Stability Studies in Relation to IR Data of some Schiff Base Complexes of Transition Metals and their Biological and Pharmacological Studies

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Abstract

Schiff bases derived from salicylaldehyde and 2-substituted anilines and their Cu(II), Ni(II) and Co(II) complexes have been synthesized and characterized by their elemental analysis, TGA, IR and electronic spectral studies, molar conductance and magnetic susceptibility measurements. The mode of bonding between Cu(II), Ni(II) and Co(II) and Schiff bases has been studied by IR spectrophotometry. The shift in the band positions of the groups involved in coordination has been utilized to estimate the metal–nitrogen bond lengths. The results obtained are in good agreement with the values of metal–nitrogen modes and ligand-field splitting energy (10 *Dq*). The antimicrobial activities of the synthesized ligands and their metal complexes have been determined on Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli*) bacteria and on fungi like *Aspergillus niger*, *Aspergillus nidulense* and *Candida albicans*. The antimicrobial activity of the organic ligands increased several folds on chelation as compared to the ligand molecule alone. However, their anti-inflammatory activity showed a different pattern; the activity of some ligands was more than their respective metal chelates. It is interesting to note that only cobalt complexes exhibited anti-inflammatory activity.

Introduction

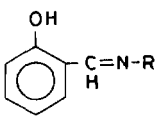
2-Substituted anilines such as anthranilic acid [1], mefanic acid [2], Dyrene (2,4-dichloro-6-(*o*-chloroaniline)triazine [3], *N*-(2,6-dichloro-*m*-tolyl)anthranilic acid [4], *N*-(2,3-xylyl)anthranilic acid [5], *N*-(β-phenylethyl)anthranilic acid [6] and several salicylates [7–9] have been reported to be strong anti-inflammatory and antipyretic agents. Sorenson [1] observed that copper complexes of some anti-inflammatory and non-anti-inflammatory ligands when administered subcutaneously into the rat produce a greater anti-inflammatory effect in several animal models of inflammation, and that copper complexes of anti-inflammatory compounds possess greater activity than the ligands themselves. The complexes have also been shown to possess antiulcer activity and less gastric irritation than the ligands [10, 11]. It was therefore thought worthwhile to synthesize some Schiff bases derived from salicylaldehyde and 2-substituted anilines in order to study the relationship between the coordinating tendency of the ligands with Cu(II), Ni(II) and Co(II) ions and also their biocidal, CNS and anti-inflammatory properties.

Experimental

All the chemicals used were A.R. grades.

Synthesis of Ligands

All the Schiff bases (Table I) of the following general structure were synthesized by condensing 1:1 molar amounts of salicylaldehyde with anthranilic acid, 2-aminophenol, 2-aminothiophenol or 2-aminopyridine in ethanol:



The purity of the synthesized compounds was tested by the TLC method.

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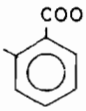
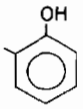
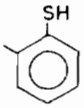
TABLE I. Synthesized Organic Ligands and their Elemental Analyses

Substituent (R)	Compound formed (abbreviation used)	Colour	Melting point (°C)	Yield (%)	Analysis: found (calc.) (%)			
					C	H	N	S
	salicylidene anthranilic acid (SAA)	orange	210	95	70.06 (69.69)	3.84 (4.59)	5.32 (5.80)	
	salicylidene-*o*-aminophenol (SAP)	orange	185	90	72.38 (73.22)	4.98 (5.19)	7.04 (6.56)	
	salicylidene-*o*-aminothiophenol (SATP)	shining yellow	145	92	67.64 (68.09)	5.03 (4.83)	7.18 (6.10)	14.36 (13.98)
	salicylidene-*o*-aminopyridine (SAPy)	yellow	68	85	73.43 (72.71)	6.07 (5.08)	13.78 (14.13)	

Synthesis of Metal Complexes

Metal complexes of Cu(II), Ni(II) and Co(II) were prepared by refluxing 1:1 molar mixture of metal acetates with salicylidene-anthranilic acid (SAA), salicylidene-*o*-aminophenol (SAP) and salicylidene-*o*-aminothiophenol (SATP) ligands for about 2 h; 1:2 molar concentrations were used in the case of salicylidene-*o*-aminopyridine (SAPy). On concentrating and cooling the resultant solution, the coloured crystals obtained were filtered under suction, washed first with water, ethanol and finally with ether and dried over P_4O_{10} under vacuum.

