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Note

THERMODYNAMICS OF METAL–PHENOXYMETHYLPENICILLIN SYSTEMS

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The usefulness of penicillins is well recognised [1–4] but their interaction with metals is poorly documented [5,6]. This note concerns the determination of the thermodynamics of the UO_2(II), Fe(III), Al(III), Cr(III) and Sn(IV) phenoxymethylpenicillin, using the Bjerrum–Calvin titration technique [7] together with different computational methods.

EXPERIMENTAL

All the chemicals used were of analytical grade. Solutions of phenoxymethyl penicillin (Na^+) and metal nitrates were prepared in cation free distilled water. The latter solutions were standardised by the standard methods. A Beckman pH-meter, model H-2, with a sensitivity of ±0.5 and calibrated with suitable buffers, was used for pH-metrically titrating the solutions (a) 4×10^{-3} M HNO_3, (b) 4×10^{-3} M HNO_3, 1×10^{-3} M ligand, and (c) 4×10^{-3} M HNO_3, 1×10^{-3} M ligand, 2×10^{-4} M metal ion. A constant ionic strength of 0.1 M was maintained by adding an appropriate quantity of potassium nitrate solution. The shapes of the curves, after correction following Van Uitert and Haas [8], and for volume of titrant (0.1 M NaOH) added, were as usual.

RESULTS AND DISCUSSION

The formation function of the system, $\bar{n}$, was evaluated from the horizontal distance between the reference curve (ligand curve) and the curve determined in the presence of a metal ion. The horizontal distance divided by the total metal ion concentration gave $\bar{n}$. Phenoxymethylpenicillin was taken in five-fold excess as compared to the metal ion to avoid the hyrolysis of metal ion. At any pH, the free ligand exponent was calculated from Bjerrum's equation

$$[L] = \frac{T_L - [ML] - 2[ML_2] - 3[ML_3] - \ldots - N[ML_N]}{1 + [H^+]/K^*}$$

TABLE 1

Protonation constant of phenoxymethylpenicillin, metal–ligand stability constants and thermodynamic functions

Metal ion	Protonation constant/ metal ligand stability constant	Temp.		ΔG^0 (kcal mole^{-1})		ΔH^0 (kcal mole^{-1})	ΔS^0 (kcal mole^{-1})
		25°C	35°C	25°C	35°C	at 35°C	at 35°C
	$\log {}^{\mathrm{P}}K^{\mathrm{H}}$	7.25	6.75				
UO_2^{2+}	$\log k_1$	7.50	7.00				
	$\log k_2$	6.00	5.50				
	$\log k$	6.75	6.25				
	$\log k_1/k_2$	1.50	1.50				
	$\log \beta_2$	13.50	12.50	−18.41	−17.62	−1.40	+52.64
Fe^{3+}	$\log k_1$	7.10	7.40				
	$\log k_2$	3.50	3.60				
	$\log k$	5.90	5.40				
	$\log k_1/k_2$	2.60	3.80				
	$\log \beta_2$	10.60	11.00	−14.45	−15.50	+0.68	+72.28
Al^{3+}	$\log k_1$	8.20	8.90				
	$\log k_2$	5.00	4.50				

	log k	6.60	6.70				
	log k_1/k_2	3.20	4.40				
	log β_2	13-20	13.40	−18.00	−18.89	+0.27	+60.44
Cr^{3+}	log k_1	6.75	6.65				
	log k_2	5.00	4.35				
	log k	6.30	5.40				
	log k_1/k_2	1.75	2.30				
	log β_2	11.75	11.00	−16.02	−15.50	+1.20	+54.23
Sn^{4+}	log k_1	7.17 [a] (7.25) [b]	7.39 [a] (7.20) [b]				
	log k_2	6.48 [a] (6.35) [b]	6.51 [a] (6.50) [b]				
	log k_3	5.62 [a] (5.65) [b]	3.61 [a] (3.50) [b]				
	log k_4	3.39 [a] (3.40) [b]	3.00 [a] (3.10) [b]				
	log k_1/k_2	(–) [a] (0.90) [b]	(–) [a] (0.90) [b]				
	log β_4	22.66 [a] (22.65) [b]	20.51 [a] (20.30) [b]	−30.90	−28.91	−1.82	+87.95

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[a] Pointwise calculation method.

