Structural and Biological Studies on Benzimidazolyl Amino Acid Complexes of Dimethyldichlorosilane

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Abstract

Several benzimidazolyl amino acid complexes of dimethyldichlorosilane are synthesized. The complexes were characterized by elemental analyses, conductivity measurements, infrared and proton magnetic resonance spectral data. The complexes are nonelectrolytes in DMF solution and exhibit 1:1 (metal:ligand) stoichiometry. Furthermore, the complexes are found to be biologically active as demonstrated by antibacterial and antiinflammatory tests.

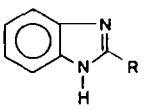
Introduction

The interaction of benzimidazoles and their derivatives with various metal ions have been studied for almost two decades [1–7]. Benzimidazoles are known to exhibit a wide variety of pharmacological properties such as antiinflammatory [8], antimalarial [9], anthelmentic [10], antiviral [11], antitumor [12], anticonvulsant [13], and antifungal [14]. Our recent efforts [15–20] are directed towards the syntheses and characterization of biologically active coordination compounds. As a further contribution in this area, we have synthesized a few benzimidazolyl amino acid complexes with dimethyldichlorosilane (DMDCS). Characterization of these compounds was performed. The antibacterial and antiinflammatory tests on these complexes were conducted; a correlation of the structure–property relationship was proposed.

Experimental

Preparation of Ligands

Benzimidazolyl amino acids were prepared according to the method developed by Cescon and Day [21]. 0.05 mol of *o*-phenylenediamine, 0.075 mol of amino acid and 50 ml of 6 N hydrochloric acid was combined. This solution was refluxed for about 70 h. The mixture was cooled; the resulting precipitate was filtered. The compound was purified by repeated crystallization from dilute hydrochloric acid. Animal charcoal was used to remove impurities from the product. The free base was obtained by dissolving the hydrochloride in a minimal amount of water. A calculated quantity of sodium bicarbonate was added to the solution. The ligands shown in Scheme 1 were prepared.



Ligand	R	Name	Melting point (°C)
A	$-CH_2-NH_2$	2-Methylamino-benzimidazole	48–51
B	$-\underset{NH_2}{\underset{\vert}{CH}}-CH_3$	2-α-Ethylamino-benzimidazole	168–170
C	$-CH_2-CH_2-NH_2$	2-β-Ethylamino-benzimidazole	154–156
D	$-\underset{NH_2}{\underset{\vert}{CH}}-CH_2-\overset{O}{\overset{\Vert}{C}}-OH$	α-(2-Benzimidazolyl)-alanine	203–205
E	$-\underset{NH_2}{\underset{\vert}{CH}}-CH_2-C_6H_4-OH$	α-(2-Benzimidazolyl)-*p*-(p-hydroxyphenyl)-ethylamine	195–197
F	$-\underset{NH_2}{\underset{\vert}{CH}}-CH_2-$(indolyl)	α-(2-Benzimidazolyl)-β-(3-indolyl)-ethylamine	212–213

Scheme 1.

Preparation of Complexes

Reagent grade dimethyldichlorosilane was used. No purification was required. The complexes were prepared by mixing equimolar quantities of the ligands with DMDCS and 200 ml of dry benzene. The mixture was shaken vigorously for 1 h. The following

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day, the separated complex was filtered; washed with dry benzene. The product was dried under vacuum over P_2O_5.

Physico-chemical Measurements

Elemental analyses were carried out by a previously described procedure [22]. Chlorine was estimated as silver chloride; nitrogen was determined by the Kjeldahl method. Carbon was estimated using microanalytical techniques.

Conductivities were measured using an Elico-CM-82 conductivity bridge (cell constant equal to 0.829 cm^{-1}). All conductivity measurements were performed at room temperature. Complexes were prepared at 10^{-3} concentrations in dimethylformamide (DMF). The infrared (IR) data in KBr matrix were obtained using a Perkin-Elmer 180 spectrophotometer. Proton magnetic resonance (PMR) spectra were scanned using a S-60-C NMR instrument. All samples were dissolved in deuterated dimethylsulfoxide, (d_6-DMSO). Tetramethylsilane, (TMS), was the internal standard.

Pharmacological Tests

Antibacterial tests

Our experiments used the cup-plate method [23]. Nutrient agar was the selected media. The microorganisms tested were *E. coli, B. subtilis, S. aureus,* and *P. vulgaris.* Testing and culture procedures were conducted as follows.

