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Energetics of Complex Formation of Calcium and Magnesium Ions with O-Donor Ligands

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Thermodynamic stability constants of the 1:1 Ca^{2+} complex with phthalate ion at three different temperatures determined by the potentiometric method are reported and the energetics of complex formation compared with that of Mg^{2+} for this ligand as well as three other O-donor ligands.

Introduction

It is well known that calcium acts as a key regulatory ion and thus controls a wide variety of events at the intracellular and membrane level. The ability to accumulate magnesium intracellularly at concentrations of about 10^{-3}mol/l but to exclude calcium so that it only occurs at about 10^{-6}mol/l is a basic feature of all cells.[1] Clearly a comparative study of the energetics of hydration and interactions of a number of O-donor and N-donor ligands of varying denticity in aqueous solutions with Ca^{2+} and Mg^{2+} would deepen our understanding of the ionic processes governing biological systems. While presenting thermodynamic data on the association of the phthalate ion with Ca^{2+}, a review of available literature covering four ligands is made with a view to obtaining a reliable comparison of the thermodynamics of ion association for these two metal ions. Unlike the transition metal ions where ligand field effects come into play, in the case of alkaline-earth cations, the short-range forces are expected to be replusive and interactions essentially electrostatic. Nancollas has drawn attention to the rather high stability values reported for EDTA complexes of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} as well as the large difference of 7 to 9 kcal/mol in ΔH value between Mg^{2+} and the large-sized alkaline-earth cations[2]. Even if a change of coordination number from 4 to 6 is assumed in keeping with the variations of the entropy change governing ion association on going from Mg^{2+} to the larger cations, the large exothermic heat change for the latter does not reconcile with the NMR data of Kula *et al.*[3]. Nor is the correlation of ionic size and characteristics such as polarisability and hydration energies of alkaline-earth cations any more satisfactory for bidentate O-donor ligands. An abnormally large endothermic change has been reported for association of Ca^{2+} with phthalate ion based on solubility measurements[4] whereas potentiometric and direct calorimetric investigations have invariably indicated a less pronounced endothermicity for phthalates compared to the malonates for a number of cations[5].

Experimental

The details of apparatus used, preparation of the reagents and the quinhydrone electrode and silver–silver chloride electrode, the procedure adopted for potentiometric titrations and the mode of calculation of the association constants have been described previously[6] and the data are given in Table I.

Results and Discussion

In Table II the stability value at 25° C obtained in this work is compared with those reported by other workers. The earlier potentiometric value using a lead amalgam electrode for monitoring the metal ion activity is different mainly because of the changes in experimental conditions including the ionic strength of the medium and the mode of calculation of ionic activities. The value obtained by the solubility method is closer to but lower than our value and it is to be noted that the solubility method involves use of excess ligand concentrations and consideration of numerous ion pairs and usually leads to lower values as has been observed by Nancollas in the case of formates and acetates[8] of alkaline-earth cations. Dunsmore and Speakman[9], based on a comparative study of four different methods applied to determination of acid dissociation constants suggest that careful pH measurements could yield very reliable results. The present values are possibly more accurate, in view of the fair

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TABLE I. Stability Constants of Ca^{2+} Phthalate Complex. [Base]: 0.4965 M, [Ligand]: 0.0100 M, [$CaCl_2$]: 0.0200 M.