Physical Measurements

All the synthesized ligands and their metal complexes were analysed for C, H, N and S by microanalytical techniques. Metal contents in the complexes were estimated by standard methods [12]. The molar conductances of the metal complexes were measured in DMSO on a Toshniwal digital conductivity meter. IR spectra were recorded in CsI matrix using a Pye-Unicam Model SP 2000 infrared spectrophotometer in the range 4000–200 cm^{-1}. The electronic spectra of the metal complexes were recorded on a Cary-14 spectrophotometer. Magnetic measurements were carried out at room temperature by Guoy's method using $CuSO_4 \cdot 5H_2O$ as the calibrant and were corrected for diamagnetism by applying Pascal's constants.

Results and Discussion

Elemental Analyses and Conductance Measurements

The low molar conductance values (0–2.0 ohm^{-1} cm^2 mol^{-1}) of all the complexes indicated their non-ionic character. All the complexes were stable at room temperature and non-hygroscopic in nature. They decomposed on heating at >200 °C and were found to be almost insoluble in water. Their solubilities varied in different common organic solvents. The 1:1 and 1:2 stoichiometries of the complexes have been concluded from their elemental analyses (Table II). The presence of coordinated water was confirmed by TGA data where loss in weight corresponding to one water molecule for copper(II) and nickel(II), and three water molecules for cobalt(II), occurs at 280 °C. No coordinated water molecules were found in the case of the metal–SAPy complexes.

IR Spectral Studies

Some important infrared absorption frequencies of the ligands and their metal complexes are given in Table III with their probable assignments. All the free Schiff bases show their characteristic azomethine and OH frequencies at around 1650 and 3500 cm^{-1}, respectively. The former shifts towards the lower frequency region in the spectra of the complexes due to involvement of the N atom of the –C=N– group

TABLE II. Analytical and TGA Data of Schiff Base–Metal Complexes

Complex	Colour	Decomposition temperature	Analysis; found/(calc.) (%)					Loss of H_2O at 280 °C (%)
			C	H	N	S	M	
Cu(II)–SAA·H_2O	green	>300	53.26 (52.41)	3.84 (3.43)	5.32 (4.32)		20.08 (19.81)	6.86 (5.61)
Cu(II)–SAP·H_2O	green	278	55.36 (54.35)	4.08 (3.76)	5.32 (4.78)		22.46 (21.71)	5.92 (6.15)
Cu(II)–SATP·H_2O	green	248	51.08 (50.55)	4.18 (3.59)	4.06 (4.53)	9.68 (10.38)	22.06 (20.57)	6.12 (5.83)
Cu(II)–$(SAPy)_2$	green	267	63.13 (62.94)	5.16 (4.40)	13.34 (12.23)		14.27 (13.87)	
Ni(II)–SAA·H_2O	brownish yellow	>300	53.93 (53.21)	3.84 (3.48)	3.92 (4.43)		18.06 (18.59)	6.84 (6.22)
Ni(II)–SAP·H_2O	brownish yellow	295	55.02 (54.22)	4.11 (3.82)	5.05 (4.86)		20.90 (20.40)	6.53 (6.25)
Ni(II)–SATP·H_2O	brown	310	51.96 (51.36)	4.07 (3.64)	5.18 (4.60)	11.34 (10.54)	20.42 (19.31)	6.10 (5.90)
Ni(II)–$(SAPy)_2$	light green	297	61.43 (63.61)	5.16 (4.44)	13.18 (12.36)		13.16 (12.95)	
Co(II)–SAA·$3H_2O$	pink	>300	48.23 (47.75)	4.10 (4.26)	4.04 (3.97)		16.54 (16.73)	15.05 (15.33)
Co(II)–SAP·$3H_2O$	peach	288	48.56 (48.17)	5.06 (4.62)	4.92 (4.32)		19.12 (18.18)	17.12 (16.66)
Co(II)–SATP·$3H_2O$	pink	293	46.13 (45.88)	4.90 (4.44)	5.08 (4.11)	10.32 (9.42)	18.18 (17.31)	16.12 (15.84)
Co(II)–$(SAPy)_2$	myrtle	>300	62.36 (63.54)	4.24 (4.44)	13.30 (12.35)		11.54 (12.99)	