(1) Media preparation for subculture growth. The microorganisms were subcultured in a liquid medium. The medium's composition was 0.5% peptone, 0.15% yeast extract, 0.15% beef extract, 0.35% sodium chloride, 0.13% potassium dihydrogen phosphate, 0.13% potassium monohydrogen phosphate dissolved in 100 ml distilled water. The medium was sterilized prior to use. The microorganisms were cultured for 24 h at 37 °C.

(2) Basal medium preparation for tests. Nutirent agar medium was prepared by dissolving bacteriological peptone (0.60%), yeast extract (0.30%) and beef extract (0.13%) in 100 ml of distilled water. This solution was filtered; then 2.1% agar was added to the medium. The media was sterilized prior to the adding 1 ml 10% glucose solution.

(3) Testing procedure. The agar broth was melted on a hot water bath, then cooled to 40 °C. About 25 to 50 ml basal medium was poured into each petri dish. The solution was allowed to solidify. The bacterial culture was sprayed over each plate. A cup of 10 mm diameter was bored in the center of each agar plate; the punched part is discarded. 0.1 ml of test compound (DMF solvent at a concentration of 200 μg/ml) was added dropwise by pipette. The petri dishes were kept cold to facilitate diffusion. The plates were incubated for 24 h at 37 °C. The extent of inhibition was measured by the inhibition zone width formed. The compound activity was measured in comparison to a phenol standard.

Antiinflammatory tests

The antiinflammatory activity measurement used was the carrageenan-induced rat paw edema assay [24]. Male and female albino rats were used as test subjects. The rats weighed between 150–200 g; the rats weight determined dosage administered. Each rat received 200 mg test compound for each kilogram body weight. Test compounds were a suspension of the ligand in a 4% gumacacea–water solution. A control group received identical treatment, but did not receive any ligand complex in the initial injections.

All rats did not eat for 24 h prior to testing. Rats were divided into different groups; each group consisted of five rats. Each group received an initial injection. After one hour, a second injection was administered. The second injection was identical for all groups. Each animal received 1 ml 0.9% sodium chloride solution containing 1% carrageenan. This solution was injected into the plantar area of the left hind paw. The paw was measured by the amount of mercury it displaced. The measurement was repeated three hours later. Differences in paw measurement and inhibition potency was compared to phenylbutazone.

Percentage inhibition was calculated using the following equation:

$$\% \text{ inhibition} = \frac{V_c - V_t}{V_c} \times 100$$

V_c is the paw edema volume found in the control group. V_t is the paw edema found in groups receiving the ligand complex.

Results and Discussion

Analytical Data

The complexes are dark brown to reddish color. The compounds are insoluble in most organic solvents with the exception of DMF and DMSO. Elemental analyses suggest a 1:1 (metal:ligand) stoichiometry and the conductivity tests indicate a non-electrolytic behavior in solutions (see Table I).

Infrared Spectra

Important IR frequency ranges with their assignments are reported in Table II. In the spectra of ligands, an intense band around 3200–3260 cm^{-1} is attributed to γ(N–H) of a free exocyclic amine group [13]. Absorption bands are produced by a combination of γ(C=C) and γ(C=N) stretching modes. These are observed in the region 1600–1620

TABLE I. Analytical and Physical Data of Complexes

Molecular formula of complex		Analysis (found (calc.))			Molar conductivity (ohm^{-1} cm^2 mol^{-1})	Melting point (°C)
		Cl%	N%	C%		
$(C_{10}H_{15}N_3)SiCl_2$	(I)	25.00 (25.81)	15.05 (15.21)	43.40 (43.47)	70.2	178
$(C_{11}H_{17}N_3)SiCl_2$	(II)	24.80 (24.48)	14.25 (14.48)	45.25 (45.51)	53.9	195
$(C_{11}H_{17}N_3)SiCl_2$	(III)	24.00 (24.48)	13.99 (14.48)	45.30 (45.51)	68.3	208
$(C_{12}H_{17}N_3O_2)SiCl_2$	(IV)	21.50 (21.32)	12.48 (12.61)	43.12 (43.24)	56.9	268
$(C_{17}H_{21}N_3O)SiCl_2$	(V)	18.05 (18.63)	11.05 (11.02)	53.60 (53.54)	70.1	246
$(C_{17}H_{21}N_4)SiCl_2$	(VI)	18.20 (17.92)	15.96 (16.16)	51.70 (51.51)	71.6	235

TABLE II. Infrared Data and their Assignments

Ligands[a]	Complexes[a]	Assignments
3200–3260	3400–3420	γ(N–H) free amine
1600–1620	1625–1640	γ(C=C) + γ(C=N)
1480–1500	1500–1520	γ(N–H) imidazole ring
980–1010	1000–1010	benzenoid ring vibrations
720–730	750–795	heterocyclic ring
875–892	900–1000	breathing modes
	1400–1415	γ(C–H)
	695–710	γ(Si–N)
	520–530	γ(Si–Cl)
	650–665	γ(Si–C)

