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Mode of Coordination and Stability of Cu(II) and Zn(II) Complexes with Adenosine, Deoxyadenosine, Cytidine and Deoxycytidine

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Summary. Stability constants of Cu(II) and Zn(II) complexes with nucleosides have been determined from a computer analysis of potentiometric titration results. Spectral investigations prove that in acidic solution adenosine coordinates to Cu(II) *via* its N1 or N7 atoms, while at $pH > 7$ only N7 is involved. Similar interactions are observed for dAdo complexes. Spectral and potentiometric studies suggest that Zn does not form stable complexes with dAdo. In the case of cytidine and deoxycytidine, the preferred site of coordination is the N3 atom of the nucleoside. Oxygen atoms from the carbonyl groups are not involved in Cu(II) or Zn(II) coordination. The results of the spectral investigation have excluded the ribose and deoxyribose moieties of all studied ligands from participation in the interactions. In general, the mode of coordination of nucleosides and deoxynucleosides with Cu(II) and Zn(II) has been found analogous.

Keywords. Complexes; Mode of coordination; Nucleosides; Stability constants.

Art der Koordination und Stabilität von Cu(II)- und Zn(II)-Komplexen mit Adenosin, Deoxyadenosin, Cytidin und Deoxycytidin

Zusammenfassung. Mittels einer Computeranalyse von Ergebnissen aus potentiometrischen Titrationen wurden Stabilitätskonstanten für Komplexe aus Cu(II) bzw. Zn(II) und Nucleosiden bestimmt. Spektroskopische Untersuchungen zeigen, daß Adenosin in saurer Lösung über N1 oder N7 an Cu(II) koordinieren kann, während bei $pH > 7$ nur N7 reagiert. Analoges wird für die Komplexe mit dAdo beobachtet. Aus spektroskopischen und potentiometrischen Untersuchungen geht hervor, daß Zn mit dAdo keine stabilen Komplexe bildet. Im Fall von Cytidin und Deoxycytidin ist N3 die bevorzugte Koordinationsstelle des Nucleosids. Die Sauerstoffatome der Carbonylgruppen sind an der Bindung an Cu(II) und Zn(II) nicht beteiligt. Die spektroskopischen Ergebnisse schließen eine Beteiligung der Ribose- und Deoxyriboseeinheiten an den Wechselwirkungen aus. Allgemein wurde für Nucleoside und Deoxynucleoside ein analoger Koordinationsmodus gefunden.

Introduction

At present there is no doubt that metal ions react with nucleic acids and their fragments [1, 2]. The investigation of acid-base properties of nucleic acid fragments and their complex formation reactions with metals is considered of great importance

regarding the biological and clinical role of these compounds [3, 4, 5]. One of the essential problems, unexplained so far, is their coordination in solution. Complexes of purine nucleosides show metal bonding *via* their N1 or N7 donor nitrogen atoms, whereas in the case of pyrimidine bases, the bond most frequently involves N3 [6, 7, 8]. *Cis*-[Pt $(NH_3)_2$ Cl_2], widely applied for cancer treatment, most probably forms an intrastrand chelate involving atom N7 of the purine bases of the *DNA* [9, 10, 11]. Determination of the structure of nucleic acid complexes in solution contributes to the understanding of the antitumor effect of platinum compounds, the role of metals in *DNA* replication and transcription, the catalytic activity of *RNA* and the catalytic activity of cation-nucleotide complexes as centers of certain enzymes. Hence, investigations of model systems with nucleotides [1, 12–14] and nucleosides [3, 15, 16] have been performed. Compared to monomers, phosphate groups in polynucleotides are characterized by lower ability to coordinate metals, which is a consequence of steric hindrance imposed by ribose or deoxyribose [17]. Interaction of metal ions can lead to changes in bioligand conformation. The character of these changes, depending on the kind of metal, is related to the made of coordination in complexes. Metals of the main groups evidently interact with donor oxygen atoms of phosphate groups of nucleotides, whereas transition metals also react with donor atoms of the bases [1, 2, 18]. For cations of such metals as zinc or cadmium, the interaction is very weak and becomes relatively stronger for typical transition metals such as nickel, cobalt, or copper [8, 17, 19].