TABLE III. Important IR Frequencies of Schiff Bases and their Metal Complexes

Compound	ν(OH)	Coordinated water molecule	ν(CH=N–)	ν(M–O)	ν(M–N)
SAA	3500(w)		1648(s)		
Cu(II)–SAA·H_2O		3440(s), 850(w), 720(w)	1615(s)	420(s)	350(m)
Ni(II)–SAA·H_2O		3445(s), 860(w), 700(w)	1625(s)	420(s)	352(s)
Co(II)–SAA·$3H_2O$		3440(m), 845(w), 720(w)	1626(s)	418(s)	352(s)
SAP	3450(w)		1640(s)		
Cu(II)–SAP·H_2O		3460(s), 860(w), 710(w)	1608(s)	445(s)	325(m)
Ni(II)–SAP·H_2O		3440(m), 840(w), 700(w)	1617(s)	450(s)	330(s)
Co(II)–SAP·$3H_2O$		3450(m), 855(w), 705(w)	1618(s)	445(s)	340(m)
SATP	3500(w)		1650(s)		
Cu(II)–SATP·H_2O		3450(m), 850(m), 700(w)	1620(s)	450(s)	355(m)
Ni(II)–SATP·H_2O		3450(m), 845(w), 705(w)	1630(s)	448(s)	360(w)
Co(II)–SATP·$3H_2O$		3440(s), 855(w), 700(w)	1630(s)	448(s)	365(m)
SAPy	3480(w)		1636(s)		
Cu(II)–$(SAPy)_2$			1610(s)	448(s)	260(m)
Ni(II)–$(SAPy)_2$			1619(s)	445(s)	280(m)
Co(II)–$(SAPy)_2$			1619(s)	445(s)	285(s)

[13], whereas the ν(OH) bands almost disappear due to the deprotonation of the OH group. Strong bands around 1550 cm^{-1} in SAA and around 1600 cm^{-1} in SAPy are probably due to the carboxylic group and the pyridine nitrogen, respectively. These bands are shifted towards the lower frequency region in the

spectra of their metal complexes, suggesting the involvement of the carboxylic group and the pyridine nitrogen in coordination [14]. A weak band around 2570 cm^{-1} in SATP is probably due to an SH stretching vibration which disappears in the spectra of its metal chelates, showing deprotonation during chelation. The presence of coordinated water molecules in all the complexes except the metal–SAPy complex is indicated by a sharp band around 3450 cm^{-1} and two somewhat weaker bands around 850 and 700 cm^{-1}, which could be assigned to OH stretching, rocking and wagging vibrations, respectively [15]. The appearance of some new bands in the IR spectra of the metal complexes in the regions 450, 360 and 310 cm^{-1} are probably due to the formation of M–O, M–N and M–S bonds, respectively, developed through complexation [16].

The foregoing results and discussion on Schiff base complexes denote that as a result of their chelation the C=N bands are apparently shifted to lower wavenumbers. Also other bands suffer some displacement in position. It is, however, of interest to mention that the magnitude of the frequency shift was dependent on the nature of both the transition metal ion and the ligand involved in chelation. This is probably due to a change in the electrostatic field of the metal ions and in the vibrational dipoles of the ligand [17]. Since all the metal ions under investigation have the same change, thus the distance between the metal ion and the coordinating centre would be the main factor affecting band shifts. The magnitude of the frequency shifts has been used and established elsewhere [17] in determining the distance between the metal ion and the coordinating group, which is approximately equivalent to the length of the coordination bond. According to Karagonius and Peter [18], shifts in the IR spectra of organic ligands on coordination to metal ions are comparable to those shifts of the ligand bands when absorbed on a salt substrate. Thus, both cases can be treated more or less in the same manner.

The values of the coordination bond length (r) can be determined from the relation [18].

$$\Delta\nu = \left(\frac{32\pi\alpha}{a^2}\right)\left(\frac{\nu_{x=y} - \nu_{x-y}}{l}\right) \exp\left(-2\pi\sqrt{\frac{2r}{a}}\right)$$

where α = bond polarisability, $\Delta\nu$ = shift in the oscillator frequency ($\nu_{\text{ligand}} - \nu_{\text{complex}}$), a = lattice constant of the metal salt used, ν_{x-y} = frequency of the oscillator with single bond, $\nu_{x=y}$ = frequency of the oscillator with double bond, and l = length of the oscillator coordinated to the metal ion.

This relation denotes that log $\Delta\nu$ would be a linear function of (r), as shown in the calibration curves (Fig. 1). Values of (r) can directly be computed or determined graphically [19]. The values of (r) and M–N frequencies for all the metal complexes under investigation are given in Table IV. It is evident from Table IV that the shift in azomethine vibrations and the calculated coordination bond lengths of the transition metal complexes of Schiff bases are in the following sequence.

