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Substituent Effects in the Protonation and Complexation with Copper(II) Ions of Organic Monophosphate Esters. A Potentiometric and Calorimetric Study

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Potentiometric and calorimetric studies have been made of the aqueous complexation of a set of organic monophosphate esters with protons and copper(II) ions. The esters are *p*-nitrophenyl phosphate, 1-naphthyl phosphate, phenyl phosphate, α-D-glucose 1′-phosphate, glyceryl phosphate, and methyl phosphate. The substituents of these phosphates cover a wide range of electron-withdrawing or -donating character. Conditions were 25 °C and I = 150 mM [Cl$^-$]. In the computation of the formation constants and the enthalpies of the various copper(II)–phosphate ester complexes, the complexation of chloride by copper(II) ions was ignored. If desired, corrections to the formation constants may be made by adding 0.05 to the logarithmic values. The effect of copper(II)–chloride complexation on the enthalpies of the copper(II)–phosphate ester complexes is considered to be small under the conditions of the calorimetric measurements. All the protonation and copper(II) complexation reactions were found to be endothermic but to have a favorable increase in entropy. Analysis of the data indicates that whereas electronic inductive effects do play some role in determining the proton and copper(II) complex stabilities, the enthalpy and entropy changes are dominated by desolvation of reactants. Additional factors that determine the thermodynamic properties are concluded to be (i) an electron-withdrawing mesomeric effect in the case of *p*-nitrophenyl phosphate, (ii) the size of the substituent, in particular, solvation of methyl phosphate is especially strong owing to the high electric field surrounding the dianion, and (iii) the disruption or rearrangement of intramolecular hydrogen bonds upon protonation or copper(II) complexation of glyceryl phosphate.

Introduction

It has long been recognized that metal ions are very important to many vital functions of the living organism.[1–4] Among their roles are complex formation to yield compounds of higher reactivity or of different transport features. Numerous enzymatic and metabolic processes require the presence of metal ions as catalysts. A very important class of ligands are phosphate esters, which serve as phosphate group and energy transmitters as well as energy storage mediums both in animals and plants. Much has been published about complex formation between phosphate esters and metal ions.[5–17] Investigations of the protonation equilibria showed a correlation between the pK_a values and the electron-donating or electron-withdrawing action of the substituent.[5,6] The same has been postulated to hold for metal complexation equilibria,[18] but a rigorous study has not yet been presented. Such a study is the subject of this paper, in which is reported investigations of stability constants for the complexation of copper(II) ions with a set of monophosphate esters. The substituents have been chosen to cover a wide range of nucleophilicities. From the various possible nucleophilicity scales like Hammet or Taft σ values,[19,20] NMR chemical shifts,[6,21] O–H stretching frequencies,[6] and pK_{ROH} values[22] of the substituent alcohols, ROH, the last was chosen because it is the only scale for which a complete set of experimentally determined constants exists. The pertinent pK_{ROH} values are given in Table I. If the above assumption is true that the thermodynamic features are mainly determined by the electronic induction effects of the substituent, it is expected that with increasing protonation or metal stability constant, i.e. increasing negative ΔG, there will be a decreasing reaction enthalpy, ΔH. Determination of the reaction enthalpies of the protonation and the copper complex formation has therefore been carried out in order to be able to identify any additional influences.

Table I. pK_a Values of the Substituent Alcohols

alcohol	pK_a	T/°C	concn of ionic medium/M	solvent	ref
p-nitrophenol	7.14	25	0.04	water	*a*
1-naphthol	9.416	25	0.04	water	*b*
phenol	9.999	25	0.05	water	*a*
glucose	12.46	25	0	water	*c*
glycerol	14.15				*d*
methanol	16.05	20	1 (LiCl)	methanol	*e*

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Experimental Section

Materials and Preparations. Methyl phosphate was obtained as a 2:1 mixture of sodium chloride and disodium methyl phosphate pentahydrate by hydrolyzing methyl dichlorophosphate in water in the presence of sodium hydroxide (molar ratio CH_3OPOCl_2:NaOH = 1:4) and subsequent evaporation of the water. Methyl dichlorophosphate was synthesized from methanol and phosphoryl chloride (1:1 molar ratio) in ether and purified by distillation on a water pump. *p*-Nitrophenyl phosphate (disodium hexahydrate salt, Sigma 104), 1-naphthyl phosphate (free acid, synthesized by M. M. Armstrong[23]), phenyl phosphate (disodium dihydrate salt, Aldrich), α-D-glucose 1′-phosphate 4-hydrate (disodium salt, Sigma), and glyceryl 2-phosphate (disodium salt, Sigma) were used as supplied after examining the substances by proton and phosphorus NMR spectroscopy as well as microanalysis before use. *p*-Nitrophenyl phosphate and 1-naphthyl phosphate were weighed out separately for each

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experiment. Of the other ligands stock solutions were prepared; they were not kept for more than 6 h. The orthophosphate content of the stock solutions was determined by the very sensitive phosphomolybdate test[24] before and after all titrations to ensure that no hydrolysis occurred during the use of the solutions. Sodium hydroxide solutions (1-5 mM) were prepared under nitrogen by using Merck ampules and standardized against dried potassium hydrogen phthalate (Merck p.a. 99.9-100.5%) and protected against atmospheric carbon dioxide by soda lime. Hydrochloric acid solutions (1-500 mM) were prepared by using Merck ampules and standardized against sodium hydroxide or borax. Solutions containing copper(II) ions were prepared from $CuCl_2 \cdot 2H_2O$ (Merck p.a. >99%) and standardized against EDTA (Merck Titriplex III p.a. >99%) with murexide indicator.[25] All solutions were adjusted to a chloride concentration of 150 mM by the addition of accurately weighed sodium chloride (BDH "Aristar"). All solutions were prepared by using carbonate-free, boiled-out, glass-distilled water. The potentiometric titrations were carried out in a purified nitrogen atmosphere generated by passing nitrogen (Afrox) through concentrated potassium hydroxide, Fieser's solution,[26] an empty wash bottle, and 150 mM sodium chloride solution before admitting it to the vessel. It was released via a trap containing 150 mM sodium chloride solution to prevent back diffusion of oxygen and carbon dioxide.