This paper presents results of spectral and potentiometric studies of the complexes of adenosine (Ado), deoxyadenosine (dAdo), cytidine (Cyd) and deoxycytidine (dCyd) with copper(II) and zinc(II) in solution. Particular attention has been paid to the investigation of complex species of deoxy-nucleosides, as no literature exists in this field. The studies were directed at elucidating the coordination modes and stabilities of the transition metal complexes with fragments of nucleic acids and the role of metals in biological processes.

Experimental

In our investigations we have used Ado·HCl, Cyd·HCl and dCyd·HCl obtained from the Institute of Bioorganic Chemistry, Polish Academy of Science, Poznan, as well as Ado and dAdo from Sigma Chemical Company. The results of elemental analyses of all compounds were in agreement with the calculated percentage within 0.5%. Additionally, for Ado and dAdo their melting points were measured giving 235 °C and 187 °C, respectively, which is in agreement with literature data [20]. Copper(II) and zinc(II) were used in the form of their perchlorates whose preparation is described elsewhere [21]. The concentration of Cu(II) and Zn(II) in the studied solution was determined by a complexometric method [21]. Potentiometric measurements were carried out using a Radiometer PHM 26c *pH*-meter equipped with a TTT11 titrator and an ABU 1c autoburette. A previously calibrated GK 2401C electrode was employed in the measurements [22]. The concentrations of Ado, dAdo, Cyd and dCyd in the titrated samples ranged from $1.0 \cdot 10^{-3}$ to $1.5 \cdot 10^{-3}$ *M* at a metal to ligand ratio from 1:4.5 to 1:6.5. All titrations were performed under an argon atmosphere at an ionic strength of $\mu = 0.1$ ($NaClO_4$) at 20 ± 1 °C using CO_2-free NaOH solution (0.0464 *M*) as the titrant. The water used in the all experiments was twice distilled and free of CO_2.

Regarding the possibility of rupture of the glycoside bond in dAdo [23], its stability was tested on the basis of the differences in absorbance of adenine and adenosine. The greatest difference occurs at $pH = 12.0$ at which for dAdo, $\alpha(\max) = 259$ nm [20]. By mixing 7 cm^3 of 4.10^{-3} *M* dAdo solution,

3 cm^3 of $1.0 \cdot 10^{-3}$ *M* HCl, 2 cm^3 of 1 *M* $NaClO_4$ solution, and 8 cm^3 of H_2O, we prepared the same system as that used for the subsquent potentiometric titration. From the solutions prepared this way, 2 cm^3 samples were taken every minute for the period of 10 min. Each of the samples was added to 48 cm^3 of NaOH of such concentration that the *pH* of the final solution was 12. VIS spectra of all samples of the solutions obtained in this way were recorded and the extinctions at α(max) and at $\alpha = 265$ nm (which corresponds to α(max) of adenine) were determined. Then, $R = E\{\alpha(\max)\}/\{E(\alpha = 265)\}$ was calculated. It was found that in systems with stable glycoside bond (obtained by preparing a nucleoside solution of $pH = 12$ without previous acidification [24]) the value of *R* was 1.26. Similar values were found for all solutions indicating that in the studied systems the glycoside bond was not broken.