Cu(II) < Ni(II) < Co(II)

Furthermore, the values of the M–N frequencies

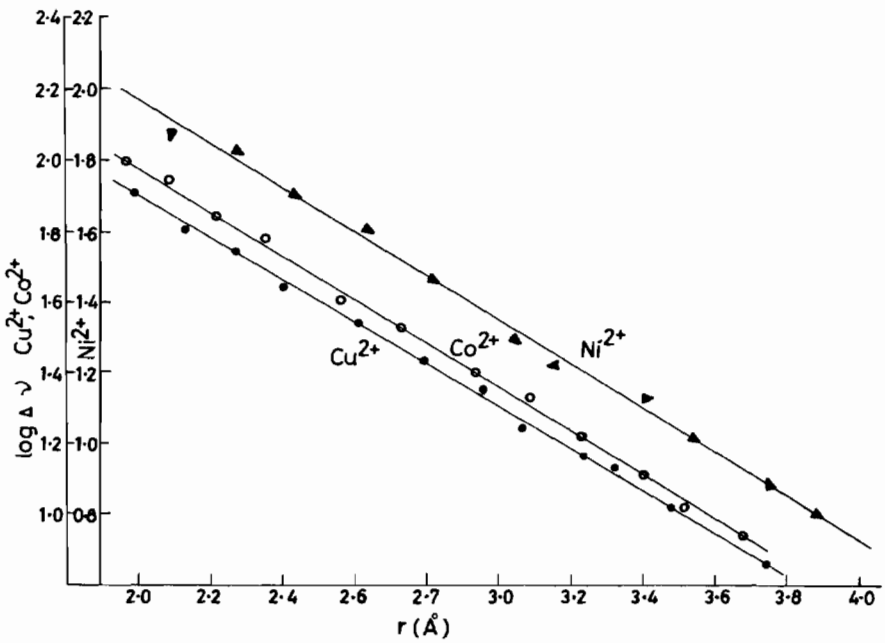


Fig. 1. A diagrammatic representation of the relationship between log $\Delta\nu$ and the coordination bond length.

TABLE IV. Coordination Bond Lengths and Ligand Field Splitting Energies (10 *Dq*) of Schiff Base–Metal Complexes

Complex	Azomethine frequency shift ($\Delta\nu$) $\nu_{ligand}-\nu_{complex}$	log $\Delta\nu$	r (Å)	10 *Dq*
Cu(II)–SAA·H_2O	33	1.5185	2.643	7796
Ni(II)–SAA·H_2O	24	1.3802	2.952	6432
Co(II)–SAA·$3H_2O$	23	1.3617	2.995	4428
Cu(II)–SAP·H_2O	32	1.5051	2.662	7539
Ni(II)–SAP·H_2O	23	1.3617	2.995	5893
Co(II)–SAP·$3H_2O$	22	1.3424	3.085	4568
Cu(II)–SATP·H_2O	30	1.4771	2.715	8250
Ni(II)–SATP·H_2O	20	1.3010	3.082	7986
Co(II)–SATP·$3H_2O$	20	1.3010	3.096	6919
Cu(II)–$(SAPy)_2$	26	1.4150	2.810	7562
Ni(II)–$SAPy)_2$	17	1.2304	3.195	6805
Co(II)–$(SAPy)_2$	17	1.2304	3.200	6538

decrease in the same order as the azomethine vibrations, revealing thereby the strength of the metal–nitrogen bond in decreasing order. The shorter coordination bond lengths for the copper complexes could be attributed to the increase in the strength of the electrostatic field of the copper ion as a result of the smaller ionic radius of the Cu(II) ion than that of either Ni(II) or Co(II) ions (Fig. 2). Further support for this explanation is given by the greater number of d-electrons in Cu(II) ions than for either Ni(II) or Co(II) ions. The latter two ions have almost similar ionic radii and thus their replacement with one another has no consistent effect on the coordination bond lengths (Fig. 2 and Table IV).