Potentiometric Titrations. The potentiometric method has been described in detail elsewhere.[23] The ligand and copper(II) ion concentrations varied between 1 and 15 mM. The potentiometric data were analyzed by using the program library ESTA,[27-30] and thus overall formation constants

$$\beta_{pqr} = [M_pL_qH_r]/[M]^p[L]^q[H]^r$$

were obtained by the procedure described earlier.[23]

Calorimetric Measurements. The calorimetric results were obtained by using an isothermal titration calorimeter, Tronac Model 550.[31,32] The titrant was added with a 2.5-mL Gilmont precision microburet at constant speed. It turned out to be impossible to perform the protonation titrations under the same conditions as the potentiometric work because of the small reaction heats. Protonation enthalpies were determined from titrations of 20-25 mL of 50 mM ligand solution with 450 mM hydrochloric acid at 25 °C. The chloride concentration of ligand solutions was adjusted to 55 mM in order to keep the ionic strength as close as possible to 150 mM. The effect due to changing ionic strength is generally found to be very small.[33] Copper complexation enthalpies were determined such that a maximum change of the number of moles of the complex of interest, ML, occurred during the titration. A 25-mL volume of 5 mM ligand solution (150 mM Cl^-) at various pH was titrated against 120 mM copper chloride solution. To check the standardization of the calorimeter, four titrations of 10 mM sodium hydroxide (150 mM Cl^-) against 125 mM hydrochloric acid (150 mM Cl^-) were carried out. These yielded $\Delta H^{\ominus} = -57.4 \pm 2.9$ kJ mol^{-1} for the heat of neutralization. This value, when compared with a literature[34] value of -55.85 ± 0.08 kJ mol^{-1}, was taken as indicating satisfactory standardization of the calorimeter, considering that the purpose of the present paper was to seek trends rather than to obtain definitive protonation and complexation enthalpies.

The heat of dilution of hydrochloric acid was measured in separate experiments by titrating the hydrochloric acid into 55 mM sodium chloride solution. The heat of dilution of the copper chloride solution was measured by titrating the copper solution into 150 mM sodium chloride solution. The protonation enthalpies were calculated from the corrected heats, Q, according to

$$\Delta H^{\ominus}_{LH} = Q/(\text{moles of LH formed}) \tag{1}$$

and the results for different titrations were averaged. In order to obtain the copper complex formation enthalpies, the equation

$$\sum_i n_i \Delta H_i^{\ominus} = Q \tag{2}$$

has to be solved (n_i is the number of moles of complex i generated, and $\Delta H_i^{\ominus}$, the enthalpy of complex i). The change in the number of moles of each compound present was calculated with the SPEC program of ESTA.[27-30] Provided there are more equations (experiments) than unknowns, the value of $\Delta H_i^{\ominus}$ may be obtained by minimizing

$$\sum_j \left(\frac{Q_{\text{exp},j} - Q_{\text{calc},j}}{Q_{\text{exp},j}} \right)^2 = \sum_j \left(\frac{Q_{\text{exp},j} - \sum n_{ij} \Delta H_j^{\ominus}}{Q_{\text{exp},j}} \right)^2 \tag{3}$$

The index, j, refers to a given titration.

Results

1. Potentiometric Results. Logarithms of the protonation and formation constants derived from the potentiometric results are presented in Table II together with the pH range used for the measurements, the number of titrations performed, the number of data points in each titration, and statistics pertaining to the refinements. Included in Table II, for comparative purposes, are corresponding literature values that are available.

1.1. Protonation Constants. Agreement between the protonation constants obtained in this work and the corresponding literature values is generally satisfactory and in some cases excellent. In order to assess some of the comparisons in greater detail the protonation constants of this work were adjusted to an ionic strength of 100 mM, thus facilitating a direct comparison with literature values reported at the latter ionic strength. Three types of adjustment were made, one using the Davies[35] equation and two using the Murray-Linder[36] approach, with two different values of the empirical parameter, c, namely -0.1 (standard deviation 0.02) and -0.3 (standard deviation 0.06) as applied to the monoprotonated phosphate ester species. In both the series of Murray-Linder adjustments, c was put equal to -0.1 (standard deviation 0.02) for the proton and the unprotonated phosphate ester. The following values were used for the Debye-Hückel size parameter, $\mathring{a}_i$: H^+, 9.0 Å (standard deviation 2.0 Å); unprotonated phosphate ester, 6.0 Å (standard deviation 1.0 Å); monoprotonated phosphate ester, 5.0 Å (standard deviation 1.0 Å). The JESS[37] software package was used to carry out all the ionic strength adjustment calculations. The results are presented in Table III, from which it may be seen that the three adjusted log β_{011} values for any one ligand agree with each other to within 0.01. Second, the agreement between the adjusted protonation constants and corresponding literature values is generally eminently satisfactory.

1.2. Formation Constants. Complexation experiments could be conducted only in the lower pH region because precipitates occurred at alkaline pH's. Although none of the precipitates was analyzed, they were believed to have been metal hydroxides because they always occurred in the pH region expected for these compounds. The exceptions were the titrations with ligand 3 (phenyl phosphate), where precipitates occurred at lower pH, and with ligand 6 (methyl phosphate). In the case of the latter, much effort had to be invested in optimizing the conditions for the titrations (initial ligand concentration below 2 mM; $4 < \text{pH} < 6$) in order to avoid precipitate formation.