[b] Bjerrum integral method.

where K_* is the dissociation constant of phenoxymethylpenicillin, which was evaluated with the help of the expression

$$\log {}^{\mathrm{P}}K_n^{\mathrm{H}} = B + \log \frac{\bar{n}_{\mathrm{H}} + (n-1)}{(n - \bar{n}_{\mathrm{H}})}$$

where B = pH-meter reading, ${}^{\mathrm{P}}K^{\mathrm{H}}$ = practical proton–ligand stability constant (${}^{\mathrm{P}}K^{\mathrm{H}} = 1/K_*$)

On examination of the pH-metric curves, the metal ligand curve was found to be below the ligand curve, indicating the occurrence of complexation. The gradual increase of the $\bar{n}$ value pointed to the involvement of the anionic form of phenoxymethylpenicillin in complexation. The $\bar{n}$ value approached ~2 for UO_2(II), Al(III), Fe(III) and Cr(III) phenoxymethyl penicillin systems and ~4 for Sn(IV) phenoxymethylpenicillin, pointing to the existence of 1:2 and 1:4 stoichiometry, respectively.

Metal–ligand stability constants were read from the plot of pL vs. $\bar{n}$ which nearly satisfied the conditions of Bjerrum's integral method. For the Sn(IV) phenoxymethylpenicillin system ($\log k_1/k_2$ being + 0.90), this method could not be applied. The pointwise calculation method together with the following equations was used for the Sn(IV) phenoxymethylpenicillin system.

$$\log k_1 = \mathrm{pL} + \log \frac{\bar{n}}{(1-\bar{n})}$$

$$\log k_2 = \mathrm{pL} + \log \frac{(\bar{n}-1)}{(2-\bar{n})}$$

$$\log k_3 = \mathrm{pL} + \log \frac{(\bar{n}-2)}{(3-\bar{n})}$$

$$\log k_4 = \mathrm{pL} + \log \frac{(\bar{n}-3)}{(4-\bar{n})}$$

The overall changes in free energy (ΔG^0), enthalpy (ΔH^0) and entropy (ΔS^0) have been determined using well-known temperature coefficients and the Gibbs–Helmholtz equation. The data reveal a decrease in the values of $\log {}^{\mathrm{P}}K^{\mathrm{H}}$, $\log k_1$ and $\log k_2$ with the increase of temperature for the UO_2(II) and Cr(III) phenoxymethylpenicillin systems. This indicates that a low temperature is favourable for complexation because of the decrease in the number of collisions with the decrease in kinetic energy of molecules and hence their stabilities are lowered. For the Sn(IV) phenoxymethylpenicillin system, $\log k_1$, $\log k_2$, $\log k_3$ and $\log k_4$ values also decrease with increase of temperature. In the case of the Fe(III) and Al(III) phenoxymethylpenicillin systems, the values of $\log k_1$ and $\log k_2$ increase with increase of temperature, indicating that higher temperatures favour the reaction. The formation of complexes, with the exception of the Fe(III) and Al(III) phenoxymethylpenicillin reactions, which are endothermic in nature (providing an explanation for the increase in the formation constant with increase in temperature), are exothermic reactions which support the decreasing value of the formation constants with increase in temperature.

The free energies of formation (ΔG^0) for the Fe(III) and Al(III) phenoxymethylpenicillin systems have higher negative values as the temperature increases, showing that complex formation is a spontaneous process; in other systems, less negative values of ΔG^0 have been observed with increase of temperature. The entropy values (ΔS^0) are positive in all cases, indicating a favourable entropy for formation of complexes (Table 1).

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