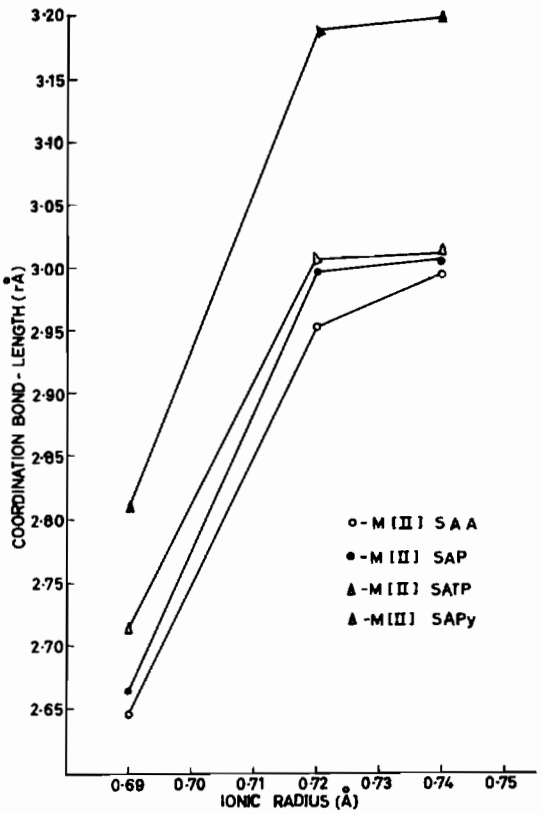


Fig. 2. Relationship between the coordination bond length of Cu^{2+}, Ni^{2+} and Co^{2+} complexes with SAA, SAP, SATP and SAPy and ionic radii of the Cu^{2+}, Ni^{2+} and Co^{2+} transition metals.

Magnetic and Electronic Spectral Studies

The magnetic and electronic spectral studies confirm the geometries of the complexes as follows.

Copper(II) complexes

The μ_{eff} values of the complexes are in the range 1.73–2.36 B.M., which corresponds to one unpaired electron. All the complexes except Cu(II)–SAPy possess square-planar geometry, as evidenced by the appearance of only one band in the electronic spectra around 700 nm with two shoulders on either side at 550 and 880 nm. These bands could be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$, $^2B_{1g} \rightarrow {}^2B_{2g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions, respectively [20]. In the case of the SAPy complex, only one band around 700 nm is probably due to the $^2E_g \rightarrow {}^2T_{2g}$ transition, which indicates a octahedral configuration [21].

Nickel(II) complexes

The diamagnetic character of all the nickel(II) complexes is indicated by their square-planar geometry, which is also supported by their electronic spectra having two bands around 525 and 415 nm, probably due to $^1A_{1g} \rightarrow {}^1A_{2g}(\nu_3)$ and $^1A_{1g} \rightarrow {}^1B_{1g}(\nu_2)$ transitions, respectively [22]. In the electronic spectrum of the Ni(II)–SAPy complex, two absorption bands are noticed in the region of 900 and 600 nm which may be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transitions, respectively, indicating

TABLE V. Minimum Inhibitory Concentrations (MIC) ($-\log_{10}$ M) of SAA, SAP, SATP, SAPy and their Cu(II), Ni(II) and Co(II) Complexes

Compound	Bacteria		Fungi		
	S. aureus	*E. coli*	*A. niger*	*A. nidulense*	*C. albicans*
SAA	3.50	3.68	>3.38	3.38	3.98
SAP	3.45	3.62	3.32	>3.32	>3.32
SATP	3.36	3.48	3.36	3.48	3.66
SAPy	3.42	>3.07	>3.07	3.42	>3.07
Cu(II)–SAA·H_2O	3.63	4.11	4.41	3.80	4.40
Ni(II)–SAA·H_2O	4.10	<4.70	4.40	4.70	3.62
Co(II)–SAA·$3H_2O$	4.15	4.45	<4.45	3.85	4.45
Cu(II)–SAP·H_2O	3.77	<4.67	4.36	3.77	4.67
Ni(II)–SAP·H_2O	3.45	3.76	4.36	4.61	4.66
Co(II)–SAP·$3H_2O$	<4.71	4.41	4.11	3.63	4.41
Cu(II)–SATP·H_2O	3.79	4.39	4.92	4.69	3.79
Ni(II)–SATP·H_2O	4.86	3.48	4.69	4.39	4.86
Co(II)–SATP·$3H_2O$	3.83	3.83	4.13	3.83	4.87
Cu(II)–$(SAPy)_2$	4.57	3.96	3.96	4.57	3.79
Ni(II)–$(SAPy)_2$	4.86	3.96	4.26	3.96	3.96
Co(II)–$(SAPy)_2$	4.56	4.26	4.86	3.78	4.56

an octahedral geometry [23], as evidenced by its magnetic moment value (3.14 B.M.).