Overlapping sets of formation curves were obtained for the copper(II)-p-nitrophenyl phosphate and -phenyl phosphate systems, suggesting the presence of only mononuclear binary complexes.[38] Indeed, the best refinements were obtained by assuming ML as the only ligand-metal complex. For the other systems nonoverlapping formation curves were found, indicating the presence of not only mononuclear binary but also other types of complexes, e.g. hydroxo complexes.[38] Figure 1 shows a typical formation curve. The strong backfanning pattern at low pL is indicative of the presence of hydroxo complexes. Indeed, the best refinements were obtained by postulating the presence of the hydroxo complexes MLH_{-1} and in some cases MLH_{-2} in addition

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Table II. Logarithms of Formation Constants (β_{pqr}) (d = Standard Deviation in log β; nt = Number of Titrations; np = Number of Data Points; R = Hamilton Factor)

ligand[h]	cation	*pqr*	log β_{pqr}	*d*	nt	np	pH range	*R*	T/°C	I/M (ionic medium)	ref
1	H^+	011	4.987	0.001	5	275	2.2–8.5	0.005	25	0.15 (NaCl)	*a*
	H^+	011	4.96						25	1 (KCl)	*b*
	H^+	011	5.05						25	0.10 ($NaNO_3$)	16
	Cu^{2+}	110	2.148	0.004	9	509	2.6–6.3	0.015	25	0.15 (NaCl)	*a*
	Cu^{2+}	110	2.33						25	0.10 ($NaNO_3$)	16
2	H^+	011	5.740	0.005	4	301	2.0–8.0	0.002	25	0.15 (NaCl)	*a*
	H^+	011	5.85						25	0.1	*c*
	Cu^{2+}	110	2.635	0.006	6	207	2.0–6.0	0.003	25	0.15 (NaCl)	*a*
		1 1 -1	−3.840	0.021					25	0.15 (NaCl)	*a*
3	H^+	011	5.827	0.002	9	394	2.2–10.0	0.012	25	0.15 (NaCl)	*a*
	H^+	011	5.823						25	0.1	*c*
	H^+	011	5.85						25	0.1 ($NaNO_3$)	16
	Cu^{2+}	110	2.611	0.005	11	414	2.8–5.4	0.010	25	0.15 (NaCl)	*a*
	Cu^{2+}	110	2.77						25	0.10 ($NaNO_3$)	16
4	H^+	011	5.9767	0.0003	5	245	2.5–8.6	0.001	25	0.15 (NaCl)	*a*
	H^+	011	6.04						30	0.145	*e*
	Cu^{2+}	110	2.736	0.003	11	726	2.5–6.5	0.011	25	0.15 (NaCl)	*a*
		1 1 -1	−4.080	0.018					25	0.15 (NaCl)	*a*
		1 1 -2	−11.026	0.049					25	0.15 (NaCl)	*a*
5	H^+	011	6.1054	0.0005	7	366	2.0–11.0	0.001	25	0.15 (NaCl)	*a*
	Cu^{2+}	110	2.808	0.008	8	357	2.4–6.5	0.015	25	0.15 (NaCl)	*a*
		1 1 -1	−3.728	0.037					25	0.15 (NaCl)	*a*
		1 1 -2	−10.312	0.070					25	0.15 (NaCl)	*a*
6	H^+	011	6.251	0.001	5	261	2.5–9.5	0.018	25	0.15 (NaCl)	*a*
	H^+	011	6.58						22.5		*f*
	H^+	011	6.2						25	0.1 (NaCl)	*g*
	Cu^{2+}	110	2.819	0.007	6	391	4.0–6.0	0.059	25	0.15 (NaCl)	*a*
		1 1 -1	−3.25	0.02					25	0.15 (NaCl)	*a*

[a] This work. Standard deviations used for calculating weighting factors: concentrations 0.1%; electrode intercept 0.1 mV; electrode slope 0.05 mV/− log H^+; titre volume 0.001 mL; emf 0.1 mV. [b] Bourne, N.; Williams, A. *J. Org. Chem.* **1984**, *49*, 1200. [c] Mäkitie, O.; Mirttinen, S. *Acta Chem. Scand.* **1971**, *25*, 1146. [d] Mäkitie, O.; Konttinen, V. *Acta Chem. Scand.* **1969**, *23*, 1459. [e] Trevelyan, W. E.; Mann, P. F. E.; Harrison, J. S. *Arch. Biochem. Biophys.* **1952**, *39*, 419. [f] Burton, C. A.; Llewellyn, D. R.; Oldham, K. G.; Vernon, C. A. *J. Chem. Soc.* **1958**, 3574. [g] Brintzinger, H.; Hammes, G. G. *Inorg. Chem.* **1966**, *5*, 1286. [h] Ligands: (**1**) *p*-nitrophenyl phosphate; (**2**) 1-naphthyl phosphate; (**3**) phenyl phosphate; (**4**) α-D-glucose 1′-phosphate; (**5**) glyceryl 2-phosphate; (**6**) methyl phosphate.

Table III. Logarithms of the Protonation Constants (β_{011}) of Table II Corrected by Three Methods to an Ionic Strength of 100 mM and Comparable Literature Values (I = 100 mM, T = 25 °C)

ligand[f]	Davies eq cor[a]	Murray-Linder cor 1[b]	std devn.[b]	Murray-Linder cor 2[b]	std devn[b]	lit value	ref
1	5.04	5.03	0.06	5.04	0.06	5.05	*c*
2	5.79	5.78	0.06	5.79	0.06		
3	5.88	5.87	0.05	5.88	0.07	5.85	*c*
						5.82	*d*
4	6.03	6.02	0.06	6.03	0.07		
5	6.15	6.14	0.06	6.15	0.07		
6	6.30	6.29	0.06	6.30	0.06	6.2	*e*

[a] Reference 35. [b] Reference 36 (size parameter $\mathring{a}_i$/Å, standard deviation/Å: H^+, 9.0, 2.0; ligand, 6.0, 1.0; monoprotonated ligand, 5.0, 1.0. Empirical parameter *c*, standard deviation: (1) H^+, −0.1, 0.02; ligand, −0.1, 0.02; monoprotonated ligand, −0.1, 0.02; (2) H^+, −0.1, 0.02; ligand, −0.1, 0.02; monoprotonated ligand, −0.3, 0.06. [c] Reference 16. [d] Mäkitie, O.; Mirttinen, S. *Acta Chem. Scand.* **1971**, *25*, 1146. [e] Brintzinger, H.; Hammes, G. G. *Inorg. Chem.* **1966**, *5*, 1286. [f] Refer to Table II for identities of the ligands.