Titre (ml)	E (mV)	I × 10^3	[HA^-] × 10^3	[A^{2-}] × 10^3	[MA] × 10^3	K ($l\ mol^{-1}$)
Temp: 20°C, E° = 47.48 mV						
0.04	15.10	70.85	7.948	0.778	0.791	429
0.06	14.44	71.28	7.705	0.978	0.941	409
0.08	13.83	71.70	7.391	1.192	1.116	401
0.12	12.76	72.54	6.627	1.626	1.534	411
0.14	12.25	72.96	6.207	1.860	1.746	412
0.16	11.76	73.38	5.769	2.095	1.967	416
0.18	11.26	73.80	5.321	2.350	2.172	413
0.20	10.76	74.22	4.862	2.612	2.375	410
0.22	10.27	74.64	4.396	2.861	2.596	413
0.24	9.73	75.06	3.925	3.159	2.769	402
						Av. 416
Temp: 25°C, E° = 47.47 mV						
0.10	12.80	72.12	6.991	1.332	1.412	467
0.12	12.23	72.54	6.606	1.569	1.603	453
0.14	11.72	72.96	6.190	1.789	1.827	457
0.16	11.20	73.38	5.758	2.033	2.034	452
0.18	10.70	73.80	5.311	2.273	2.254	452
0.20	10.20	74.22	4.855	2.519	2.473	451
0.22	9.65	74.64	4.392	2.819	2.641	434
0.24	9.12	75.06	3.922	3.088	2.843	431
0.26	8.59	75.47	3.447	3.328	3.076	437
0.28	7.99	75.89	2.970	3.615	3.264	431
						Av. 447
Temp: 35°C, E° = 47.43 mV						
0.08	12.18	71.70	7.323	1.086	1.259	528
0.14	10.57	72.96	6.169	1.665	1.961	550
0.16	10.05	73.38	5.741	1.880	2.196	550
0.18	9.47	73.80	5.302	2.157	2.375	523
0.20	8.95	74.22	4.848	2.393	2.602	521
0.22	8.42	74.64	4.386	2.638	2.825	518
0.24	7.86	75.06	3.918	2.903	3.029	510
0.26	7.26	75.47	3.445	3.195	3.210	495
						Av. 524

agreement reported in the case of zinc phthalate with the results of precise measurements using the hydrogen electrode[10].

The success of the electrostatic approach in predicting parameters such as lattice energies, heats of hydration and the activity coefficients of bivalent alkaline-earth cations in halide salt solutions and their poor complexing power with respect to neutral ligands has led to the assumption that the interactions involved in ion-association reactions are essentially electrostatic. If this were to be the case, one should expect a linear variation of the free energy change for the metal complex formation with the ionic potential and the order of stability should be the inverse order of the ionic radius[11]. While the dissociation constants of some of the complexes of alkaline-earth cations fall in this sequence[12], such simple correlations fail in a number of instances[13]. The uncertainty about Mg^{2+} in the alkaline-earth series of cations has given rise to a number of generalisations: (i) In the case of association reactions (*e.g.*, the hydroxide ion) following the stability sequence Mg > Ca > Sr > Ba, the size of the

TABLE II. $Log_{10}K$ Values of CaPh at 25 °C.

Method	$Log_{10}K$	Reference
Potentiometry using amalgam electrode of the third kind	1.07 (Ionic strength of medium 0.15)	7
Solubility	2.42	4
Potentiometry using Quinhydrone electrode	2.64	Present work

