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Cu(II) and Pd(II) Complexes with Adenine and Histidine Derivatives

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Some derivatives of adenine (I, II, III, IV) and histidine (II, V) were prepared using the Mannich Reaction. Their structure was established from IR and mass spectral data. These derivatives were then used as ligands for the preparation of Cu(II) and Pd(II) complexes, which may have biological action. The structures of the complexes were investigated by IR and E.S.R. spectroscopy. Finally a complex of (II) with Fe(III) was prepared and studied by IR, E.S.R. and Mössbauer spectroscopy.

Introduction

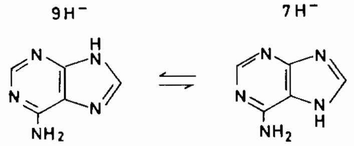
As has already been reported in the literature, certain purine derivatives, *e.g.* 6-mercaptopurine as well as various transition metal complexes with purine derivatives exhibit a remarkable biological activity [1–3].

The subject of this paper is the preparation of adenine derivatives with certain biological substances, for example amino acids, by means of Mannich reaction and further preparation of copper(II) and palladium(II) complexes with these derivatives. According to the literature, Cu(II) complexes exhibit an antirheumatic action, while Pd(II) complexes have in certain cases cytostatic effect. As already known, the main problem in designing biologically active complexes lies in the ease with which the metallic ion carrier can permeate the cell membrane; moreover it must be an essential factor for the cell (for example, cystine or histidine).

Experimental

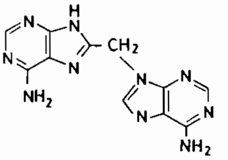
Adenine derivatives have been successfully prepared by the Mannich reaction. The optimum pH value for the reaction is the one obtained by addition of a few drops (2–3) of concd. hydrochloric acid in alcohol.

Adenine exists in solution in the form of two tautomers, a fact indicating the mobility of the imidazole hydrogen [4]:

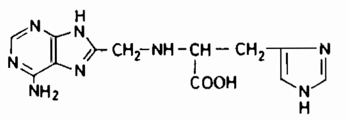


Adenine can be considered both a weak monoacidic base and a weak monobasic acid ($pK_1 = 2.30$; $pK_2 = 8.96$). The acidity is tentatively due to the imidazole hydrogen [4]. Thus adenine can act in the Mannich reaction as an amine, forming an imonium ion and this can further give a product of electrophilic substitution reaction at the aromatic system of adenine.

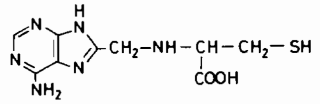
Five derivatives have been prepared, that is:
(I) 8-adenine methylene adenine
(II) 8-adenine methylene histidine
(III) 8-adenine methylene cysteine
(IV) 8-adenine methylene cystine
(V) histidine methylene histidine



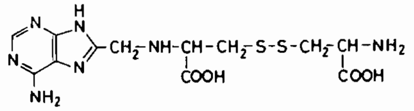
I



II



III



IV

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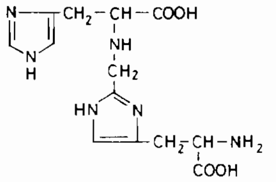
TABLE I. Analytical Values for compounds (I)–(V).

Comp.	C		N		H		S	
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
I	46.8	45.9	49.6	49.0	3.6	3.2	–	–
II	47.7	46.8	37.1	36.8	4.7	4.4	–	–
III	40.3	39.6	31.3	31.0	4.5	4.2	11.9	11.0
IV	37.2	36.5	25.3	25.4	4.4	4.2	16.5	16.1
V	48.4	47.8	26.1	26.0	5.6	5.3	–	–

TABLE II. Analytical Values for Pd(II) Complexes.

Comp.	C		N		H		S		Pd		Colour	M.P.
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found		
Ib	28.7	27.7	30.5	30.1	2.2	2.0	–	–	23.1	22.9	Yellow brown	240(d)
IVb	27.3	26.8	18.6	18.4	3.0	2.9	12.1	11.9	20.1	19.5	Yellow	206(d)
Vb	33.7	32.5	18.1	18.0	3.7	3.5	–	–	23.0	22.5	Yellow	232(d)



V

8-Adenine methylene adenine (I)

0.02 mol (2.66 g) of adenine, 0.01 mol (0.9 g) of paraformaldehyde and a few drops of hydrochloric acid are added to 100 ml of ethanol. The mixture was heated under reflux and stirred for 24 hours. A precipitate is formed, which is then filtered, thoroughly washed with $NaHCO_3$ solution to neutralization and vacuum dried above P_2O_5. M.p. 279° (dec).

