Interaction of Diphenyltin(IV) Dichloride with Some Selected Bioligands[1)]

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The interaction of diphenyltin(IV) with selected bioligands having a variety of model functional groups were investigated using the potentiometric technique. The hydrolysis constants of diphenyltin(IV) cation and the stepwise formation constants of the complexes formed in solution were calculated using the non linear least-squares program MINIQUAD-75. The participation of different ligand functional groups in binding to organotin is discussed. The concentration distribution of the various complex species was evaluated as a function of pH.

Key word equilibrium study; diphenyltin(IV) dichloride; amino acid; peptide; DNA constituent; dicarboxylic acid

Among organotins, dialkyl derivatives exhibit greater antitumour activity than the corresponding mono-, tri-, and tetraalkyl derivatives.[2)] The activity of the tri- or tetra-alkyl derivatives may be explained by dealkylation *in vivo* which yields the corresponding active dialkyl derivatives. If one ranks specific alkyl organotins in terms of antitumour activity of the parent compounds, the diethyl and diphenyl derivatives have the highest activity *in vivo* provided that one takes no cognizance of their toxicity.[3)]

Accepting the hypothesis that R_2Sn^{2+} are the usual active species for the antitumour action of organotins,[4)] a good antitumour agent should be easily dissociable following administration to animals. This requires weak bonds between tin and the donor atom of the coordinated organic compounds which are readily hydrolysable. If the compound is hydrolytically unstable, the R_2Sn moiety will be released too soon, and if it is too stable, it may be released too slowly and consequently lower activity will be observed. Such a mechanism also adds weight to the proposition for the $R_2SnX_2L_2$ adducts, where it was shown that relatively long Sn–N bonds were a requirement for activity, and that predissociation of the ligand L_2 may be an important feature of the mode of action of this particular class of compounds. Therefore, there is a relationship between the stability of the organotin compounds and their antitumour activity.

In continuation of our studies on organotin(IV) complexes,[5—11)] the present paper aims to study the diphenyltin(IV) complex formation equilibria with some selected bioligands, with the hope that such types of coordinating ligands might possess favorable properties, possibly as carriers in body fluids.

Experimental

Materials and Reagents Diphenyltin(IV) dichloride (DPT) was obtained from Merck Chem. Co. The ligands used were glycine, proline, methionine, serine, histidine, histamine, ornithine, lysine, aspartic acid, glutamic acid, mercaptoethylamine, mercaptopropionic acid, penicillamine, glutathione, cyclobutane dicarboxylic acid (CBDCA), oxalic acid, malonic acid, succinic acid, adipic acid, fumaric acid, glycylglycine, glycylalanine, glycylleucine, glycylmethionine, glutamine and aspargine. These were supplied by Fluka Chem. Co. The DPT was converted to the perchlorate form by suspension in dioxane, addition of 1.98 eq of $AgClO_4$ and stirring over night. The precipitate (AgCl) was filtered and the resulting final solution was diluted to a 75% dioxane–water solution. The concentration of DPT was checked potentiometrically. Solutions of histidine, ornithine, lysine were prepared in the protonated form by dissolving in equimolar HNO_3 solution. Carbonate free sodium hydroxide stock solutions were prepared by diluting the contents of British Druy House (BDH) concentrated volumetric solutions vials. These solutions were systematically checked by titration against potassium hydrogen phthalate.

Procedure and Measuring Techniques Potentiometric titrations were performed using a Metrohm 686 titroprocessor equipped with a 665 dosimat (Switzerland-Herisaue). The titroprocessor and electrode were calibrated with standard buffer solutions, prepared according to National Bureau of Standard (NBS) specifications.[12)] The titrations were carried out in a purified nitrogen atmosphere using a titration vessel as described previously.[13)] The temperature was maintained constant by a colora ultrathermostat. pK_w in 75% dioxane–water solution was determined as described previously.[14)] For this purpose, various amounts of standard NaOH solution (in 75% dioxane) were added to a solution containing 0.10 M $NaNO_3$. The value of $-\log[H]$ was calculated from the amount of base added. The product of [OH] and [H] was taken and the mean value obtained for the log concentration product was $\log K_w = 16.21$. This value is in good agreement with that previously determined in 70% dioxane as $\log K_w = 16.0$.[14)]

