Selenium and Tellurium Complexes with 2-Substituted Benzimidazoles

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Received July 21, 1982

Several 2-substituted benzimidazole complexes of selenium(IV) and tellurium(IV) were prepared and characterized using conductivity measurements, and infrared spectral data. Elemental analyses confirmed a 1:2 (metal:ligand) stoichiometry. Some of the complexes proved to be biologically active as evidenced by positive anti-inflammatory activity.

Introduction

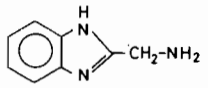
Recently there has been a considerable amount of interest in the complexation chemistry of benzimidazoles with various metal ions [1–4]. Benzimidazoles with an alpha-amino acid homologue in the 2-position of the imidazole ring are known to exhibit enhanced biological activity [5–7]. In general benzimidazoles form 1:2 (metal:ligand) complexes in which the coordination to the metal ion is through the nitrogen in the 1-position [8]. Since the benzimidazole complexes of selenium and tellurium have not been reported extensively in the literature, a series of substituted benzimidazole complexes were synthesized, characterized and their biological activity determined. The complexes have been characterized using infrared spectral data as well as conductance measurements. The biological activity has been evaluated using anti-inflammatory activity tests.

Experimental

All chemicals used in this work were of reagent grade. The substituted benzimidazoles were prepared according to a method published previously [9]. 0.01 mol of the corresponding amino acid, and 0.01 mol of o-phenylenediamine in 5.5 N hydrochloric acid were refluxed for 70 h. The reaction mixture was then allowed to cool, and the precipitate formed was then recrystallized using 0.4 N hydrochloric acid. The benzimidazole salt was then converted to the free amine by dissolving the salt in a minimum amount of water and then neutralizing with sodium bicarbonate. The purity of the resulting precipitate was then checked by determining the melting point. The N-(2-methylenebenzimidazole) salicylaldimine was prepared by reacting benzimidazolylmethylamine with salicylaldehyde in ethanol.

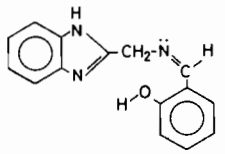
The following 2-substituted benzimidazoles were prepared:

(A)



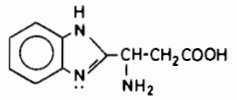
Benzimidazolylmethylamine

(B)



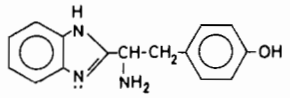
N-(2-methylenebenzimidazole)salicylaldimine

(C)



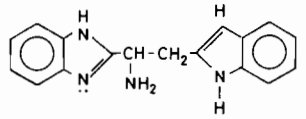
3-benzimidazol-3-amino propionic acid

(D)



1-benzimidazolyl-2(4-hydroxyphenyl)ethylamine

(E)



1-benzimidazolyl-2-(3-indolyl)ethylamine

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TABLE I. Analytical and Physical Data for 2-substituted Benzimidazole Complexes of Selenium(IV) and Tellurium(IV).

S. No.	Ligand	Complex No.	Empirical formula of the complex	M.P. °C	%M	%N	%Cl	Molar Cond. (ohm^{-1} cm^2 mol^{-1})
1	A	I	$(C_8H_9N_3)_2SeCl_4$	125	15.25 (15.33)*	16.35 (16.31)	27.58 (27.57)	112.80
2	B	II	$(C_{15}H_{12}N_3O)_2SeCl_2$	80	12.20 (12.15)	12.80 (12.92)	10.93 (10.92)	80.00
3	C	III	$(C_{10}H_{11}N_3O_2)_2SeCl_4$	190	12.49 (12.51)	13.22 (13.31)	22.50 (22.51)	164.88
4	D	IV	$(C_{15}H_{15}N_3O)_2SeCl_4$	210	10.82 (10.86)	11.49 (11.55)	19.56 (19.53)	150.00
5	E	V	$(C_{17}H_{16}N_4)_2SeCl_4$	290	10.20 (10.16)	14.50 (14.42)	17.21 (18.28)	132.00
6	A	VI	$(C_8H_9N_3)_2TeCl_4$	300	22.70 (22.65)	14.84 (14.91)	25.21 (25.20)	123.64
7	B	VII	$(C_{15}H_{13}N_3O)_2TeCl_4$	165	16.49 (16.54)	10.80 (10.89)	18.40 (18.41)	169.40
8	C	VIII	$(C_{10}H_{11}N_3O_2)_2TeCl_4$	300	18.80 (18.78)	20.94 (20.90)	12.00 (12.36)	80.26
9	D	IX	$(C_{15}H_{15}N_3O)_2TeCl_4$	220	16.45 (16.46)	10.45 (10.83)	18.35 (18.31)	130.00
10	E	X	$(C_{17}H_{16}N_4)_2TeCl_4$	330	15.50 (15.53)	13.60 (13.63)	17.25 (17.29)	160.00