Computer analysis of the results of potentiometric measurements was performed using the SCOGS [25] and SUPERQUAD [26] computer programs. For each metal/ligand system, at least 15 titration curves were evaluated. Analysis of statistical parameters was used to verify the models [27]. The distribution of individual complex species was calculated using the HALTAFALL program [28]. In the equilibrium studies, we disregarded the self-stacking effect found in solutions of purine and pyrimidine nucleosides [29]. Samples for ^{1}H NMR, ^{13}C NMR, and IR studies were prepared by dissolving Ado·HCl, dAdo·HCl, Cyd·HCl, dCyd·HCl, $Cu(ClO_4)_2$ and $Zn(ClO_4)_2$ in D_2O obtaining the desired *pH* value by adding DCl or NaOH. *pH*-measurements were corrected according to the formula $pD = pH + 0.40$ [30]. The ligand concentration in samples for NMR studies was 0.05 *M* at a metal to ligand ratio of 1:100 for copper and 1:20 for zinc. ^{1}H NMR spectra were recorded on a 587A TESLA spectrometer using dioxane as internal standard, the positions of the NMR signals were converted relative to TMS. IR spectra were recorded on an IFS 113 v BRUKER spectrometer in a KRS-5 cuvette. The ligand concentration in samples for IR studies was 0.05 *M* at a metal to ligand ratio of 1:2. In the visual range, the absorption spectra of nucleoside complexes with Cu(II) were recorded on an UV 160 SHIMADZU spectrometer for nucleoside concentrations from 0.01 to 0.05 *M* and metal to ligand ratios from 1:3.5 to 1:5.

Results and Discussion

Potentiometric studies

The protonation constants of the studied ligands are presented in Table 1. The results are in agreement with those reported earlier and obtained under similar conditions and with a similar procedure of determinations [16, 31]. The ^{1}H NMR spectrum of cytidine indicates that the preferred protonation site is N3 [6]. In the case of purine bases, N1 reveals much greater basicity than N7 [1, 2].

The results of the computer analysis of potentiometric titrations of metal/nucleoside systems are given in Table 1. The calculations were performed for a relatively narrow *pH* range because precipitation occurs outside this range. Only for the system Cu/Ado no precipitations was observed in a wide *pH* range. The titration curves obtained for Zn/dAdo coincide with the curve obtained for the ligand alone, which proves that the formation of Zn-dAdo complexes under our experimental conditions can be excluded. In all cases, the stability constants of copper complexes are higher than those of zinc complexes which confirms a greater affinity of the former metal to donor nitrogen atoms [32]. Computer analysis did not indicate the presence of *ML* (OH) species as an intermediate between *ML* and $ML(OH)_2$. Presumably, this form occurs in such a narrow *pH* range that its presence cannot be experimentally detected. According to the distribution curve for the CuAdo compound, complexation begins at $pH = 3$, and about 42% of metal is bound in the *ML*

Table 1. Overall stability constants ($\log\beta$) of nucleoside complexes with H^+, Cu(II) and Zn(II)

Ligand	Range of *pH*	Species M_p	L_q	H_r	Equilibria	$\log\beta$
Ado	3.4–11.1	0	1	1	$H^+ + L = HL^+$	3.92(1)
	3.5–10.2	1	1	0	$Cu^{2+} + L = CuL^{2+}$	2.88(15)
		1	1	−2	$Cu^{2+} + L + 2H_2O = CuL(OH)_2 + 2H^+$	−11.41(8)
		1	1	−3	$Cu^{2+}L + 3H_2O = CuL(OH)_3^- + 3H^+$	−20.92(14)
	3.5–8.3	1	1	0	$Zn^{2+} + L = ZnL^{2+}$	2.51(9)
		1	1	−2	$Zn^{2+} + L + 2H_2O = ZnL(OH)_2 + 2H^+$	−14.00(6)
dAdo	3.3–11.1	0	1	1	$H^2 + L = HL^+$	4.13(2)
	3.3–7.3	1	1	−2	$Cu^{2+} + L + 2H_2O = CuL(OH)_2 + 2H^+$	−11.73(12)
Cyd	3.6–11.1	0	1	1	$H^+ + L = HL^+$	4.49(1)
	3.6–7.4	1	1	0	$Cu^{2+} + L = CuL^{2+}$	2.25(9)
		1	1	−2	$Cu^{2+} + L + 2H_2O = CuL(OH)_2 + 2H^+$	−12.09(3)
	3.7–8.1	1	1	−2	$Zn^{2+} + L + 2H_2O = ZnL(OH)_2 + 2H^+$	−14.54(7)
dCyd	3.7–11.1	0	1	1	$H^+ + L = HL^+$	4.61(1)
	3.7–7.2	1	1	0	$Cu^{2+} + L = CuL^{2+}$	2.25(7)
		1	1	−2	$Cu^{2+} + L + 2H_2O = CuL(OH)_2 + 2H^+$	−11.86(2)
	3.7–8.2	1	1	−2	$Zn^{2+} + L + 2H_2O = ZnL(OH)_2 + 2H^+$	−14.74(14)

