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STUDIES ON THE SYNTHESIS OF SOME NEW AMINOLYSED PRODUCTS: THEIR BIOLOGICAL ACTIVITY AND CHELATES

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SUMMARY

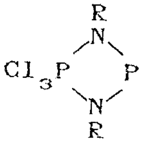
Interaction of 1,3-diaryl -2, 4- hexachlorocyclodiphosphazanes of the types (Ia–c) with some primary amines furnished the expected amino-derivatives. The elucidation of such aminolysed derivatives are essentially based on physical and chemical evidence. Accordingly, structure (II) was suggested.

The pKa, s of these compounds as well as their binary complexes with Co II, Ni II and Cu II in solution were studied spectrophotometrically and conductometrically. The determination of the micro amounts of these metals were also discussed.

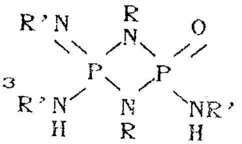
INTRODUCTION

The synthesis of halogenocyclodiphosphazanes was first reported by Michaelis (1903, 1915). Subsequent works, e.g. Trippette (1962), Flint (1969), Ibrahim (1969, 1979) and Islam (1974) also reported examples of cyclodiphosphazanes. The starting material 1,3-diaryl- 2, 2, 2, 4, 4,4- hexachlorocyclodiphosphazanes (Ia-c) were prepared essentially by the method of Chapmann (1962) and Zhumorova (1967). These compounds are known to be hydrolytically unstable. However, it has been shown that the aminolysis of these compounds is the essential process for their stabilization.

Many aspects in the synthesis of these compoinds indicate that further study is needed. For instance, their biological activity, metal complexes and the possible uses as microanalytical reagents particularly for Co (II), Ni (II) and Cu (II) contents.



(I)



(II)

a) R = C_6H_5- a) R = C_6H_5- ; R' = C_6H_4OH-o

b) R = $C_6H_5CH_2$- b) R = $C_6H_5CH_2$- ; R' = C_6H_5NH-

c) R = $C_6H_4CH_3$-o c) R = C_6H_5- ; R' = $C_6H_4NH_2$-o

d) R = $C_6H_4CH_3$-o ; R' = $C_6H_5CH_2$-

EXPERIMENTAL

All chemicals used were of analytical grade. Microanalysis and molecular weight determinations were carried out at the microanalytical unit, Cairo University. Melting points were determined by the capillary method and were uncorrected The infrared spectra were recorded on a PYE UNICAM 8000 SP spectrophotometer (KBr discs). Electronic absorption spectra were measured on Shimadzu uv-vis spectrophotometer. The PMR spectra were scanned by a Varian EM-3601, 60 MH_z spectrometer.

Conductometric measurements were done using a PYE conductance bridge and conductivity cell of the dipping type at 30 °C.

Reaction of hexachlorocyclodiphosphazane (I) with arylamines:

A solution of arylamine in dry benzene (or dioxane in case of (IIa) (100 ml) was added dropwise to a cold benzene solution of hexachlorocyclodiphosphazane (I) [(0.01 mole) in 100 ml benzene while stirring for one hour. The formed amine hydrochloride was filtered off at the pump. The filtrate was concentrated and the precipitate was crystallized from a suitable solvent to give IIa-d. The analytical data and some physical properties are collected in Table 1.

Stock solutions (10^{-2}M) of the cyclodiphosphazanes (IIa-d) and the metal salts $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$ were prepared by dissolving the requisite amounts of each in pure ethanol. The metal content has been standardized such as the procedure of Vogel (1959). Buffer solutions consisting of boric acid, borax, succinic acid and sodium sulphate were prepared as given by Britton (1952).

RESULTS AND DISCUSSION

A- Aminolysis of hexachlorocyclodiphosphazanes:

The reaction of hexachlorocyclodiphosphazanes (Ia-c) with o-toluidine, phenylhydrazine, benzylamine and o-aminophenol furnished a series of hydrolytically stable aminolyzed products for which structures (IIa-d) were suggested. The structures of these compounds were substantiated by their elemental analyses (Table 1), infrared, electronic and PMR spectra. The infrared spectra exhibited a doublet band at 700-750 cm^{-1} characteristic to cyclic υ (P-N) mode, Shaw (1967), a band at 1280-1300 cm^{-1} characteristic of the exocyclic ν(P=N), a band at 2550–2600 cm^{-1} characteristic of exocyclic ν(P–NH) and a band at 1200–1220 cm^{-1} characteristic of ν (P=O). The ultraviolet spectra in ethanol showed the characteristic absorption band at 250–290 nm corresponding to n-π^* transition for the phosphazane four-membered ring, Becke-Goering (1963). The structure of compound IId, as a representative example, was further confirmed on the basis of its 60 MHz and 100 MHz PMR spectra. The PMR spectrum exhibited a triplet signal at σ 3.2 ppm characteristic for the metyhlene protons and another signal at σ 3.4 ppm characteristic for the o-tolyl group existing in the 1,3 positions of phosphazane ring. So, the assigned structure was 1,3 -diary-2,4- diarylamino -4- oxo -2- arylimino cyclodiphosphazane (IIa-d) Additional details about the structure and the reaction mechanism of these compounds via x-ray diffraction and thermolysis will be published elsewhere.

B- Biological Activity:

The anti-microbial activity of the compounds under consideration was evaluated against the bacteria; *B.subtilis*, *B. mycoide* and *B. cereus*. It was found that compounds IIa and IIc have a significant biological

Table 1. Analytical data and some physical properties of the prepared compounds.

Compound	Colour	Solvent of crystallization	m.p. °C	Molecular formula	M.W. calc. (found)	% calc. (found)			
						C	H	N	P
IIa	pale brown	toluene-ethanol	145	$C_{30}H_{27}N_5P_2O$	535.6 (545.6)	67.3 (67.6)	5.1 (5.4)	1.1 (1.0)	11.6 (11.8)
IIb	pale yellow	toluene-ethanol	241	$C_{32}H_{33}N_5P_2O$	608.6 (614.5)	63.9 (63.4)	5.6 (5.4)	1.4 (1.8)	10.2 (10.4)
IIc	brown	ethanol	175	$C_{30}H_{30}N_5P_2O$	538.5 (539.9)	67.2 (67.4)	5.0 (5.2)	1.3 (1.5)	10.7 (11.1)
IId	colourless	toluene-ethanol	227	$C_{35}H_{37}N_5P_2O$	605.6 (614.7)	64.4 (64.1)	6.2 (6.4)	1.6 (1.8)	10.5 (10.4)

activity. The results of potency were in the range 125–500 icc (international count coefficient).

C- Determination of pKa values:

The pKa values of the hexachlorocyclodiphosphazanes (IIa-c) were determined in the pH range 2.14-11.0 from the variation of absorbance versus pH by the following methods: (a) the half -height Issa, (1972), (b) the logarithmic, Issa (1971) and (c) the modified colleter methods, Colleter (1960) making use of the equation:

$$K = \frac{(C_{H_3^+} - C_{H_2^+})\,M}{M-1}$$

where, $$M = \frac{A_3 - A_1}{A_2 - A_1} \cdot \frac{C_{H_1^+} - C_{H_2^+}}{C_{H_1^+} - C_{H_2^+}}$$

A_1, A_2 A_2 are the absorbances at three different hydrogen ion concentrations, CH_1^+, CH_2 and CH_2^+. The data by the three methods are collected in Table 2. The mean values of pKa for the compounds (IIa-c) are 3.6, 4.6 and 4.4 respectively.

D- Spectrophotometric measurements:

The reaction of hexachlorocyclodiphosphazane derivatives with Co II, Ni II and Cu II was followed spectrophotometrically to deduce the stoichiometry of the reactants and the formation constant of the complexes. In all measrements, the absorbance of the complex solutions was measured against a blank similarly prepared but containing no metal. On increasing the concentration of the components (ligand: metal) an apparent red shift in the band of the complexes is observed indicating the probable formation of more than one type of complexes. The results

Table 2. The pKa values determined spectrophotometrically by the different methods for the cyclodiphosphazane compounds.

compound	half heght	limiting logarithmic	colleter	Mean
IIa	3.65	3.45	3.70	3.6
IIb	4.55	4.55	4.66	4.6
IIc	4.40	4.20	4.60	4.4

showed the formation of complexes with the stoichiometry 1:1 and 1:2 (metal: ligand). The identity of the formed complexes was tentatively assigned from the solid IR spectra. The important absorption band in all complexes studied is found at 430-500 cm^{-1}. This band is not found in the IR spectra of the free ligands and it can be assigned to ν M-L originated in ν M-O with sufficient coupling from ν-M-N, Kovacic (1967), Hanock (1970). Based on the spectral changes, results of microanalysis of the solid complexes as well as conductometric studies, it can be concluded that the neutral molecules of cyclodiphosphazane are coordinated to each of the metal ion studied as bidentate ligands. The two bonding sites are the oxygen of the P=O and the nitrogen of the imino groups in one side of the cyclophosphazane molecule.