The protonation constants of the ligands were determined by titrating 40 ml of ligand solution (2.5×10^{-3} M). The hydrolysis constants of diphenyltin(IV) diperchlorate were determined by titrating 40 ml of organotin(IV) solution (2.5×10^{-3} M). The formation constants of organotin(IV) complexes were determined by titrating 40 ml of solution containing the ligand (2.5×10^{-3} M) and organotin(IV) with concentrations of 1.25×10^{-3}, 6.25×10^{-4} and 3.125×10^{-4} M. The ionic strength was adjusted to 0.1 M by $NaNO_3$.

The equilibrium constants were evaluated from titration data, defined by Eqs. 1 and 2.

$$l(\mathrm{M})+p(\mathrm{L})+q(\mathrm{H}) \rightleftharpoons (\mathrm{M})_l(\mathrm{L})_p(\mathrm{H})_q \quad (1)$$

$$\beta_{lpq}=\frac{[(\mathrm{M})_l(\mathrm{L})_p(\mathrm{H})_q]}{[\mathrm{M}]^l[\mathrm{L}]^p[\mathrm{H}]^q} \quad (2)$$

Where M, L and H represent organotin(IV), ligand and proton respectively. The calculations were performed using the computer program[15)] MINIQUAD-75 by means of an IBM 486 computer. The stoichiometries and stability constants of the complexes formed were determined by examining various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere.[15)] The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constant of the ligand and formation constants of the corresponding complexes. Table 1 lists formation constants together with standard deviations and the sum of square of residuals as was obtained from the MINIQUAD-75 program. The Concentration distribution diagrams were obtained using the SPECIES program.[16)]

Results and Discussion

The acid dissociation constants of the ligands have been reported[17)] and their acid dissociation constants determined under the same experimental conditions used for determining the stability constants of organotin(IV) complexes. It is found that pK_a values of the ligands in 75% dioxane–water solutions are higher than those reported in water. This may

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Table 1. Formation Constants of Diphenyltin(IV) Complexes