to ML. The hydroxo complexes can be rationalized by assuming proton removal from the hydration sphere of the complex ML. Because hydroxo complexes occurred just before the onset of precipitation and in small concentrations, only few data could be collected in the respective pH region. Thus the stability constants could not be evaluated as precisely as with those obtained for the ML complexes. A commonly encountered problem was that often it was possible to refine either of the stability constants for the complexes ML_2 or MLH_{-1} in addition to ML but not both simultaneously. In most cases the fit including MLH_{-1} was significantly better. Only for the complexation of copper(II) and *p*-nitrophenyl phosphate was the model containing ML_2 significantly better than that containing MLH_{-1}, with respect to both objective function and R value as well as at the 95% confidence level of the Hamilton test.[39] Nevertheless the species ML_2 was discarded because the formation constants of simple phosphate esters are generally so small (1.2 < log β < 2.8) that a bis complex would seem very unlikely, especially since not even chelating phosphates form such complexes.[40,41] The final results are summarized in Table II. The only corresponding literature values are those for the copper(II)–*p*-nitrophenyl phosphate and –phenyl phosphate systems obtained by Massoud and Sigel[16] in 100 mM sodium nitrate at 25 °C. In order to compare these literature values with those in Table II, which apply to 150 mM sodium chloride, corrections have to be applied for the effect of chloride complexation of copper(II) and also for the differing ionic strengths.

In principle, allowance can be made for copper(II)–chloride complexation by multiplying the formation constants of Table II by the factor

$$1 + [Cl^-]\beta_{CuCl} + [Cl^-]^2\beta_{CuCl_2} + [Cl^-]^3\beta_{CuCl_3} + [Cl^-]^4\beta_{CuCl_4}$$

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Table IV. Comparison of the Logarithmic Formation Constants, log β_{110}, for the Monocomplexes of Copper(II) Ions and the Ligands of Table II, with Values Estimated from the Base-Line Equation of Massoud and Sigel[16] for the Correlation of Copper(II) Ion–Phosphate Coordination and Phosphate Group Basicity[a]

ligand[h]	log β_{110} measd at I = 150 mM and corrected for $CuCl^+$ formn[d]	Davies eq cor[e]	Murray–Linder cor 1[f]	std devn[f]	Murray–Linder cor 2[f]	std devn[f]	est by Massoud–Sigel eq[g]	std devn[g]
1	2.20	2.27	2.30	0.10	2.31	0.08	2.34[b]	0.44
2	2.69	2.76	2.81	0.09	2.80	0.07	2.68	0.47
3	2.66	2.73	2.78	0.09	2.77	0.08	2.72[c]	0.47
4	2.79	2.86	2.91	0.08	2.90	0.07	2.78	0.48
5	2.86	2.93	2.98	0.09	2.97	0.08	2.84	0.48
6	2.87	2.94	2.99	0.09	2.98	0.06	2.91	0.49

[a] The log β_{110} values Table II have first been corrected for $CuCl^+$ formation and subsequently adjusted to I = 100 mM by three methods. [b] Experimental value of Massoud and Sigel[16] = 2.33. [c] Experimental value of Massoud and Sigel[16] = 2.77. [d] Correction applied by adding 0.05 to the log β_{110} values of Table II; estimated error for each corrected value = 0.01. [e] Reference 35. [f] Reference 36 (size parameters $\mathring{a}_i$/Å, standard deviation/Å; Cu^{2+}, 6.0, 1.0; ligand, 6.0, 1.0; complex, 4.0, 0.8. Empirical parameter c, standard deviation: (1) Cu^{2+}, −0.1, 0.02; ligand, −0.1, 0.02; complex, −0.5, 0.1; (2) Cu^{2+}, −0.1, 0.02; ligand, −0.1, 0.02; complex, −0.3, 0.06. [g] Reference 16, Table V. Standard deviations calculated from propagation of error formula.[43] [h] Refer to Table II for identities of the ligands.

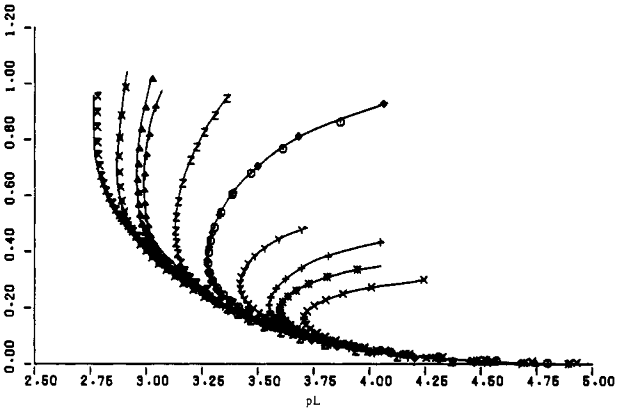

Figure 1. Theoretical formation curves for the α-D-glucose 1′-phosphate–copper(II) system calculated from the β values of Table II and plotted with experimental $\bar{Z}$ points. Initial concentrations/10^{-3} M of L (ligand) and M (metal) are as follows: (⊙) 0.00298 and 0.00304; (△) 0.00414 and 0.00203; (+) 0.00221 and 0.00445; (×) 0.00217 and 0.00654; (◇) 0.00275 and 0.00273; (↑) 0.00379 and 0.00190; ($\bar{X}$) 0.00510 and 0.00172; (Z) 0.00328 and 0.00236; (Y) 0.00316 and 0.00528; (☆) 0.00449 and 0.00189; (✱) 0.00254 and 0.00635.

