hydrogen bonding for the chromium complex while for the nickel complex HL coordinates to Ni(II) ion. The thermal curves of other complexes are quite similar to one another. The DTA curves exhibit a wide endothermic peak at 90—140 °C and the corresponding TG curves show mass fraction losses of 6.40—6.78 %, attributed to dehydration on heating. The complexes then decompose in the range of 230—300 °C without melting, followed by degradation and complete burning at around 720—800 °C. The amount of residues corresponds to the contents of metal oxides in the complexes. The thermal data are listed in Table 2. The representative equations for the formation of the complexes can be presented as

$$M^{n+}Cl_n \cdot hH_2O + nNaL = ML_n \cdot mH_2O + nNaCl + (h-m)H_2O$$

(where M = Mn, Co, Cu, Zn, Fe; n = 2 or 3; h= 2, 4 or 6; m = 2 or 3)

$$CrCl_3 \cdot 6H_2O + 3NaL + HL = CrL_3(HL) \cdot 2H_2O + 3NaCl + 4H_2O$$

$$NiCl_2 \cdot 6H_2O + 2NaL = NiL(HL)OH + 2NaCl + 5H_2O$$

The antiinflammatory action results are presented in Table 3. It is obvious that both of the antiinflammatory edema models reveal the enhanced activity of the Cu(II) complex relative to the free ligand (HL) and its sodium salt (NaL) at the same dose due to pharmacological synergy resulting from the coordination effect of the Cu(II) ion bond to HL. On the other hand, the enhancement of the lipophilicity of the Cu(II) complex relative to the ligand may lead to a larger stabilizing action on lysosomal and erythrocyte membranes, which is quite an important part of the mechanism of action for nonsteroidal antiinflammatory agents [10, 11]. On the other hand, when HL is administered in the form of the Cu(II) complex, the concentration of the low-molecular mass pharmacoactive copper complex in plasma is increased more effectively, presumably from the circulation pool of serum albumin bound to copper. Thirdly, the enhanced antiinflammatory activity also may result from the unsaturated coordinating nature of the Cu(II) complex which may further coordinate to the phosphatide in membranes. Additionally, the larger inhibition to inflammation of the Cu(II) complex may also be due to the replacement of Cu(II) of some ions involved in reactions which synthesize and liberate inflammatory substances like histamine and 5-hydroxytryptamine.

Table 3. Data of Antiinflammatory Tests[a]

Groups	Rat paw edema		Mouse ear edema	
	Mean edema	Inhib.	Mean edema	Inhib.
	%	%	%	%
Physiol. brine	36.7 ± 4.4		16.2 ± 1.35	
HL	16.0 ± 3.2	56.4	6.8 ± 0.81	58.0
NaL	14.9 ± 2.4	59.4	6.5 ± 0.33	59.9
$CuL_2 \cdot 2H_2O$	9.1 ± 1.1	75.2	3.8 ± 0.25	76.5

a) $P < 0.02$ in all experiments.

EXPERIMENTAL

The D-naproxen purchased from the Southwest Second Pharmaceutical Factory, China, was a medically pure sample. The contents of metal were determined by complexometric titration against EDTA. Elemental analyses of carbon and hydrogen were obtained on an Erba 1106 elemental analyzer. IR spectra were obtained on a Nicolet 170SX infrared spectrometer in KBr pellets. Thermal analyses were carried out with a PCT-2 differential thermal analyzer. ^{1}H NMR spectra were recorded on an FT-80A NMR spectrometer in DMSO-d_6 solution, using TMS as an internal reference. All reagents were of anal. grade.

Sodium Salt of Naproxen

Naproxen was dissolved with an equimolar amount of NaOH solution in water. The reaction mixture was put on a water bath to evaporate until a crystal film appeared; upon cooling the white product separated out.

Complexes

The ratios n(metal):n(ligand) of divalent and trivalent ions used were 1:2 and 1:3, respectively, in each case. The 5—10 cm^3 methanol solutions of hydrous metal chlorides were added to the mixture of 1.5 g of naproxen and NaOH (φ_r = 1.5:1) in 25 cm^3 of methanol except for $CrCl_3 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ which were soluble in water as solvent. The overquantities of naproxen for higher acidity were avoided because of hydrolysis of metal ions. The complexes were usually precipitated immediately or within a short time after mixing the reactants. After 0.5 h of stirring, the solid complexes were isolated by filtration, washed until free of chlorides with the corresponding solvent (methanol or water) and finally dried in a desiccator over molecular sieves under vacuum.

Inhibition of Formaldehyde-Induced Rat Paw Edema

Forty male rats weighing (140 ± 10) g were chosen and divided stochastically into four groups of 10 to which the following agents were administered: *1.* physiological brine (control group); *2.* HL; *3.* NaL; *4.* Cu(II) complex. Each group received physiological brine or the test drugs dissolved or suspended in a solution containing 0.2 % Tween-80 in water, by garaging a volume of 20 cm^3 kg^{-1} and a dose of 20 mg kg^{-1} according to their calculated data. One h after oral administration the initial volume of rat hind paw was measured and 0.1 cm^3 of 2.5 % formaldehyde was injected into the subplantar area of the right hind paw. After 24 h the volume of this paw was remeasured. Mean fraction edema and fraction edema inhibition were calculated.

Inhibition of Croton Oil-Induced Mouse Ear Edema

Forty male mice weighing 26—30 g were chosen and divided stochastically into four groups of 10 as mentioned above. The mice were anaesthetized with ether and then received the test materials dissolved or suspended in an aqueous solution containing 0.2 % Tween-80, by garaging a volume of 20 cm^3 kg^{-1} and a dose of 20 mg kg^{-1}. One h after oral administration, the croton oil mixture consisting of 2 % croton oil, 20 % absolute ethanol, 5 % distilled water, and 73 % diethyl ether was smeared onto the right ear of each mouse, while the inner and outer surfaces of the ear each received 0.05 cm^3. The test mice were sacrificed and both ears of the mice were removed 4 h after the administration of the vehicle. The ear pieces were punched out with a 9 mm borer and weighed. Mean edema degree and fraction edema inhibition were calculated [12].

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