complex in the *pH* range from 5 to 7 (Fig. 1). The formation of hydroxocomplexes begins at a *pH* of about 6.5, while at *pH* values over 8.5 the total amount of metal is bound in the complex. In the system Zn/adenosine, the maximum amount of metal bound in the ML comples reaches 30% (Fig. 1). The $ML(OH)_2$ complex, which is the only stable form in the Cu – dAdo system, is formed at alkaline *pH* values.

Complexation of Cyd and dCyd is observed starting from $pH = 3.5$ for systems with Cu(II) and from $pH = 7.5$ for systems with Zn(II) (Fig. 2). ML type complexes bind at most 30% or 18% of the total amount of copper for Cyd and dCyd, respectively. It should be mentioned that only hydroxocomplexes are formed in the system with Zn(II).

Some authors suggest that in the systems of adenosine with Cu or Zn, complexes with $\log\beta$ value below 1 are formed [14, 33, 34]. Treating Ado as a ligand which can be protonated only at N1 and N7 ($\log K_{N1} = 3.6$ and $\log K_{N7} = 0.2$, [14]), one can easily calculate that under the conditions of our experiment only about 5% of Cu and less than 1% of Zn would undergo coordination. It is rather obvious that in such a systems spectral change in the ligand due to metallation would be experimentally difficult to observe. However, such changes have been found in the studied Cu/Ado system. The assumption that Ado undergoes protonation only at N1 does not effect the results of the calculations.

Spectral investigation of the systems of Ado and dAdo with Cu(II) and Zn(II)

The change in chemical shifts observed in the NMR spectra of the studied systems as well as changes in UV-VIS and IR band positions allowed us to draw conclusions

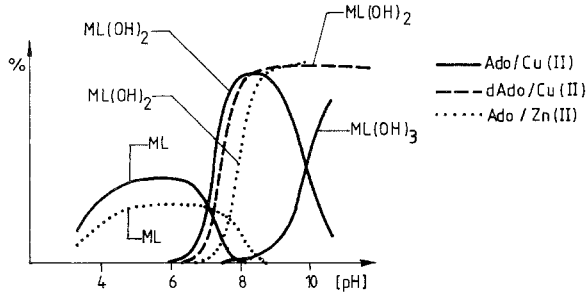


Fig. 1. Distribution diagram for the systems Ado/Cu(II), dAdo/Cu(II), and Ado/ Zn(II); percentages of the species refer to total metal; $C_{\text{Ado, dAdo}} = 0.0015\,M$; $C_{\text{Cu(II), Zn(II)}} = 0.00024\,M$

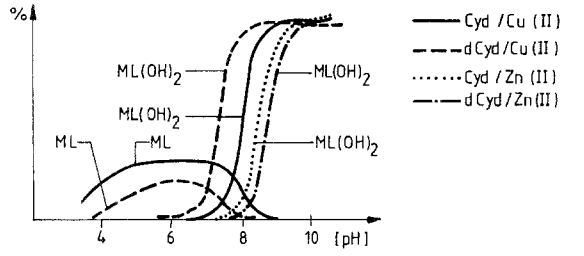
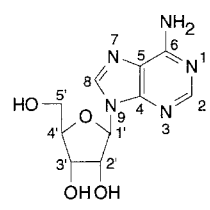
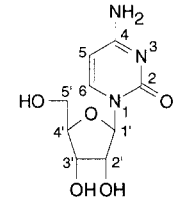


Fig. 2. Distribution diagram for the systems Cyd/Cu(II), dCyd/Cu(II), Cyd/Zn(II), and dCyd/Zn(II); percentages of the species refer to total metal; $C_{\text{Cyd, dCyd}} = 0.0015\,M$; $C_{\text{Cu(II), Zn(II)}} = 0.00024\,M$

concerning the mode of coordination. The observed ^1H and ^{13}C NMR signals were assigned to particular atoms on the basis of literature data [35–38]. Numbered formulae for the ribonucleosides are given below.