System	l	p	q[a]	log β[b]	S[c]	System	l	p	q[a]	log β[b]	S[c]
DPT	1	0	−1	−0.15 (0.04)	1.0E−7	Glutathione	0	1	1	10.89 (0.02)	4.8E−7
	1	0	−2	−4.12 (0.05)			0	1	2	20.13 (0.02)	
	2	0	−1	0.17 (0.08)			0	1	3	25.27 (0.04)	
Glycine	0	1	1	9.82 (0.01)	3.2E−8		1	1	0	18.73 (0.02)	4.8E−9
	0	1	2	13.44 (0.02)			1	2	0	28.89 (0.03)	
	1	1	0	13.76 (0.08)	4.0E−9		1	1	1	25.29 (0.05)	
	1	2	0	22.14 (0.08)		CBDCA	0	1	1	7.78 (0.00)	2.7E−9
Valine	0	1	1	9.68 (0.01)	3.7E−8		0	1	2	12.88 (0.01)	
	0	1	2	13.44 (0.02)			1	1	0	12.31 (0.04)	7.7E−9
	1	1	0	13.55 (0.07)	6.0E−9		1	2	0	17.26 (0.07)	
	1	2	0	21.57 (0.09)			1	1	1	16.69 (0.05)	
Methionine	0	1	1	9.62 (0.01)	3.4E−8	Oxalic acid	0	1	1	5.39 (0.04)	6.7E−8
	0	1	2	13.49 (0.02)			0	1	2	7.98 (0.06)	
	1	1	0	13.60 (0.04)	1.8E−9		1	1	0	12.31 (0.07)	3.3E−8
	1	2	0	21.13 (0.06)			1	2	0	16.11 (0.09)	
Serine	0	1	1	9.71 (0.01)	5.3E-−8	Malonic acid	0	1	1	7.51 (0.00)	6.3E−9
	0	1	2	13.48 (0.03)			0	1	2	11.76 (0.01)	
	1	1	0	14.09 (0.06)	4.8E−9		1	1	0	12.01 (0.03)	3.1E−9
	1	2	0	22.10 (0.07)			1	12	0	16.67 (0.05)	
	1	1	−1	9.02 (0.07)			1	1	1	15.45 (0.04)	
Histidine	0	1	1	9.66 (0.01)	2.1E−7	Succinic acid	0	1	1	7.18 (0.00)	5.0E−9
	0	1	2	15.29 (0.02)			0	1	2	13.34 (0.01)	
	1	1	0	14.30 (0.05)	3.0E−10		1	1	0	12.27 (0.01)	2.7E−10
	1	2	0	21.18 (0.04)			1	2	0	15.94 (0.01)	
	1	1	1	18.97 (0.04)			1	1	1	17.46 (0.01)	
Histamine	0	1	1	9.34 (0.00)	1.5E−8	Adipic acid	0	1	1	7.06 (0.00)	2.1E−9
	0	1	2	14.59 (0.01)			0	1	2	13.94 (0.01)	
	1	1	0	14.85 (0.05)	1.1E−8		1	1	0	12.39 (0.03)	1.7E−9
	1	2	0	20.46 (0.09)			1	2	0	15.94 (0.04)	
Ornithine	0	1	1	10.68 (0.00)	7.3E−8		1	1	1	18.16 (0.03)	
	0	1	2	19.47 (0.01)		Fumaric acid	0	1	1	6.01 (0.00)	5.6E−9
	1	1	0	17.69 (0.06)	1.7E−9		0	1	2	11.26 (0.01)	
	1	2	0	22.63 (0.06)			1	1	0	10.93 (0.02)	5.4E−9
	1	1	1	23.38 (0.06)			1	2	0	14.41 (0.05)	
Lysine	0	1	1	10.42 (0.00)	2.5E−9		1	1	1	15.11 (0.04)	
	0	1	2	19.60 (0.01)		Glycylglycine	0	1	1	7.81 (0.01)	3.3E−9
	1	1	0	17.99 (0.06)	1.3E−9		1	1	0	12.95 (0.01)	5.9E−9
	1	2	0	22.21 (0.04)			1	2	0	17.12 (0.06)	
	1	1	1	23.67 (0.06)			1	1	1	17.94 (0.01)	
Aspartic acid	0	1	1	10.26 (0.00)	3.8E−8	Glycylalanine	0	1	1	8.04 (0.00)	2.2E−9
	0	1	2	15.43 (0.01)			1	1	0	12.97 (0.06)	1.2E−8
	1	1	0	13.60 (0.06)	1.7E−8		1	2	0	17.92 (0.09)	
	1	2	0	21.68 (0.05)			1	1	1	18.26 (0.04)	
Glutamic acid	0	1	1	10.14 (0.01)	5.7E−8	Glycylleucine	0	1	1	8.29 (0.01)	1.4−8
	0	1	2	15.85 (0.01)			1	1	0	13.17 (0.06)	1.3E−8
	1	1	0	13.51 (0.05)	9.3E−9		1	1	1	18.76 (0.03)	
	1	2	0	21.06 (0.03)		Glycylmethionine	0	1	1	7.97 (0.01)	1.3E−8
Mercaptoethylamine	0	1	1	12.46 (0.01)	2.1E−7		1	1	0	12.77 (0.10)	2.1E−7
	0	1	2	20.82 (0.01)			1	1	1	16.71 (0.10)	
	1	1	0	18.91 (0.06)	3.0E−9	Glutamine	0	1	1	9.46 (0.01)	4.3E−8
	1	2	0	25.84 (0.06)			1	1	0	13.54 (0.04)	3.8E−8
Mercaptopropionic acid	0	1	1	12.37 (0.01)	7.8E−8		1	1	1	17.24 (0.03)	
	0	1	2	19.07 (0.01)		Aspargine	0	1	1	9.22 (0.01)	3.1E−8
	1	1	0	20.69 (0.09)	2.9E−8		1	1	0	13.24 (0.04)	3.2E−8
	1	2	0	29.35(0.09)			1	1	1	16.87 (0.03)	
Penicillamine	0	1	1	12.41 (0.01)	1.2E−7						
	0	1	2	20.73 (0.02)							
	1	1	0	19.85 (0.06)	4.8E−8						
	1	2	0	27.84 (0.09)							
	1	1	1	24.37 (0.03)							

a) l, p and q are the stoichiometric coefficient corresponding to DPT, (amino acids, diacids and peptides) and H^+ respectively. *b*) Standard deviations are given in parentheses. *c*) Sum of square of residuals.

be due to the increased basicity of the ligand donor groups.