[a]Frequency ranges (cm^{-1}).

cm^{-1}. In view of the published data [25], the band at 1480–1500 cm^{-1} is assigned to γ(N–H). In the spectra of complexes, these bands have a shift. The γ(N–H) stretch is observed at 3400–3420 cm^{-1}. This suggests participation of the exocyclic amine group in coordination. The metal ion is coordinated through pyridine nitrogen of the imidazole ring. This is substantiated by a shift of frequency due to γ(C=C) and γ(C=N) at about 1625–1640 cm^{-1}. Positional shift to 1500–1520 cm^{-1} is due to γ(N–H) of imidazole nucleus. This indicates coordination to the metal ion through pyridine nitrogen of the imidazole nucleus [26]. In view of earlier observations [27], the regions 980–1010 cm^{-1} and 875–1000 cm^{-1} are respectively assigned to benzenoid and heterocyclic ring breathing modes.

A shoulder band observed around 1410 cm^{-1} is assigned to γ(C–H) vibrations of Si–C–H linkage. The weak band at 660 cm^{-1} is attributed to γ(Si–C) stretch [28]. Two intense bands are observed in the regions 705 cm^{-1} and 525 cm^{-1}. These bands are respectively assigned to γ(Si–N) and γ(Si–Cl) stretches [29].

Proton Magnetic Resonance Spectra

In the ligands, the signals observed at 1.72 ppm, 3.7 ppm, 6.5–7.5 ppm and at 7.8 ppm are respectively assigned to the protons of exocyclic amine group, 2-methyl-amino benzimidazole, phenyl group and imidazole ring NH group. In the complexes, however, the protons of exocyclic amine group are observed at 3.25 ppm. This further supports the possibility of coordination through a exocyclic amine. Methyl protons do not exhibit positional shift. Protons of the benzimidazole moiety are shifted to the region 7.0–8.0 ppm. Similarly, the signal position shift at 8.05 ppm is due to the NH group proton found in the imidazole ring. This substantiates coordination of the metal ion through pyridine nitrogen [26]. A sharp doublet, in region 1.0–1.5 ppm is attributed to proton signals eminating from DMDCS. The doublet was not observed in the ligands.

Biological Tests

Antibacterial tests

The data are presented in Table III. Phenol is used as test comparison. All ligands show activity against the microorganisms studied. The 2-methylamino benzimidazole ligand demonstrated the best activity. Substitution of a α or β-methyl group in the side chain greatly lowered activity in regard to three microorganisms. *P. vulgaris* was equally susceptible to all methylamino benzimidazole ligands. The indole substitution on the β-carbon atom, (ligand F), had the lowest effect on activity. The complexes possess bacteriostatic properties superior to the parent ligands.

Antiinflammatory tests

The results are presented in Table IV. The data for phenylbutazone are included as a comparison. Amongst the complexes, 2-methylaminobenzimi-

TABLE III. Antibacterial Tests of Ligands and Complexes

Ligands/ Complexes	Zone of Inhibition (mm)			
	E. coli	*B. subtilis*	*S. aureus*	*P. vulgaris*
A	20	15	23	20
I	28	24	22	24
B	14	12	17	20
II	23	16	21	24
C	16	14	15	18
III	24	20	20	23
D	18	15	17	19
IV	20	[a]	21	18
E	18	17	12	18
V	17	17	17	24
F	13	14	12	15
VI	21	19	17	20
Phenol (Standard)	15	18	18	29

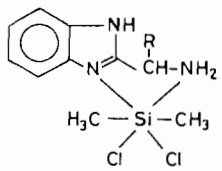
[a]Not determined.

TABLE IV. Antiinflammatory Tests of Complexes

Complex	Dose (mg/kg)	Initial reading	Reading after 3 h	Edema formed	% Inhibition
I	200	4.4	5.9	1.5	50
II	200	6.6	7.02	1.92	37
III	200	4.3	6.7	2.4	31
IV	200	5.6	7.46	1.86	40
V	200	4.2	6.06	1.86	40
VI	200	4.6	6.96	2.36	30
Gramacacea	4%	6.00	9.99	3.97	

dazole shows the highest percent of inhibition (50%). However, substitution of a methyl group onto α-carbon atom reduces the activity (37% reduction). The least activity was observed for complexes **III** and **VI** (30% activity).

In summation, the physico-chemical and spectral studies suggest the following chemical structure for these complexes.



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