8-Adenine methylene histidine (II)

0.01 mol of adenine, 0.01 mol of histidine hydrochloride, 0.01 mol of paraformaldehyde and two drops of concd. hydrochloric acid are added to 50 ml of ethanol. The suspension is heated under stirring to reflux for 32 hours. The precipitate is filtered, thoroughly washed with $NaHCO_3$ solution to neutralization and vacuum dried above P_2O_5. M.p. 304° (dec).

In an analogous way are prepared 8-adenine methylene cysteine (III), and 8-adenine methylene cystine (IV). M.p. 192, 236 (dec) resp.

Histidine methylene histidine (V)

0.02 mol of histidine hydrochloride, 0.01 mol of paraformaldehyde and 3–4 drops of concd. hydrochloric acid are added to 50 ml of ethanol. The mixture is heated under stirring to reflux for 24 hours. A precipitate is formed, which is then filtered, thoroughly washed with a $NaHCO_3$ solution to neutralization and vacuum dried above P_2O_5. M.p. 210 (dec).

In order to take the mass spectra (MS) the derivatives are purified by boiling them in ethanol for 1 hour and then filtering the hot solution. As the MS indicate, there are negligible adenine impurities with no practical meaning. Analytical results for these derivatives are given in Table I.

For the preparation of the Pd(II) complexes with these derivatives the same procedure is used: 0.001 mol of the corresponding compound and 0.001 mol of $PdCl_2$ are added to 50 ml of anhydrous acetone. The mixture is heated during stirring for 1 hour at 40–50 °C, and then a few drops of hydrochloric acid or 0.002 mol of NaCl are added for better solubilizing of $PdCl_2$. The whole is then heated during stirring for one more hour. A yellow precipitate is formed, which is then filtered, successively washed with acetone and ether and vacuum dried.

Table II gives the analytical results for the complex compounds of Pd(II).

For the preparation of Cu(II) complexes, 0.001 mol of anhydrous cupric chloride and 0.001 mol of the corresponding derivative are added to 50 ml of anhydrous ethanol. The mixture is stirred and heated to reflux for 1 hour. A light green precipitate is formed, which is then filtered, successively washed with acetone and ether and vacuum dried.

TABLE III. Analytical Values for Cu(II) Complexes.

Comp.	C		N		H		S		Cu		Colour	M.p.
Ia	36.6	36.0	36.7	36.3	2.6	2.5	–	–	16.6	16.2	Blue-Green	310(d)
IVa	31.8	31.0	21.6	21.3	4.0	3.9	14.1	13.6	7.0	7.2	Blue	225(d)
Va	34.2	34.0	18.4	17.9	4.6	4.4	7.8	7.5	13.9	14.0	Green	201(d)

Table III gives the analytical data for Cu(II) complexes.

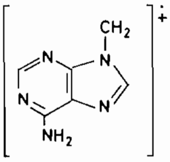
The analytical data are in accord with the accepted structures of the complexes.

The IR spectra were taken with a Perkin-Elmer 700 and a Perkin-Elmer 203 instrument. The E.S.R. spectra were taken with a Varian E-4 instrument and the mass spectra with a Hitachi-Perkin-Elmer instrument.

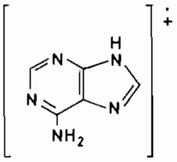
Discussion

For establishing the structures of the compounds prepared by the Mannich reaction, we used both IR and mass spectrometry; the latter along with peaks that are indicative of the molecular weight gives also spectra that characterize the molecular structure of the compounds.

For example in the case of compound (I) the observed MS peak for m/e = 149 corresponds to ion (a), while that for m/e = 135 corresponds to ion (b).



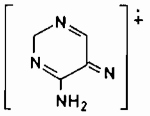
(a)



(b)

The peak for m/e = 108 corresponds to the distance of HCN from (b) [5, 6]. In the IR spectra typical are the ν_{as} $-CH_2-$ vibration at 2700 cm^{-1}, ν_s $-CH_2-$ at 2620 cm^{-1} and δ_s at 1460 cm^{-1} as well as the wagging and twisting vibration at 1350–1150 cm^{-1}, which are not observed in the IR spectrum of adenine.

In the case of compound (II) the same peaks are observed in the mass spectrum as for compound (I); these are typical of ions (a) and (b). Also those for m/e = 27, m/e = 41 and m/e = 120 are respectively due to $HCN^{\cdot+}$, $NH_2CH_2^{\cdot+}$, CO_2 and the ion (c)



In the IR spectrum of compound (II) the association vibration NH_3^+ at 2050 cm^{-1} is not observed, a fact that can be explained by a reaction of the a-amino group of histidine [7]. Typical are the peaks at 1450 cm^{-1} (sh) and 705 cm^{-1}, due to δ_s $-CH_2-$ and ρ $-CH_2-$ vibrations respectively.