Ado



Cyd

At a *pH* of about 5, *i.e.* in the range where *ML* type complexes dominate, the NMR spectra of the Cu/Ado system reveal characteristic shifts of the signals ascribed to H2 or H8 (Table 2), which clearly indicates the involvement of N1 and N7 in the coordination. This conclusion is confirmed by ^{13}C NMR studies (Table 3). Even though NMR spectroscopy has severe limitations in the case of the investigation of paramagnatic ions (discussed for example in [39–41)]), the analysis of NMR results in combination with the results of other methods can provide essential information on the mode of coordination.

Although the N1 atom in adenosine is characterized by much greater basicity compared to N7, the latter is the preferred site of metallation [14, 16].

Table 2. ^{1}H NMR (ppm) signals of Ado, dAdo and their complexes with Cu(II)

	Ado	Ado/Cu		dAdo		dAdo/Cu		
pH	5.3–11.0	5.3	8.3	11.0	5.5–11.0	6.0	9.5	11.0
H(2)	8.11	8.95	8.10	8.14	8.13	8.13	8.12	8.12
H(8)	8.26	8.95	9.03	8.95	8.29	8.32	8.99	8.99

Table 3. ^{13}C NMR signals (ppm) of Ado, dAdo and their complexes with Cu(II) and Zn(II)

pH	C(2)	C(5)	C(6)	C(8)	C'(5)	C'(4)	C'(2)	C'(3)	C'(1)
Ado									
5.3–11.0	152.54	119.38	156.12	140.17	61.46	85.67	70.51	73.65	88.23
	Ado + Cu(II)								
5.3	152.16	116.16	155.57	144.56	61.46	85.67	70.51	73.65	88.23
8.3	152.54	116.18	156.14	140.56	61.46	85.67	70.51	73.65	88.23
11.0	152.54	116.15	156.04	140.56	61.46	85.67	70.51	73.65	88.23
	Ado + Zn(II)								
7.0	151.86	118.92	155.82	139.95	61.46	85.65	70.52	73.64	88.23
dAdo									
5.5–11.0	152.75	119.32	156.13	140.19	64.07	116.92	74.01	75.45	88.03
	dAdo + Cu(II)								
9.5	152.77	116.22	156.11	140.59	64.08	116.90	74.01	75.46	88.03

In the case of dAdo, the ^{1}H NMR signals of Cu/dAdo are not different from the signals of the free ligand in the *pH* range below 7. This is consistent with the results of the potentiometric studies and the ^{13}C NMR investigations (Table 3).
Conclusions concerning the Cu/Ado and Cu/dAdo systems are also supported by the measurements of absorption spectra (VIS). In the Cu/dAdo system at *pH* values to 4.0, 5.0 and 6.0, the positions of α(max) are 823, 805, and 812 nm, respectively, which corresponds to hydrated Cu(II). Above *pH* 7, the d–d band is shifted to about 750 nm. On the other hand, in the case of the Cu/Ado system, α(max) is shifted to about 760 nm already at a *pH* of about 5.

Analysis of space filling models excludes the possibility of formation of a chelate compound with two nitrogen atoms involved. The results suggests the presence of the Cu/nucleoside systems with two monofunctional forms coordinated through N1 or N7. The absorption energy value also distinctly indicates the monofunctional coordination (α(max) of about 750 nm) [42].