The acid–base chemistry of diphenyltin(IV) has been characterized by fitting its potentiometry to various acid–base models. The fitted model was found to be consistent with the formation of $Ph_2Sn(OH)^+$, $Ph_2Sn(OH)_2$ and $(Ph_2Sn)_2OH^{3+}$ species. Polymeric species such as $M_2(OH)$, $M_2(OH)_4$, $M_3(OH)_2$, $M_4(OH)_5$ and $M_4(OH)_6$ reported for dimethyltin(IV)[18—21] were rejected. This may be due to the very poor solubility of hydrolysed diphenyltin(IV) species. It should be mentioned that the first and second deprotonations of [Ph_2Sn-

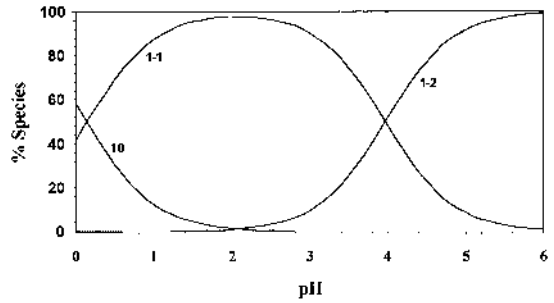

Fig. 1. Concentration Distribution of Various Species as a Function of pH in the DPT–OH System (Concentration of 2.5 mmol/l)

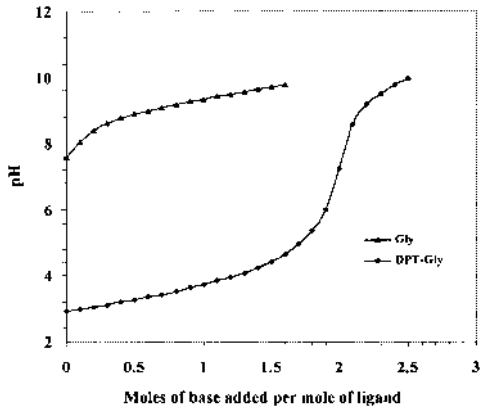

Fig. 2. Potentiometric Titration Curves of DPT–Glycine System

$(H_2O)_2]^{2+}$, are more acidic than those for $[(CH_3)_2Sn(H_2O)_2]^{2+}$. This can be attributed to the electroaccepting property of the phenyl groups. The concentration of the monohydroxo species increases with an increase of pH, attaining a maximum of 97.6% at *ca*. pH 2.0. A further increase in pH is accompanied by a decrease in the monohydroxo species and an increase in dihydroxo species.

Potentiometric titration curves of the diphenyltin(IV)–glycine system, taken as being representative, are shown in Fig. 2. In the organotin complex curve, there is a significant lowering from that of free glycine indicating formation of organotin complexes by release of protons. Different equilibrium models have been attempted to fit the experimental potentiometric data for diphenyltin complexes. The model that best fit the experimental potentiometric data was found to depend on the structural configuration of the ligand.

Combined results of all ligands investigated shows the formation of 1 : 1 and 1 : 2 complexes. There was no evidence for the formation of polymeric species. Glycine, valine and methionine form the species of stoichiometric coefficients 110 and 120. The formation constant values of the 110 complexes are higher than those of dimethyltin(IV) species.[8] This is explained in terms of the electron-accepting property of the phenyl group. The amino acid methionine has an extra binding centre on the thioether group and the thioether group has been reported to participate in transition metal ion complex formation.[22] However, the formation constant of the methionine complex is in close agreement to those of glycine and valine, if the difference in the acid dissociation constant of the amino acids is considered. This indicates that methionine chelates diphenyltin(IV) by the amino and carboxylic groups and not by the thioether group. The concentration distribution for glycine complex, taken as a representative, is given in Fig. 3. The deprotonated species 110 predominates at pH *ca*. 3.4 attaining a maximum of 80.4%. The hydroxo complex $[DPT–OH]^+$ plays a major role at pH=1.2 with a formation degree of 83.2%. The deprotonated species 120 reaches the maximum concentration of 70.0% at pH *ca*. 7.4.