The apparent stability constant, Kf, is determined from the results of molar ratio, Yoe (1944) and continuous variation, Job (1928) methods using the relation;

$$Kf = \frac{A / Am}{(1-A / Am)^{n+1} \cdot n^2 [L]^n}$$

where;

A = the absorbance at a given ligand concentration

Am = the limiting absorbance

n = stoichiometric ratio.

The calculated Kf and the free energy $\triangle G$ of the complexes are given in Table 3. The data indicates that the complexes are significantly stable and the 1:2 ratios are more stable than the 1:1 ratios. In general, the stability of the complexes of the same ligand goes in the order Cu II > Co II > Ni II.

Table 3. The compositions, stability constants (K_f l. mol^{-1}) and the free energies ($-\Delta G$ in Kcl. mol^{-1}) at 30°C for Co^{2+}, Cu^{2+} and Ni^{2+} -complexes.

Ratio	Metal ion	L_1		L_2		L_3		L_4	
		K_f	$-\Delta G$	K_f	$-\Delta G$	K_f	$-\Delta G$	K_f	$-\Delta G$
1:1	Co	4.1×10^{6}	9.17	5.5×10^{6}	9.35	1.2×10^{6}	8.43	6.9×10^{6}	9.48
1:2		3.2×10^{12}	17.34	1.3×10^{10}	14.02	8.4×10^{11}	16.53	2.0×10^{15}	21.22
1:1	Cu	8.4×10^{6}	9.60	1.2×10^{7}	9.75	3.0×10^{7}	10.37	7.1×10^{8}	12.27
1:2		1.5×10^{12}	16.88	9.0×10^{11}	16.58	1.1×10^{10}	13.92	4.8×10^{11}	16.20
1:1	Ni	2.8×10^{6}	8.94	2.0×10^{6}	8.74	3.0×10^{5}	7.59	2.5×10^{6}	8.87
1:2		3.2×10^{12}	17.34	8.9×10^{11}	16.57	5.5×10^{10}	14.89	2.3×10^{11}	15.76

The compositions of the formed complexes in solutions were further confirmed by conductivity measurements in ethanol medium. The conductance-molar ratio curves are characterized by well defined breaks denoting the probable formation of 1:1 and 1:2 complexes. The plots of specific conductance versus the volume of the complexing agent added to the metal ion solution showed a gradual increase in conductance indicating the probability of releasing hydrogen from the ligand during the formation of complex. Further increase in conductance after the stoichiometric break may be attributed to the partial acid dissociation of the free ligand molecules. The latter is assumed to be enhanced by the masking effect of the dissociated ligand in the complex.

E- Sensitivity and reproducibility:

The different concentration ranges of metal ions at which Beer's law is obeyed as well as the values of molar absorptivity and the standard deviation for 10 samples each containing 0.5 ml of 10^{-4}M metal ion solution and 0.5 ml of 10^{-4} M reagent solution are given in Table 4. The sensitivity of the different metal ions consistently increases toward the considered ligands in the order Ni II > Co II > Cu II. This may reflect a comparable decreased stabilization in probable chelating ring formed on complexation as indicated by the red shift of λmax of the reagent.

Table 4. Sensitivity of the reactions of Co II, Ni II and Cu II with hexachlorocyclodiphosphazanes (L_{1-3}).

Mean absorb.	st. deviation	system	λmax complex	λmax reagent	Range of B's law, ug / ml	molar absorptivity ε
2.22	0.018	Co^{2+}—L_1	420	285	0.59 – 3.54	4500
0.716	0.0089	Cu^{2+}—L_1	430	285	0.13 – 7.62	5000
0.248	0.0019	Ni^{2+}—L_1	290	285	0.11 – 1.13	1500
0.446	0.0149	Co^{2+}—L_2	269	283	0.59 – 3.54	1080
0.95	0.0063	Cu^{2+}—L_2	260	283	0.64 – 9.60	8000
0.332	0.0109	Ni^{2+}—L_2	270	283	0.59 – 3.54	2900
0.395	0.0041	Co^{2+}—L_3	478	255	0.12 – 2.95	1400
2.224	0.0182	Cu^{2+}—L_3	260	255	0.12 –10.16	3313
0.331	0.0049	Ni^{2+}—L_3	478	255	0.059– 0.83	1500

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