According to the results of the potentiometric studies, $ML(OH)_2$ complexes are the predominant forms for both ligands above $pH = 7$. As a consequence of metallation, the ^{1}H NMR signals due to H8 (Table 2) are significantly shifted, which together with the results of absorption measurements (VIS) clearly indicates a monofunctional coordination involving only N7. Most probably, the presence of two

OH^- groups in the dominant Cu*L* $(OH)_2$ complex as well as spatial restrictions related to the presence of the $-NH_2$ group near N1 are responsible for the fact that this nitrogen atom is not involved in the coordination. This suggestion has been confirmed by ^{13}C NMR studies which reveal no changes in the signals attributed to the C2 atom with increasing *pH* (Table 3), which is a neighbor of N1, and a significant decrease in changes of signals from C6. The changes observed for the systems of Ado and dAdo are similar which suggests the same type of copper coordination by the two ligands. This suggestion is also supported by close values of stability constants of CuAdo $(OH)_2$ and CudAdo $(OH)_2$ complexes. In the whole studied range of *pH* values, no change of chemical shifts at ribose or deoxyribose atoms were found (Table 3, signals C'1 to C'5).

A low thermodynamic stability of the Zn(II) complexes with Ado is responsible for the limited possibility of observation of spectral changes, particularly because of precipitation. The spectra were recorded at an Ado:Zn ratio of 20:1 and the differencies of ^{13}C NMR frequencies were often only of an order of 0.1 ppm. However, a detailed analysis of the spectra allowed us to conclude that the character of these changes is the same as that observed for the supernatant solutions (Table 3) in systems of relatively higher concentration of metal for which the changes in the shifts are much more pronounced. The differences in the signal positions of the ligand and its complex with metal suggest participation of atoms N1 and N7 (in the range where the ZnAdo complex dominates) in coordination with formation of a mixture of two monofunctional complexes. The above results are in agreement with those of the studies of adenosine in *DMSO* solution [43].

An attempt was made to obtain additional information from ^1H NMR studies. However, changes in chemical shifts were too insignificant to enable us to draw reliable conclusions for the Zn(II)/Ado system.

No changes in ^{13}C shifts were detected in the Zn/dAdo system which confirms the results of potentiometric investigations implying that Zn complexes with dAdo are not formed, at least not in a detectable concentration.

Spectral investigation of the systems of Cyd and dCyd with Cu(II) and Zn(II)

Unfortunately, ^1H NMR spectroscopy of the ligands does not provide information on their coordination because of the specific location of hydrogen atoms in the Cyd (dCyd) molecule. In the range where CuCyd complex dominates, the ^{13}C NMR spectrum reveals significant shifts of the signals due to C2 and C4 (Table 4).

The shift values suggest a coordination via the N3 atom of the nucleoside and possibly also via the O_2 atom. However, the participation of the latter can be excluded by the IR results. In relation to the metal-free solution, the 1652 cm^{-1} stretching band from the C=O group is unchanged in the Cu/Cyd system. On the other hand, characteristic changes in the N3–C2 (1617 cm^{-1}) and the N3–C4 (1524 cm^{-1}) band positions are observed. Positions of particular IR bands have been attributed to a Cyd molecule on the basis of literature data [44–46]. The changes in ^{13}C NMR (Table 4) and IR (Fig. 3) signals observed for Cu/dCyd are analogous to those obtained for the Cyd system, which also suggests coordination through N3 and excludes involvement of the O2 atom.

Table 4. ^{13}C NMR signals (ppm) of Cyd, dCyd and their complexes with Cu(II) and Zn(II)