*Figures in the parentheses are calculated values.

The selenium(IV) and tellurium(IV) complexes were prepared by mixing the respective metal tetrachloride with the substituted benzimidazole in dry benzene in the molar ratio 1:2. Table I correlates each ligand A–E with its corresponding selenium(I–V) or tellurium(VI–X) complex.

The resulting complex was then filtered, washed repeatedly with anhydrous benzene using a Soxhlet extractor, and finally dried under vacuum over P_2O_5.

Elemental analyses were carred out by a procedure discussed elsewhere [10]. Selenium and tellurium were determined as their respective metals. Chlorine was determined as the silver chloride precipitate, while sulfur was determined as the barium sulfate salt. The method of Kjeldahl was used to determine the nitrogen content of the complexes.

Conductivities were measured in dimethylformamide (DMF) using an Elico-CM-82 conductivity bridge with a cell having a cell constant of 0.829 cm^{-1}. All conductivity measurements were performed at room temperature using 10^{-3} *M* solutions of complex.

The infrared spectra (IR) from 4000 to 200 cm^{-1} were obtained using a Perkin-Elmer 180 spectrophotometer. Samples were prepared as KBr pellets.

The anti-inflammatory activity test was carried out by using the carrageenan-induced rat paw edema assay of Winter *et al.* [11]. 100 mg/kg body weight was found to be a safe dose level for substituted benzimidazole complexes of selenium(IV) and tellurium(IV) in acute toxicity studies. Phenylbutazone known to have substantial anti-inflammatory activity was used as a reference compound. 4% gumaceria was used as a control.

Results and Discussion

Analytical Data

All the complexes of selenium(I–V) are hygroscopic but have limited solubility in water while the complexes of tellurium(VI–X) are amorphous in nature. All the complexes are insoluble in common organic solvents but soluble in dimethylformamide (DMF) and dimethylsulfoxide (DMSO). The elemental analyses (see Table I) agree well with 1:2 (metal: ligand) stoichiometry. The molar conductivities of most of the selenium and tellurium complexes range from 113 to 170 ohm^{-1} cm^2 mol^{-1} suggesting 1:2 electrolyte behavior. Complexes II and VIII may be 1:1 electrolytes.

Infrared Spectra

Important infrared frequencies and their assignments are tabulated and available upon request from the author to whom all correspondence should be addressed.

The infrared spectra of the ligands (A–E) show broad absorption bands in the vicinity (3500–3000 cm^{-1}) [12, 13]. The band in the range 3420–3460 cm^{-1} is assigned to the N–H stretching vibration of the free amino group (NH_2), while the lower frequency bands around 3340–3200 cm^{-1} are assigned to the NH stretch of the benzimidazole moiety. The bands in the range 3070–2900 cm^{-1} can be attributed to C–H stretches. Although there are three or four adjacent bands in the range 1615–1475 cm^{-1}, the highest frequency band is assigned to the C=N stretch [1, 12, 14]. This assignment is corroborated by the infrared spectra of N-(2-methylenebenzimidazole)salicylaldimine ligand B, which has two absorption bands at 1615 and 1600 cm^{-1}, the former band assigned to the azomethine stretch, while the latter is assigned to the C=N stretch of the imidazole ring. The bands at 1615–1595 cm^{-1} and 1590–1575 cm^{-1} show the least variation in frequency for the 2-substituted benzimidazoles, and the bands correspond to the C=N stretch and an aromatic C=C stretch respectively. The aromatic C=C vibrations give rise to two bands in the range 1590–1475, but the frequencies vary considerably depending upon the nature of the substituent in the 2-position [15]. Ligand B exhibits three bands in the range 1575– 1470 cm^{-1}, but the appearance of an additional band can be attributed to C=C stretches in the salicylidenyl moiety of the ligand. Substitution in the 2-position of the benzimidazole is accompanied by the appearance of intense bands at 1480 cm^{-1}, 1440 cm^{-1} and 1420 cm^{-1} [14, 16]. The band at 1265 cm^{-1} in ligand B is attributed to a phenolic C–O stretch. Benzenoid ring breathing modes exhibit absorption bands at 1000 cm^{-1} and at 960 cm^{-1}, while heterocyclic ring breathing modes appear near 880 cm^{-1} and 760 cm^{-1}.