where β_{CuCl}, β_{CuCl_2}, β_{CuCl_3}, and β_{CuCl_4} are the overall formation constants for the complexes, $CuCl^+$, $CuCl_2$, $CuCl_3^-$, and $CuCl_4^{2-}$, respectively. With use of the constants for the copper(II)–chloride complexes published by Ashurst and Hancock,[42] the SPEC program of ESTA[27–30] was run on solutions containing 150 mM chloride and copper(II) in the range 1–15 mM (i.e. the range of concentrations used in the potentiometric titrations reported in this paper). The output showed the $Cu_2(OH)_2$ complex to dominate, the $CuCl^+$ complex to incorporate between 2.4 and 7.4% of the total copper, and the formation of the remaining copper(II)–chloride complexes to be negligible. Thus, in practice, the factor for correcting the formation constants of Table II reduces to

$$1 + [Cl^-]\beta_{CuCl}$$

In the application of this correction factor, a difficulty arises in finding an appropriate value for β_{CuCl}. Whereas the most recently reported copper(II)–chloride constants are those of Ashurst and Hancock,[42] these apply to an ionic strength of 5 M and hence are not strictly applicable in the present exercise. Taking the constants of Ashurst and Hancock[42] as well as those of other authors, Martell and Smith[40] have published recommended values for the complex $CuCl^+$ applicable to ionic strengths of 0, 0.5, 1.0, and 5.0 M. By interpolation it would appear that a reasonable value for β_{CuCl} corresponding to an ionic strength of 150 mM would be in the range 0.72–0.95. Substitution into the foregoing correction factor implies that the logarithmic constants of Table II may be corrected for copper(II)–chloride complexation by adding 0.05 ± 0.01. log β_{110} values corrected in this manner are presented in the second column of Table IV.

The log β_{110} values of Table II, corrected for copper(II)–chloride complexation as described in the previous paragraph, were corrected further so as to correspond to an ionic strength of 100 mM, that is the ionic strength applicable to the constants of Massoud and Sigel.[16] Three series of adjustments were made, one using the Davies[35] equation and two using the Murray–Linder[36] approach. Again, the JESS[37] software package was used for the calculations.

In the application of the Murray–Linder approach, the empirical parameter, c, for the copper(II)–ligand complex was taken as −0.5 (standard deviation 0.1) in the first set and as −0.3 (standard deviation 0.06) in the second set of calculations. In both sets c was set equal to −0.1 (standard deviation 0.02) for the copper(II) ion and for the unprotonated phosphate ester. The Debye–Hückel size parameter, $\mathring{a}_i$, was set to the following values in both sets of calculations: copper(II) ion, 6.0 Å (standard deviation 1.0 Å); unprotonated phosphate ester, 6.0 Å (standard deviation 1.0 Å); copper(II)–ligand complex, 4.0 Å (standard deviation 0.8 Å). The adjusted logarithmic constants are listed in columns 3, 4, and 6 of Table IV. It may be seen from this table that there is good agreement between the log β_{110} values adjusted by the Murray–Linder approach and the respective experimental constants obtained by Massoud and Sigel[16] for the copper(II)–p-nitrophenyl phosphate and the copper(II)–phenyl phosphate complexes.

Further evidence for the consistency of the log β_{110} values of this work with those of Massoud and Sigel[16] may be obtained by using the correlation established by the latter authors between copper(II) ion–phosphate coordination and phosphate group basicity. From their pK_a and log $K^{Cu}_{Cu(R\text{-}MP)}$ (≡log β_{110}) values for p-nitrophenyl phosphate, phenyl phosphate, n-butyl phosphate, D-ribose 5′-monophosphate, uridine 5′-monophosphate, and thymidine 5′-monophosphate, these authors found the data to fall near a straight line, which could be represented by the equation

$$y = 0.453x + 0.055 \qquad (4)$$

In eq 4, x represents the pK_a value of a phosphate ester and y represents log $K^{Cu}_{Cu(R\text{-}MP)}$. Equation 4 has been applied to the ligands of the present work by taking log β_{011} (=pK_a) from Table III (i.e. adjusted to an ionic strength of 100 mM). The estimated log β_{110} values are listed in column 8 of Table IV. The corresponding standard deviations of these estimates (column 9) were calculated from the propagation of error formula[43] by using the standard deviations in columns 4 and 6 of Table III and those given in Table V of ref 16. It may be seen from Table IV that the log β_{110}'s of the present work are consistent with the Massoud–Sigel[16] correlation (eq 4) to well within the limits of uncertainty.

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Table V. Correlations between Copper(II) Ion–Phosphate Complex Stability and Phosphate Group Basicity: Slopes (*m*) and Intercepts (*b*) for the Linear Regression Equations of log β_{110} versus log β_{011} (=pK_a) (d_m = Standard Deviation in *m*; d_b = Standard Deviation in *b*)

source of data	*m*	d_m	*b*	d_b
ref 16, Table V	0.453	0.056	0.055	0.340
this paper, Table II	0.554	0.034	−0.596	0.198
this paper, Table III (log β_{011}) and Table IV, columns 4 and 6 (log β_{110})	0.564	0.036	−0.515	0.214

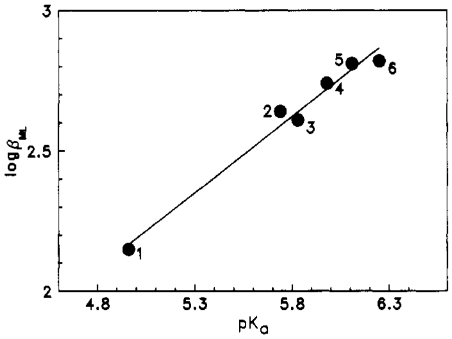

Figure 2. Plot of the logarithms, log β_{110}, of the formation constants for the complexes, ML, formed between copper(II) and the monophosphates against pK_a for the protonated ligands.

Yet further evidence for the consistency of the present measurements with those of Massoud and Sigel[16] may be seen in Table V, in which is presented the linear regression parameters, with standard deviations, obtained by least squares analysis of (i) Massoud and Sigel's[16] data (eq 4), (ii) log β_{110} versus log β_{011} of Table II, i.e. the original data applicable to I = 150 mM and with CuCl$^+$ formation ignored, and (iii) log β_{110} of Table IV (corrected for CuCl$^+$ formation and adjusted to I = 100 mM) versus log β_{011} of Table III (i.e. adjusted to I = 100 mM). The data of (ii) are plotted in Figure 2. It may be seen from Table V that the three slopes ± two standard deviations overlap well. A similar situation holds for the three intercepts. It would appear, therefore, that the two regression lines of the present work (ii) and (iii) do not differ significantly from the Massoud–Sigel correlation eq 4.