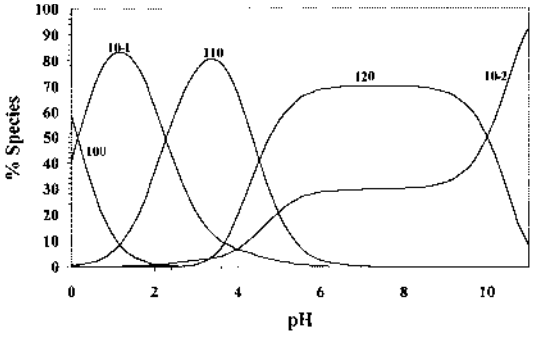

Fig. 3. Concentration Distribution of Various Species as a Function of pH in the DPT–Glycine System (at Concentrations of 1.25 and 2.5 mmol/l, Respectively)

Serine was found to form complexes 110, 120, and 11−1. The formation of species 11−1 reveals that the β-alcoholato group participates in complex formation through ionization of the OH group. This behaviour is well documented for some transition metal ion complexes of serine.[23]

Histidine, lysine, ornithine, penicillamine, and glutathione form the complexes 110, 120 and 111. The acid dissociation constant of the protonated complex ($\log\beta_{111}-\log\beta_{110}$) is 4.67 for histidine. This is in fair agreement with the acid dissociation constant of the imidazole residue of the histidine (pK_a=5.63), if the increase of acidity as a result of complex formation, is considered. Further, it should be recognized that the stability constant of the deprotonated complexes of histidine and histamine are in fair agreement and higher than those of amino acid complexes. This indicates that histidine coordinates by the amino and imidazole nitrogen groups, as histamine does.

Lysine and ornithine have a single carboxylic and two amino groups as binding sites. The formation constants of their 110 complexes are significantly higher than those of amino acids. This indicates that lysine and ornithine chelate by the two amino groups. Also, aspartic acid and glutamic acid having two carboxylic and amino groups are chelating as substituted glycinate, based on the fair agreement between their stability constant values and those of amino acids.

Penicillamine and glutathione have various binding sites *viz*. carboxylic, amino and sulfhydryl groups. The stability constant of their 110 complexes are in fair agreement with that of mercaptoethylamine (where the binding sites are the amino and sulfhydryl groups) and mercaptopropionic acid (where the binding sites are the carboxylic and sulfhydryl groups) and higher than those of α-amino acids (where the binding sites are the amino and carboxylic groups). This indicates that penicillamine and glutathione bind partly as an (N–S) donor and partly as an (O–S) donor and not as an (N–O) donor . The concentration distribution for penicillamine complex is given in Fig. 4. The protonated species 111 prevails with a formation percentage of 89.1 at pH *ca*. 1.8; the deprotonated species 110 reaches a maximum concentration of 72.3% at pH *ca*. 6.4. The hydroxo-complexes are less pre-

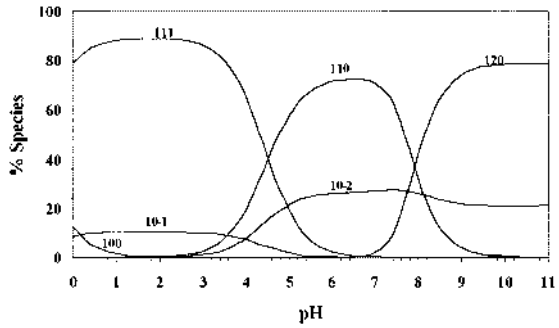

Fig. 4. Concentration Distribution of Various Species as a Function of pH in the DPT–Penicillamine System (at Concentrations of 1.25 and 2.5 mmol/l, Respectively)