In the case of compound (III), along with mass spectrometry which also gives the same characteristic peaks as in the case of compounds (I) and (II), much emphasis was given to IR spectroscopy as well as to the chemical procedures of structure elucidation. Thus the characteristic vibration at 2550 cm^{-1} is due to the free –SH group (Ch. Mandzos Thesis, Athens University, 1964), the existence of which is also revealed by a characteristic chemical reaction [8]. In the IR spectrum of compound (III) the vibration at 2150 cm^{-1} which exists in the corresponding spectrum of the free amino acid and is typical of a a-amino group substitution, fails to appear.

In the case of compound (IV) there are characteristic peaks in the mass spectrum, which correspond to m/e = 149, m/e = 135, m/e = 108 and also m/e = 27, m/e = 29. These have the same meaning as in the previous cases.

Similarly, in the IR spectrum of this compound typical are the vibrations for δ_s $-CH_2-$ and ρ $-CH_2-$ at 1460 cm^{-1} (sh) and 740 cm^{-1} respectively. These fail to appear in the spectra of adenine and cystine; there is instead a vibration at 2160 cm^{-1}, which is due to the free δ NH_2 of cystine (Ch. Mandzos, *op. cit.*). The same is value for compound (V), where the 1450 cm^{-1} and 720 cm^{-1} vibrations, corresponding to δ_s $-CH_2-$ and ρ $-CH_2-$ respectively, are typical for this compound and are not found in the amino acid spectrum. Also, the 2980 cm^{-1} vibration is due to the ν_s $-CH_2-$ and the 2050 cm^{-1} to the δNH_2.

For structure elucidation of metal complexes with these compounds both IR and E.S.R. spectroscopies were used.

The following complexes were prepared:

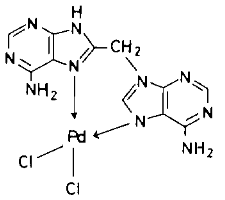
1. (I) with Cu(II) and Pd(II) Ia, Ib
2. (II) with Cu(II) IIa
3. (III) with Cu(II) IIIa
4. (IV) with Cu(II) and Pd(II) IVa, IVb
5. (V) with Cu(II) and Pd(II) Va, Vb

The preparation of a Fe(III) complex with compound (II) was also achieved; this was also confirmed by Mössbauer spectroscopy.

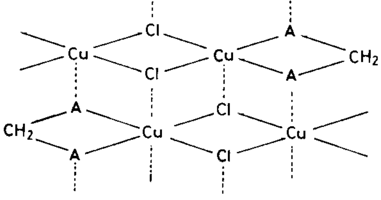
Analytical results for Pd(II) complexes are presented in Table II, while those of Cu(II) complexes in Table III.

For the complex Ib a square planar configuration is valid, as suggested by IR spectra interpretation and the analytical results. Thus the peaks at 340 and 335 cm^{-1} are due to stretching vibrations of Pd–Cl bonds, the chlorine atoms being at the *cis* position [12], while those at 550 and 552 cm^{-1} belong to vibrations of Pd–N bonds, where N is also part of a heterocyclic system [9]. Similarly, the 3040, 1090 and 1280 cm^{-1} vibrations of the free ligand disappear in the complex, a sure sign that complexation has occurred. The E.S.R. spectrum is also typical for square planar complexes. The hyperfine splitting of the spectrum confirms the existing interaction of the unpaired electron density of the metal with the two nitrogen atoms (I = ½).

Based on these data we suggest for the structure of the complex the one presented below:



Concerning the structures of Ia there are some reservations to maintain. In the IR spectrum of the complex there are peaks at 340 and 325 cm^{-1} (sh) corresponding to Cu–N vibrations [15] as well as a triple peak of moderate intensity at 280–270 cm^{-1} which may be attributed to Cu–Cl vibrations [10]. On the other hand the E.S.R. spectrum shows an equilibrium of the g-factor, so that $g_{\parallel} = g_{\perp} = g_y = 2.138$, with a feeble fine structure, typical of an environment of two nitrogen atoms being linked to Cu(II). It is possible that the axial positions of the octahedron are occupied by Cl or H_2O; equally possible is the structure shown below, in which the Cl atoms are forming bridges with Cu atoms, the latter being also linked to ligand A (Comp. (I)). To this fact concurs also the existence of a broad g-factor value.

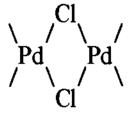


For complexes IIa and IIIa the same is true as in the case of the complex Ia; here an octahedral form is generally accepted, in which Cu(II) is coordinated with two organic ligands, being linked to the nitrogen atoms of the five membered ring of the adenine moiety and to the carboxyl groups of the histidine moiety, with the Cl atoms perpendicular to copper and to the plane formed.