anionic ligands is such that the stability is a direct function of the ionic potential and that the non-bonded interactions between the atoms of the ligand are not significant. (ii) In the case of ion-association reactions conforming to the stability order $Mg < Ca > Sr > Ba$ as in the case of malate and tartrate complexes, the smallness of the magnesium ion results in the so called 'crowding effect' because of the non-bonded interactions among the ligand atoms. (iii) Ion-association reactions conforming to the former stability order but where the decrease in stability is not linear with the ionic potential; this effect is attributed to the attenuation of the repulsive forces between the nonbonded atoms on account of chelation. The analysis of the stability order is further complicated by the possibility that the stability data could refer to either of the two stages of the process of complex formation, the first stage corresponding to the formation of an ion-pair $M(H_2O)A$ and the second to the formation of a more covalent complex $MA(H_2O)_m$. While the phthalate anion might find it easier to displace the water of hydration from the larger calcium ion compared to Mg^{2+}, it is seen from Table III that malonate ion does not encounter any such difficulty in forming a more stable complex with Mg^{2+} than with Ca^{2+}. To see if the differences in hydration characteristics could account for the differences in the stabilities, it is necessary to consider the thermodynamics of hydration of Mg^{2+} and Ca^{2+}. Goldman and Bates[14] have calculated the thermodynamic functions for hydration considering the solvent as consisting of discrete molecules in the primary hydration shell and have concluded that for both the magnesium and calcium ions best agreement between the theoretical thermodynamic transfer functions from the standard state in the gas to the standard state in solution and the experimental values were obtained only if the same number of water molecules, *i.e.*, 5 is assumed to be involved in the primary hydration shell. The difference in $T\Delta S_t$ values between Mg^{2+} and Ca^{2+} is not appreciable and is less than 1.7 kcal/mol, evidently because the more pronounced perturbing effect on the surrounding solvent in the case of Mg^{2+} on account of stronger electrostatic field is offset by the loss of space available for primary hydration compared to Ca^{2+} which has a larger radius. Having ruled out differences in hydration characteristics between Ca^{2+} and Mg^{2+} as a principal basis for the explanation of the differences in the stabilities of phthalate complexes it would be worthwhile to consider the changes in enthalpy and entropy functions governing the association reactions concerned. It can be seen from Table III that in association reactions with unidentate O-donor ligands the hydration shell of Mg^{2+} is more strongly preserved than in the case of Ca^{2+} as reflected in the differences in entropy values between the metal ions in their association reactions with both formate and acetate ions. In the case of bidentate O-donor ligands the entropy effect is accentuated both for Ca^{2+} and Mg^{2+} on account of greater charge neutralisation and consequent breakdown of the co-ordinated water molecules compared to the relatively polar complexes formed in interactions with unidentate ligands. However, unlike the malonates of magnesium and calcium which have very nearly the same entropies of association, the ΔH and ΔS values vary appreciably for the phthalates. In so far as association of Ca^{2+} with phthalate compared to the malonate is concerned, the less pronounced endothermicity and slightly lesser values of entropy of association are in keeping with the pattern observed in the case of a number of other bivalent metal ions including the transition metal ions[5, 15]. The greater endothermicity governing association of phthalate ion with Ca^{2+} com-

TABLE III. Thermodynamic Parameters.

MA	ΔG at 25 °C (Kcal mol^{-1})	ΔH (Kcal mol^{-1})	ΔS (Cal deg^{-1} mol^{-1})	Ref.
Mg^{2+} H CO_2^-	−1.94	−1.77	0.6	8
Ca^{2+} H CO_2^-	−1.94	+0.98	10	8
Mg^{2+} CH_3 CO_2^-	−1.69	−1.52	0.6	8
Ca^{2+} CH_3 CO_2^-	−1.69	+0.91	8.7	8
Mg^{2+} malonate$^-$	−3.90	+3.40	23.9	7
Ca^{2+} malonate$^-$	−3.42	+4.45	26.4	4
Mg^{2+} Phthalate$^-$	−3.44	+0.00	11.2	6
Ca^{2+} Phthalate$^-$	−3.61	+3.14	21.8	

pared to Mg^{2+} and similarly the more pronounced entropy effects are in keeping with the greater access the smaller Mg^{2+} will have in its interactions with the anionic ligand compared to Ca^{2+} and the changes in the lability of ligands in the free state compared to the metal complex. In the present study, we note that unlike in the case of the unidentate ligands where ΔG values vary in accordance with the ionisation constants of the ligand acid anions, the situation is less clear for the bidentate ligands as there is an inversion in the order of the two dissociation constants for malonic and phthalic acids. Bell[16] has pointed out the difficulty in correlating even protolytic equilibrium constants measured in polar solvents with quantitative and even qualitative considerations based on the molecular structure of the solutes, in view of the complications introduced by the solute–solvent interactions and recommends that interpretations are best confined to ΔG at a single temperature instead of dealing with separate contributions of ΔH and ΔS. While it is usually possible to explain variations in ΔH and ΔS in terms of factors like charge neutralisation, chelate effect, lability of the ligand in the free state compared to the complex, the need for caution in extending molecular effects like the 'crowding effect' and selecting the basic experimental data for comparisons cannot be adequately emphasised. For example the abnormally high endothermic change reported for association of phthalate ion with Cu^{2+} based on solubility measurements is not borne out by precise measurements employing direct calorimetry[18], although even calorimetric values have been questioned[19]. It would seem necessary to carry out experiments coverning a large number of O-donor ligands and O- and N-donor ligands with a view to determining precise ΔG values at a single temperature and obtaining ΔH values by direct calorimetry and deriving the ΔS for the ion association processes involving Mg^{2+} and Ca^{2+} for a better understanding of their roles in biological systems.

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