2. Calorimetric Results. The enthalpy, $\Delta H^\ominus$, and entropy change values, $T\Delta S^\ominus$, derived from the calorimetric measurements and the constants of Table II are presented in Table VI together with standard deviations and all available corresponding data from the literature. The agreement between the protonation enthalpies obtained in this work and the respective literature values is good.

When the copper(II) complexation enthalpies in Table IV were obtained, small concentrations of the reactants had to be used in order to avoid precipitation. In consequence, the quantity of heat generated in each titration was rather small. In order to calculate the copper complex formation enthalpies, the contributions due to the formation of LH, CuOH, and $Cu_2(OH)_2$ were calculated from the measured protonation heats and literature values[40] and subtracted before the calculation was carried out even though these three complexes contributed only 2% to the total heat. The ΔH values obtained from eq 3 turned out to be correlated, and it was found that the sum of squares did not rise significantly if only ΔH(ML)) instead of ΔH(ML) plus ΔH(MLH$_{-1}$) plus ΔH(MLH$_{-2}$) was refined. This confirms not only that the concentrations of the hydroxo complexes are an order of magnitude smaller than those of ML but also that the contributions of the hydroxo complexes to the total measured heat is negligible. Since the complexation reactions were studied in chloride medium, the formation of CuCl$^+$ ought, strictly, to be taken into account in computing ΔH(ML). In the present paper, the contribution of this source to the measured heat is neglected, however, but this can be rationalized as follows. First, CuCl$^+$ is already formed in the titrant solution. Upon titration of the latter into the ligand solution (which contains 150 mM chloride), the copper(II)–chloride equilibrium adjusts to a new position. Thus, the heat change due to this factor results from the corresponding change in the number of moles of CuCl$^+$. Speciation calculations, using the SPEC program of ESTA[27-30] together with the value of ca. 8 kJ mol^{-1} for ΔH(CuCl$^+$) given by Martell and Smith,[40] yield the conservative estimate that the heat change due to CuCl$^+$ equilibrium adjustment amounts to a maximum of only 5% of the heat change due to copper(II)–phosphate ester complexation. This is not considered to introduce serious error in the light of the previously stated purpose of the present paper, namely to consider trends rather than to obtain definitive thermochemical data.

Table VI. Thermodynamic Results for the Protonation and Copper(II) Complexation of Organic Monophosphates (*d* = Standard Deviation in the Reaction Enthalpy, $\Delta H^\ominus$; nt = Number of Titrations; Temperature = 25 °C)

ligand	cation	$\Delta H^\ominus$/kJ mol^{-1}	*d*/kJ mol^{-1}	nt	$T\Delta S^\ominus$/kJ mol^{-1} [e]	ref
1	H$^+$	7.39	0.09	4	35.86	*a*
	H$^+$	7.65				*b*
	Cu^{2+}	20.4	0.8	5	32.7	*a*
2	H$^+$	4.50	0.04	4	37.27	*a*
	Cu^{2+}	19.4	0.9	4	34.4	*a*
3	H$^+$	3.68	0.46	5	36.95	*a*
	Cu^{2+}	21.6	1.6	4	36.5	*a*
4	H$^+$	1.52	0.03	3	35.64	*a*
	H$^+$	1.803				*c*
	Cu^{2+}	21.8	1.3	5	37.4	*a*
5	H$^+$	0.94	0.05	3	35.79	*a*
	H$^+$	1.209				*d*
	Cu^{2+}	37.6	3.6	3	53.6	*a*
6	H$^+$	2.82	0.03	3	38.51	*a*
	Cu^{2+}	29.9	2.3	4	46.0	*a*

[a] This work, ionic strength ca. 0.15 M (Cl$^-$). [b] *Chem. Abstr.* **1986**, *105*, 214715x. [c] Ashby, J. H.; Clarke, H. B.; Crook, E. M.; Datta, S. P. *Biochem. J.* **1955**, *59*, 203. [d] Ashby, J. H.; Crook, E. M.; Datta, S. P. *Biochem. J.* **1954**, *56*, 198. [e] Calculated from $T\Delta S^\ominus = \Delta H^\ominus + RT \ln \beta$.

In the calculation of ΔH(ML), it was, thus, assumed that ML was the only complex and eq 1 was used. The standard deviations of the copper complexation enthalpies seem rather high (Table VI). This is a reflection of the simplifying assumption that the contributions of the hydroxo and chloro complexes are negligible as well as being a manifestation of the experimental problems: because the heat effects obtained during the titrations were small, the copper chloride solution had to be added so fast that no true equilibrium between the heat generated and the compensation heat could be reached. It was verified, however, with respect to the protonation titrations that a comparison of the initial nonequilibrium part of a titration with the nonequilibrium data of a calibration titration with constant heat input agreed with the results obtained from the respective equilibrium data to within 1%.[44] The same was assumed to hold for titrations in which the heat generation was variable due to the presence of more than one species in the solution. If only data up to metal to ligand ratios of 1:1 were used, stable results were obtained no matter which part of the titration (within the above limits) had been used for analysis. No literature data are available for comparison.