pH	C(2)	C(4)	C(5)	C(6)	C'(1)	C'(2)	C'(3)	C'(4)	C'(5)
Cyd									
6.0–9.0	157.41	166.14	96.14	141.65	90.38	73.81	69.26	83.73	60.76
	Cyd + Cu(II)								
6.4	168.40	169.37	96.14	141.59	90.34	73.82	69.31	83.79	60.76
7.6	166.41	169.37	96.14	141.70	90.34	73.86	69.32	83.78	60.81
	Cyd + Zn(II)								
7.0	156.85	165.33	96.21	141.84	90.36	73.82	69.28	83.75	60.77
8.0	156.83	165.30	96.24	141.80	90.37	73.82	69.27	83.73	60.77
dCyd									
6.2–10.0	157.49	166.42	95.98	141.32	90.83	103.82	72.57	80.51	60.02
	dCyd + Cu(II)								
6.5	167.71	170.01	95.89	141.37	90.81	103.84	72.52	80.54	60.10
7.4	167.04	169.78	95.93	141.35	90.84	103.86	72.59	80.56	60.10
	dCyd + Zn(II)								
7.0	156.42	164.10	95.66	141.60	90.82	103.82	72.55	80.50	60.04
8.0	156.72	165.47	95.79	140.98	90.83	103.83	72.55	80.51	60.03

The above conclusions are supported by the results of absorption spectra measurements (VIS). A similar value of α(max) in the systems Cu/Ado and Cu/Cyd ($\alpha = 750$ nm) indicates the monodentate coordination with only one nitrogen atom involved. As already noted in the case of Zn/Ado system, the possibilities of investigating spectral changes in the spectra of Zn/Cyd and Zn/dCyd systems are very limited. The range of concentration in which ZnCyd $(OH)_2$ and ZndCyd $(OH)_2$ occur is very narrow. This is in agreement with the earlier observations showing that the Zn-Cyd interactions are weak [47]. Fortunately, we have managed to record clear ^{13}C NMR spectra of the systems at a $M:L$ ratio of 1:7. The changes in the signal

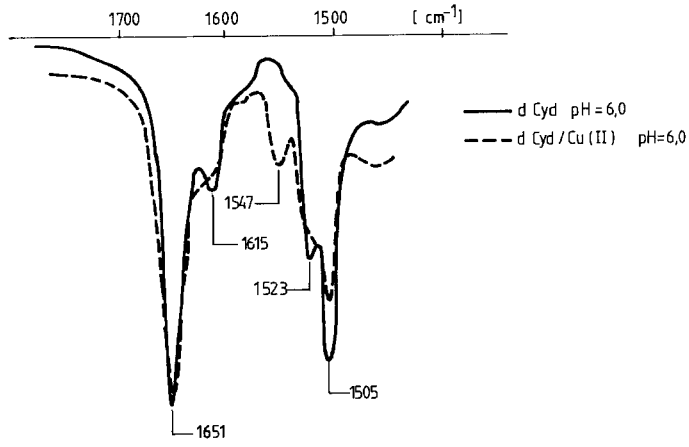


Fig. 3. IR spectra of dCyd and dCyd/Cu(II) systems

positions indicate the coordination via the N3 atom. Similarly, the change in the signals due to formation of Zn(II) complexes with dCyd also suggests the involvement of N3 in the coordination (Table 4). Unfortunately, it was impossible to obtain a good quality IR spectra of either the Zn/Cyd or the Zn/dCyd system, so the role of the O2 atom in the coordination could not be unnambiguously explained. Similar values of stability constants for ZnAdo $(OH)_2$ and ZnCyd $(OH)_2$ complexes (as well as for ZndAdo $(OH)_2$ and ZndCyd $(OH)_2$, cf. Table 1) suggest an analogous mode of coordination excluding the participation of the donor oxygen atom in Cyd and dCyd complexes. However, it should be remembered that a comparison of stability constants cannot lead to unequivocal conclusions, as it is difficult to determine exactly the influence of the combined spherical and coordination effects of the amine and carboxyl groups on the thermodynamic stability of nucleosides complexes with metals. Moreover, in the case of the compounds of the studied type, formation of outer-sphere complexes cannot be excluded [48], although there is no direct experimental evidence in support of semichelation in solution. The above discussed results clearly indicate a similar mode of metal coordination by the two types of nucleosides (oxy- and deoxynucleosides). However, explanation of the observed differences in the ability to form complexes between oxy –and deoxy-compounds at low *pH* values requires additional studies.

Acknowledgements

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