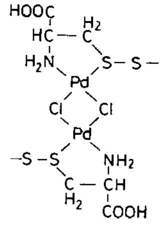
The E.S.R. spectrum, taken at room temperature, is typical of an axially compressed complex with two g-values, indicative of a predominantly $d_{x^2-y^2}$ ground state and an essentially square planar arrangement around the Cu(II) ion (a. M. N. Srivastava, R. C. Teiran, U. C. Srivastava, G. B. Bhargava, A. N. Vishnoi. *J. Inorg. Nucl. Chem., 38,* 1897 (1976); b. H. W. Richardson, J. R. Warion, W. E. Estes, W. E. Hatfield, *Inorg. Chim. Acta, 23,* 205 (1977)).

The broad ESR line excludes the presence of exchange effects between neighbouring Cu(II) ions; besides, the values $g_{\parallel} = 2.413$ and $g_{\perp} = 2.109$ for the complex IIb, and $g_{\parallel} = 2.413$ and $g_{\perp} = 2.109$ for complex IIIb are typical of a dimeric form, analogous to that of complex Ib (G. Marcotrigiano, L. Menabue, G. C. Pellacani, *Inorg. Chim. Acta, 46,* 107 (1980)).

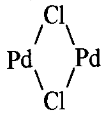
In the case of complex IVb the possible form is one of coordination of Pd with S and the $-NH_2$ of the amino group by means of a



bridge:



The IR data are heavily in favour of this form. The 512 cm^{-1} vibration is due to Pd–N bond, while those at 305, 335 and 350 cm^{-1} are due to stretching vibrations of Pd–S bond and

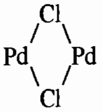


bridge [12]. A shift of the S–S vibration toward lower frequencies and the decrease in the vibration intensity at 1550 cm^{-1} in the case of free ligand compared to that of the corresponding complex, are characteristic of an occurring coordination. The E.S.R. spectrum of the compound is typical of a planar complex and shows a hyperfine structure of 6 peaks, typical of coordination with nitrogen (I = ½).

In the case of complex IVa IR spectra reveal that Cu is linked to two organic ligands and is coordinated with two nitrogen atoms of the free amino groups and two S of the cystine molecules, respectively. A strong vibration at 392 cm^{-1} is due to the Cu–S bond [13, 14]. Peaks at 375 and 280 cm^{-1} are due to stretching and lattice vibrations of the Cu–N bond [15]. The appearance of a peak at 460 cm^{-1} confirms the existence of a Cu–O bond, seemingly due to coordination of H_2O at the axial positions of the octahedral complex.

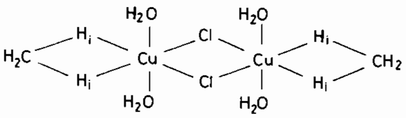
The E.S.R. spectrum of IVa displays a spatial isotropy of the g-factor with a feeble hyperfine structure, which suggests an interaction of the unpaired electron density with the nitrogen atoms of the ligand.

The IR spectrum of complex Vb displays a broad peak at 550 cm^{-1} due to stretching vibrations of Pd–N bonds, as well as peaks at 300 cm^{-1} (sh) and 370 cm^{-1} (sh), due to bond vibrations [12]. The COOH group does not participate in the complexation; thus, the intensity of its vibration and the absorption frequency remain unchanged. Based on these facts we can suppose that the Pd atom is linked to the free amino group of the ligand and to the nitrogen atom of the five membered ring, and the same is repeated through the



bridge. The ESR spectrum of the compound is similar to that of IVb, a fact suggesting the existence of two nitrogen atoms in conjugation with the unpaired electron density of the metal.

In the complex Vb the IR absorption bands at 260 and 240 cm^{-1} are due to vibrations of the Cu–Cl bonds, while those at 320 and 375 cm^{-1} to vibrations of the Cu–N bonds. The peaks at the 890, 850 and 535 cm^{-1} [13] are due to vibrations of H_2O molecules, while that at 425 cm^{-1} to vibration of Cu in coordination with H_2O. These data lead to acceptance of a possible structure for the complex as the one presented below:



This structure is also confirmed by the analytical data.

An attempt was also made for the preparation of a Fe(III) complex with compound II.

The structure was identified by Mössbauer spectroscopy. The spectrum displays a shift of 0.6 mm/sec against Fe, and the quadrupole interaction is 0.80 mm/sec. These parameters indicate the existence of Fe(III) with the possible structure for the compound:

L_3FeCl_2

where L = compound (II).

Acknowledgements

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