Discussion

1. General Results. The results in Table VI show that all the protonation and complexation reactions in the present study are endothermic and are accompanied by significant increases in entropy. This phenomenon may be interpreted by assuming each experimental enthalpy change to consist of the net result of two opposing effects, namely the exothermic protonation or complexation of the dianionic ligand and the endothermic liberation of ordered water of hydration from the reactants to form bulk water of greater disorder.[45,46] Liberation of water of hydration

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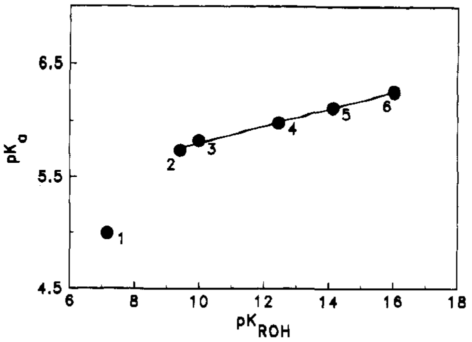

Figure 3. Plot of pK_a for monophosphates against pK_{ROH} for the corresponding alcohols. The latter is taken as a measure of the electron-withdrawing or -releasing character of the substituents.

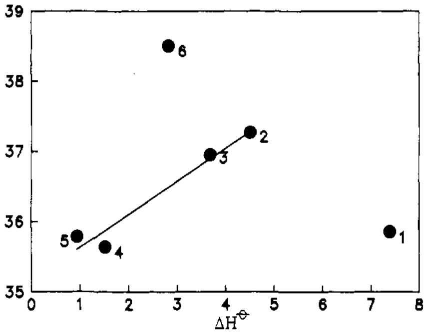

Figure 4. Plot of the entropy terms, $T\Delta S^{\ominus}$, for the protonation of the monophosphate dianions against the corresponding enthalpy changes, $\Delta H^{\ominus}$.

may be attributed to the loss of charge when the reactants form a product.[47] The magnitude of the enthalpy of desolvation exceeds the magnitude of the enthalpy of ligand–proton or –copper bond formation, for all the reactions of the present study, leading to a net unfavorable enthalpy contribution to the free energy of reaction. The latter turns out to be negative by virtue of the relatively large favorable entropy term.

2. Protonations. Figure 3 shows a plot of the pK_a (=log β_{011} obtained for the monophosphate dianions) against pK_{ROH}. This figure indicates a correlation between the acid strength of the protonated ligands and the electron-withdrawing or -releasing character of the substituents. It should be noted that such relationships are, in general, not necessarily linear.[48-50] In the case of Figure 3, linearity is evident over ligand numbers **2**–**6** but with ligand **1** (p-nitrophenyl phosphate) anomalous, the protonated form of the latter being a stronger acid than would be expected from the former linear correlation. (Please refer to Table II for ligand numbers.) In Figure 4 are plotted the entropy terms, $T\Delta S^{\ominus}$ for the protonation reactions against the corresponding enthalpy changes, $\Delta H^{\ominus}$. Ligands **2**–**5** appear to form an approximately linear relationship between these thermodynamic terms whereas ligands **1** (p-nitrophenyl phosphate) and **6** (methyl phosphate) are anomalous. The linear relationship is consistent with the view that the more ordered the water of hydration is on the dianionic ligand, the greater is the energy needed to disrupt that hydration water. (Compare with ref 51.) The protonation of ligand **1** (p-nitrophenyl phosphate) deviates from the linear relationship mainly because the enthalpy term is anomalously high. This is likely to be due to an anomalously small exothermic ligand–proton bond-forming enthalpy, which makes the protonation constant smaller than would be otherwise expected (Figure 3). This reduced phosphate–proton bond strength results from transmission across the aromatic ring of the electron-withdrawing effect of the nitro group. A likely additional factor is an electron-withdrawing mesomeric effect such as that which operates in p-nitrophenol and p-nitrobenzoic acid.[52] Given the foregoing considerations, the entropy of protonation of p-nitrophenyl phosphate may be expected to have a value comparable to that for phenyl phosphate and naphthyl phosphate. The observed lower value, however, indicates a smaller degree of disordering of water upon protonation than with the other two ligands. This may be a consequence of hydration of the nitro group due to its polar nature, which persists after protonation of the phosphate moiety has taken place.

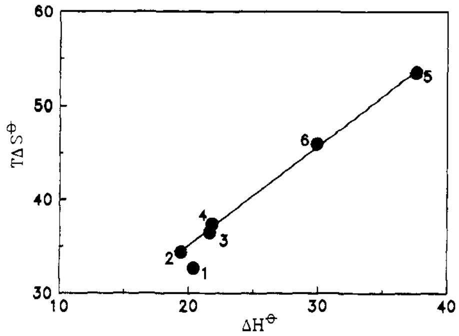

Figure 5. Plot of the entropy terms, $T\Delta S^{\ominus}$, for the formation of copper(II) complexes, ML, of the monophosphates against the corresponding enthalpy changes, $\Delta H^{\ominus}$.

The deviation of ligand **6** (methyl phosphate) from the straight line in Figure 4 may be attributed to the anomalously high entropy change of protonation. The high entropy can be explained in terms of the small size of the methyl phosphate anion in relation to the other ligands of the set. The resulting relatively strong electric field surrounding the anion produces a greater degree of electrostriction of the hydrated water molecules than exists with the other ligands. An additional factor contributing to the deviant nature of methyl phosphate may result from the electron-releasing character of the methyl group, which would tend to enhance the strength of the phosphate–proton bond, thereby making the net unfavorable enthalpy smaller than would be consistent with the other ligands of the present study.

3. Complexations. The linear plot in Figure 2 of log β_{110} for the copper complexes, ML, against pK_a for the protonated ligands suggests a linear free energy relationship.[16,17,53,54] Considering the latter in conjunction with Figure 3, it would appear that the electron-withdrawing or -releasing characters of the substituents on the ligands might constitute one of the factors determining the stability of the complexes. Greater clarity on the latter ensues, however, upon considering the enthalpy and entropy changes accompanying the complexation reactions.