Cobalt(II) complexes

These complexes appear to be in their hexa-coordinated state with μ_{eff} values of 4.75–4.96 B.M. The octahedral geometry of these complexes is further evidenced by the appearance of two main bands around 645 and 525 nm, which could be assigned to the $^4T_{1g}$ to $^4A_{2g}(F)(\nu_2)$ and $^4T_{1g}(P)(\nu_3)$ transitions, respectively. The octahedral geometry of the cobalt complexes is further confirmed by the value of the energy ratio ν_2/ν_1 (1.9–2.2) as required for octahedral complexes [23].

The obtained values of the ligand field splitting energy (10 *Dq*) calculated from electronic spectral data [24] (Table IV) of the aforementioned complexes determine the stability of the complexes and follow the following order in terms of metal ions:

Cu(II) > Ni(II) > Co(II)

This stability order of the transition metal complexes of Schiff bases is also in fair agreement with the order of Irving and William [25] and Powell and Sheppard [26].

Biological Activities

Biocidal activity

All the synthesized compounds were tested *in vitro* for their antibacterial activity against Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli*) bacteria and some fungi (*Aspergillus niger*, *Aspergillus nidulense* and *Candida albicans*) by the serial dilution method [27]. A comparative study of the minimum inhibitory concentration (MIC) values (Table V) indicates that most of the metal chelates exhibit higher antimicrobial activity than that of the involved free ligand molecule alone.

CNS activity

The synthesized Schiff bases and their metal complexes were tested for their CNS activities such as analgesic, sedative, anticonvulsant and tranquillizing activities. However, none of these compounds exhibited any significant CNS activity.

Anti-inflammatory activity

All the compounds were primarily tested in an acute model of inflammation by carrageenin-induced oedema [28]. The compounds found active were further screened for their anti-inflammatory activity using 100, 200 and 400 mg/kg doses in acute and sub-acute models of inflammation in albino rats. The anti-inflammatory ED_{50} value was determined in carrageenin-induced hind paw oedema [28] (a 6 h-study after injecting 0.5 ml of 1% *w/v* freshly prepared suspension of carrageenin in normal saline); formaldehyde-induced arthritis [29] (a 20-day study by giving 0.1 ml of 2% *v/v* formaldehyde injected subcutaneously under the planter aponeurosis in each foot on the first and third day and measurement of the inflammatory reaction by a Screw gauge); and by cotton pellet implantation granuloma [30] (a 7-day study by implanting pellets of sterilized surgical cotton weighing 9 mg in both axillae and groins and dissecting, drying and weighing the pellet on day 7 after giving the drug intraperitoneally for 6 days). Oxyphenylbutazone and hydrocortisone were taken as standard drugs for comparison.

TABLE VI. Anti-inflammatory Activities

Compound	Anti-inflammatory ED_{50} (mg/kg)		
	Carrageenin-induced oedema (per oral)	Formaldehyde-induced arthritis (intraperitoneal)	Cotton pellet granuloma (intraperitoneal)
Standard drugs			
Oxyphenylbutazone	49.5	100	89.1
Hydrocortisone	12.9	30	24.3
Active compounds			
SAA	68.0	125	170.0
SAP	100.0	205	190.0
Co(II)–SAA·$3H_2O$	85.0	165	210.0
Co(II)–$(SAPy)_2$	72.0	130	201.0

It has been reported that some trace elements like copper [31] and zinc [32] do show anti-inflammatory activity on chelation with active organic drugs. These metals do increase their anti-inflammatory action, coupled with their antiulcer action. However, our results (Table VI) indicate that ligands like SAA and SAP showed anti-inflammatory activity but their copper chelates did not show any significant anti-inflammatory activity. In the case of cobalt complexes, the anti-inflammatory activity is markedly exhibited especially in the case of SAPy, where the cobalt complex shows an activity of 41.2% at a dose level of 50 mg/kg per oral, whereas the parent compound (SAPy) exhibits only 14.3% inhibition at this dose level. In the case of SAA, the activity decreases after chelation with cobalt(II) ion. It is again interesting to report that SAP alone shows pronounced activity at the 100 mg/kg dose level which almost disappears on its chelation with all three metal ions used. Efforts are also being made to study the detailed biochemical mechanism to understand these interesting findings.

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