In the complexes, bands are observed around 3420 cm^{-1}, in the range 3340–3200 cm^{-1}, and in the range 3060–2900 cm^{-1}, These bands have not shifted, nor has there been any splitting of the N–H stretching band so that in all the complexes (except II and VII) the free amino group does not coordinate to the selenium or tellurium. The sharp band around 1600 cm^{-1} in the ligands (A–E) is shifted higher in the complexes, appearing in the range 1650–1615 cm^{-1}. All the complexes (except for II and VII) show an average 15 cm^{-1} shift to higher frequency for the C=N stretch. This shift to higher frequency indicates that the nitrogen in the 1-position of the benzimidazole coordinates to selenium or tellurium for complexes (I, II–VI, VIII–X). Further the peaks ascribed to imidazole ring breathing vibrations are also shifted on complexation, substantiating that coordination has taken place through an imidazole nitrogen. For complex II, there is a shift to higher frequency for the C=N stretch, but in addition, the C–O stretch of the salicylidene moiety also shifts to a higher frequency. It appears that N-(2-methylenebenzimidazole)-salicylaldimine is a bidentate chelating ligand coordinating to the selenium through the imidazole nitrogen and the salicylidene oxygen. This type of coordination through nitrogen and the salicylidene oxygen has been previously observed in selenium complexes with sulfonamide Schiff bases [17] and with aromatic imines [18].

Anti-inflammatory Activity Test

The anti-inflammatory activity of 2-substituted benzimidazole complexes of selenium(IV) and tellurium(IV) as well as the activity of the phenylbutazone reference compound are listed in Table II. Most of the selenium and tellurium complexes of 2-substituted benzimidazoles show significant anti-inflammatory activity.

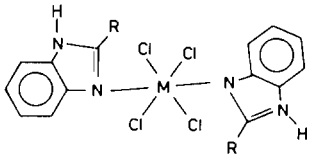
Conclusions

A few 2-substituted benzimidazole complexes of the selenium and tellurium have been prepared. The elemerntal analyses indicate that they are all 1:2 (metal:ligand) complexes. The conductance data indicate that most of the complexes are 1:2 electrolytes. The infrared data indicate that coordination occurs through one of the benzimidazole nitrogens. On the basis of the above information it can be concluded that selenium or tellurium has a coordination

TABLE II. Anti-inflammatory Activity of 2-Substituted Benzimidazole Complexes of Selenium(IV) and Tellurium(IV).

Complex/Compound	Dose level in mg	Initial reading	Reading after 3 hrs	Edema formed	% Inhibition
I	20.00	7.00	9.30	2.30	42.07
II	17.50	6.10	9.23	3.13	21.16
IV	15.00	6.20	7.80	1.60	59.70
VI	15.00	6.00	8.90	2.90	26.95
IX	15.00	6.50	8.90	2.40	39.55
X	15.50	5.90	7.37	1.47	62.97
(Reference)	16.50	5.40	5.92	0.52	86.90
4% Gumaceria (control)	16.20	6.00	9.97	3.97	–

number of six when bonded to substituted benzimidazoles. The following tentative structure is proposed for the selenium and tellurium complexes (I, III–X).



M = Se or Te
R = amino acid homologue

Acknowledgements

W. E. Rudzinski would like to thank the Welch Foundation (Grant AI-809) for partial support of this work. T. M. Aminabhavi would like to thank Professor Patrick E. Cassidy for his constant encouragement in the investigator's scientific work.

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