In Figure 5 are plotted the entropy terms, $T\Delta S^{\ominus}$ for the copper complexation reactions against the corresponding enthalpy changes, $\Delta H^{\ominus}$ (cf. Figure 4). The points evidently fall close to a straight line but with significant deviation of ligand **1** (p-nitrophenyl phosphate). As in the case of protonations, the correlation of Figure 5 suggests that the more ordered the water is in the hydration shells of the reactants, the more energy is needed to disrupt that water structure. The complexation enthalpies (range: 19.4–21.8 kJ mol^{-1}) are substantially greater than the protonation enthalpies (1.52–7.39 kJ mol), and this may be attributed to significant desolvation not only of the dianionic ligand

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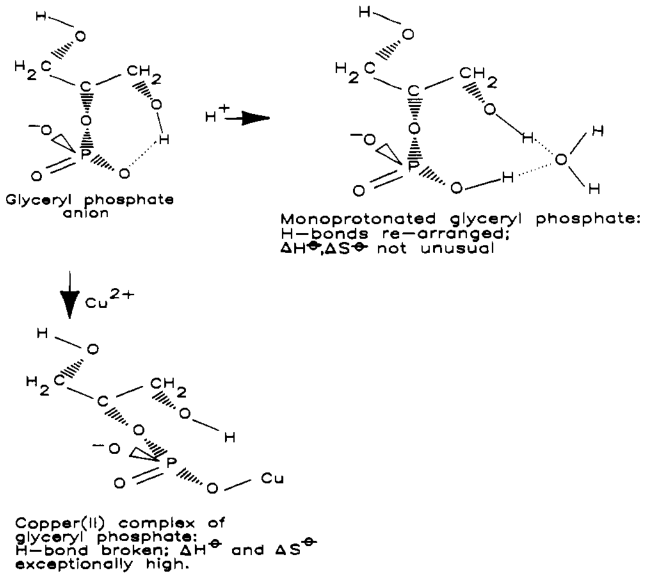

Figure 6. Speculative hydrogen-bonding schemes in the protonation and copper(II) complexation of glyceryl 2-phosphate.

but also of the copper(II) ion. The latter is supported by the work of Brintzinger[55] and of Aruga.[56] Brintzinger[55] concludes from infrared spectra that copper(II) and zinc(II) ions form predominantly inner-sphere complexes with methyl phosphate, diphosphate ($P_2O_7^{4-}$), monomethyl diphosphate ($CH_3P_2O_7^{3-}$) and ATP (adenosine 5′-triphosphate) whereas magnesium(II), calcium(II), manganese(II), cobalt(II), and nickel(II) form predominantly outer-sphere complexes with these ligands. Brintzinger[55] used thermodynamic measurements to confirm these conclusions with respect to complexation of methyl phosphate by calcium(II), magnesium(II), manganese(II), cobalt(II), nickel(II), and zinc(II) ions. Aruga[56] used Brintzinger's[55] thermodynamic data to deduce that in the complexation of methyl phosphate by manganese(II) or zinc(II) ions one molecule of water is displaced from the inner hydration shell of the cation. In the case of calcium(II) complexation, Aruga[56] concludes two water molecules to be displaced from the inner hydration shell. On the other hand, water is displaced from the outer hydration shell of magnesium(II), cobalt(II), and nickel(II) ions upon complexation by methyl phosphate, according to Aruga.[56] Thus Aruga's conclusions are at variance with those of Brintzinger[55] in respect of manganese(II) and calcium(II) ions. Although Brintzinger[55] omits copper(II) from his thermodynamic measurements and hence Aruga[56] does not consider this cation, Aruga's parameter, ΔS_p, may be estimated from the $\Delta S^\ominus$ value obtained from Table VI combined with the S° value for copper(II) ions given by Latimer et al.[57] The value obtained for ΔS_p is 17 cal deg^{-1} mol^{-1} (71 J K^{-1} mol^{-1}), which, by Aruga's argument, implies that at least two water molecules are displaced from the inner hydration shell of the copper(II) ion.

The horizontal deviation of ligand **1** (*p*-nitrophenyl phosphate) from the straight line in Figure 5 is approximately 6 kJ mol^{-1}, which is not substantially different from the horizontal deviation of this ligand from the straight line in Figure 4, namely 3–4 kJ mol^{-1}. As in the case of the protonation of ligand **1**, this anomalous complexation enthalpy, then, is likely to imply the significant operation of an electronic inductive effect of the nitro group possibly coupled with an electron-withdrawing mesomeric effect.[52] Further, the entropy term for the complexation of ligand **1** being smaller than that for ligand **3** (phenyl phosphate), suggests that water of hydration remains bound to the polar nitro group after the complex has been formed. This is analogous to the protonation reaction.

Figure 5 shows ligand **6** (methyl phosphate) to have substantially higher $\Delta H^\ominus$ and $\Delta S^\ominus$ values for complexing of copper(II) than do ligands **1–4**. As with the protonation of methyl phosphate, this may be explained by the small size of ligand **6** compared with the other ligands, which may have much more bulky substituents. Thus, electrostriction of the water bound to the ligand is the most pronounced in the case of ligand **6**, leading to a greater energy needed for disruption of this water and concomitantly greater disordering of the bound water structure than with ligands **1–4**.

Figure 5 shows the enthalpy and entropy of copper(II) complexation of ligand **5** (glyceryl phosphate) to be exceptionally high among the ligands considered in the present study. In contrast, Figure 4 shows the enthalpy and entropy of protonation of ligand **5** not to be unusual. Thus, in the formation of complexes with copper(II), desolvation of glyceryl phosphate requires more energy and there is a greater extent of disordering of the liberated water than is the case with protonation of this ligand. To explain this, it is postulated that there are intramolecular hydrogen bonds in the glyceryl phosphate dianion (Figure 6). Upon protonation, a new configuration of hydrogen bonds is formed in which a water molecule is involved. On the other hand, upon formation of a copper(II) complex molecule, one of the hydrogen bonds becomes completely broken. Thus, formation of the copper complex requires the net expenditure of a greater amount of energy than formation of the protonated species does. Further, there is a greater degree of internal freedom in the copper complex than in the protonated species.

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Registry No. *p*-Nitrophenyl phosphate, 330-13-2; 1-naphthyl phosphate, 1136-89-6; phenyl phosphate, 701-64-4; methyl phosphate, 512-56-1; α-D-glucose 1′-phosphate, 59-56-3; glyceryl 2-phosphate, 17181-54-3.

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