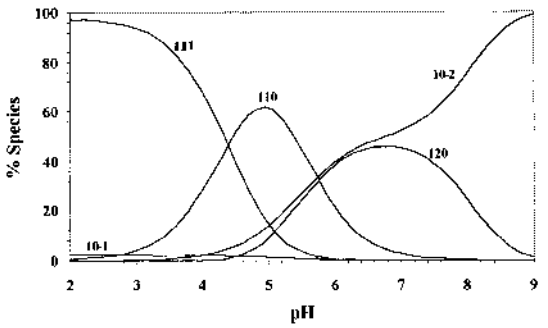

Fig. 5. Concentration Distribution of Various Species as a Function of pH in the DPT–CBDCA System (at Concentrations of 1.25 and 2.5 mmol/l, Respectively)

velant as their maximum concentrations are 10.4% at pH *ca*. 1.8 and 27.5% at pH *ca.* 7.4 for the mono- and di-hydroxo-complexes, respectively. This means that OH^- is not significantly competing with penicillamine in the reaction with diphenyltin(IV) cation. This may be due to the significantly high stability constant of diphenyltin–penicillamine complex compared with other complexes.

Addition of CBDCA to cisplatin, giving carboplatin, significantly improved the antitumour activity. Since, diorganotin(IV) species were reported to have antitumour activity, the reaction of diphenyltin(IV) with dicarboxylic acids including CBDCA is interesting. In the diphenyltin(IV)–dicarboxylic acid system, the potentiometric data fitting showed the formation of the species 110, 120 and 111. The stability constants values of the 110 complexes with a series of dicarboxylic acids forming five, six, seven and eight membered chelate rings, are in fair agreement. This indicates that the size of the chelate ring has no significant effect on the stability of complex. The concentration distribution diagram of CBDCA, taken as a representative and given in Fig. 5, shows that the protonated complex prevails with a formation degree of 97.3% at pH=2.0. The mono-hydroxo species (10−1) is not contributing in the domain of complex formation. The CBDCA complexes reach their maximum concentrations of 61.2% at pH *ca*. 5.0 and 45.7% at pH *ca*. 6.8 for 1 : 1 and 1 : 2 complexes, respectively.

Dimethyltin(IV)–peptide complexes are formed by coordination of the amino and carbonyl groups. Upon deprotonation of the amide group, the coordination sites would switch from carbonyl oxygen to amide nitrogen. Such changes in coordination centers are well documented for dialkyltin(IV)

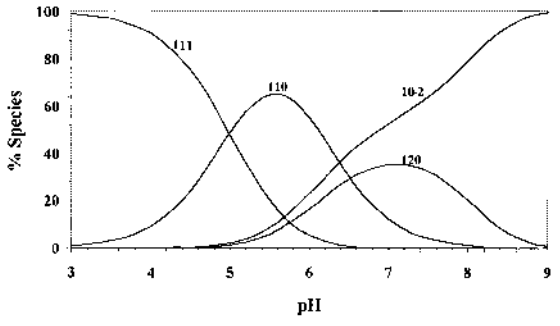

Fig. 6. Concentration Distribution of Various Species as a Function of pH in the DPT–Glycylglycine System (at Concentrations of 1.25 and 2.5 mmol/l, Respectively)

and some transition metal ion complexes of peptides. The potentiometric data of diphenyltin(IV)–peptide complexes were fitted to various models. The acceptable model was found to be consistent with the formation of the complexes with stoichiometric coefficients 110, 111 and 120. The formation of the species 11−1 as reported for the dimethyltin(IV)–peptide system,[11] through induced ionization of the peptide hydrogen was not assigned. This can be explained on the premise that the bulky phenyl group on the tin may hinder the structural change of coordination centre from carbonyl oxygen in the fromation of the 110 species, to the amide nitrogen in the formation of the 11−1 species. The concentration distribution diagram of glycylglycine, taken as a representative and given in Fig. 6, shows that the protonated complex prevails with a formation degree of 99.0% at pH=3.0. The deprotonated species 110 and 120 predominate with formation degrees of 65.1% at pH=5.6 and 35.3% at pH=7.0, respectively.

Conclusion

The activity of diphenyltin(IV) complexes, $Ph_2SnL_2X_2$ is controlled by the nature of Sn–L_2 bonds. The results show that in Ph_2Sn–penicillamine complex formation, the OH^- ion does not compete with complex formation. Consequently, the reaction with DNA should proceed better than with other diphenyltin(IV) complexes. Therefore, the penicillamine complex may have more antitumour activity. This suggests a further study on the feasibility of the use of penicillamine complexes as chemotherapeutic agents.

References and Notes

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