Thermodynamic Considerations in Co-ordination. Part XVI.[1] Formation Constants for the Cyclopentylamine– and Cyclohexylamine–Proton, Cobalt(II), Nickel(II), Copper(II), and Zinc(II) Systems

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Glass electrode potentiometric studies at 37 °C, I = 150 mM (Na)ClO_4 have been used to study cyclopentylamine-(pent) and cyclohexylamine(hex)–proton–metal^{2+} ion systems. The β values for complex formation obey the Irving–Williams series, are considerably higher than those of comparable ammonia complexes, and have the general order pent > hex > NH_3. A computer model calculation was used to establish that the concentrations of Ni^{2+} mono and bis complexes present at equilibrium qualitatively follow the pattern of carcinostatic activity of their analogous Pt^{2+} complexes.

SINCE the first report of the antitumour properties of *cis*-dichlorodiammineplatinum(II) [2] there have been three simultaneous developments. First, the medical disciplines have taken this drug as far as phase II clinical trials in man;[3] secondly, biophysical researches into the site of its activity are currently favouring a cross-linking action involving cellular DNA;[4] and thirdly, chemical research has produced compounds that are thirty to forty times more active than *cis*-$Pt(NH_3)_2Cl_2$ against the ADJ/PC6A murine plasma cell tumour (compare the therapeutic indices of *cis*-$Pt(NH_3)_2Cl_2$, 8·1; *cis*-Pt(cyclopentylamine)$_2Cl_2$, 235·7; and *cis*-Pt(cyclohexylamine)$_2Cl_2$, >267).[5]

This potentiometric investigation is aimed at elucidating the changes brought about when a co-ordinated ammonia is substituted by a cyclopentylamine or cyclohexylamine ligand, these changes producing an enhanced therapeutic index and a drop in toxicity. Unfortunately, the insolubilities of the Pt^{II} and Pd^{II} cyclopentylamine or cyclohexylamine systems completely preclude any potentiometric investigations until such times as electrodes are reproducible to microvolts and thus micromolar solutions can be studied. Meanwhile, we have investigated Ni^{II} as a model of the Pd^{II} and Pt^{II} group (albeit still a very insoluble model system) and also Co^{II}, Cu^{II}, and Zn^{II} being nearest neighbours to Ni^{II} in the first transition series.

Our established potentiometric approach was applied whereby a glass electrode was used to determine the pKs of the ligands and then this electrode and pK were employed to follow the concentrations of free hydrogen ions, of protonated ligand and thus of complexed ligand present during a titration.[6] Experimental conditions were chosen to simulate blood plasma, 37 °C and I = 150 mM in (Na)ClO_4.

EXPERIMENTAL

Cyclopentylamine (Koch–Light pure grade) (Found: C, 70·1; H, 13·2; N, 16·2. Calc. for $C_5H_{11}N$: C, 70·6; H, 12·9; N, 16·5%), and cyclohexylamine (Koch–Light puriss. grade) (Found: C, 72·5; H, 13·2; N, 14·0. Calc. for $C_6H_{13}N$: C, 72·0; H, 13·4; N, 13·8%) were used. Other reagents and formation constant measurements were as described in ref. 7.

RESULTS AND DISCUSSION

The reactions between amine ligands, metal ion, and protons (A, B, and H respectively) can be represented by equation (1), the formation constant for this generalised

$$pA + qB + rH \rightleftharpoons A_pB_qH_r \text{ (charges omitted)} \quad (1)$$

reaction being β_{pqr}. Our values of log β_{pqr} are given in the Table.

Log β_{pqr} for the species $A_pB_qH_r$ at 37 °C and I = 150 mM (Na)ClO_4. A = amine, B = metal^{2+} ion, H = H^+, s = standard deviation in log constants, n = number of titration readings for each series

B	p	q	r	log β	s	n	Complexing — log h range
A = Cyclopentylamine							
	0	0	−1	−13·63 *	0·01	30	
	1	0	1	10·033	0·004	229	
Co	1	1	0	5·700	0·09	54	2·2—4·6
Ni	1	1	0	6·824	0·06	30	2·2—3·4
	2	1	0	9·06	0·45		
Cu	1	1	0	8·006	0·07	27	2·4—3·9
	2	2	−2	12·013	0·10	27	
Zn	1	1	0	4·164	0·53	56	2·2—6·1
	2	1	0	7·832	0·52		
	2	1	−2	4·465	0·13		
A = Cyclohexylamine							
	1	0	1	9·930	0·006	241	
Co	1	1	0	5·276	0·13	48	2·2—4·7
Ni	1	1	0	5·940	0·12	50	2·2—4·1
	2	1	0	8·18	0·45		2·2—4·1
Cu	1	1	0	7·674	0·06	48	2·3—4·3
Zn	1	1	0	4·599	0·13	70	2·5—6·6

A = Ammonia has log β_{101} = 9·47 (H^+), log β_{110} = 2·11 (Co), 2·80 (Ni), 4·11 (Cu), and 2·37 (Zn).

* pK_W at 37 °C, 150 mM (Na)ClO_4.

Protonations.—Our concentration protonation constants even though they are somewhat lower than the two values available from the literature (10·65 at 25 °C, I = 0 for cyclopentylamine [8] and 10·66 at 24°, I = 0·001M for cyclohexylamine [9]), are still larger than the pK of the parent ligand (9·47 for ammonia [10]).

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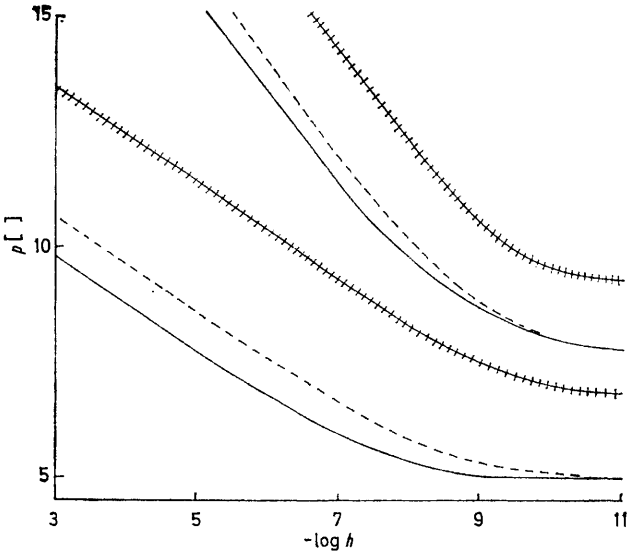
Complexing Reactions.—This report is the first potentiometric study of the metal complexes formed by cyclopentylamine (pent) and cyclohexylamine (hex) and therefore the Table quotes published formation constants for related ammonia complexes as a comparison; it may be seen that the complexing order for cobalt, nickel, and copper follows the pK order, pent > hex > ammonia whereas zinc has hex > pent > ammonia.

The limits to our studies were (i) the comparatively lower solubility of the ligands (*cf.* NH_3); both cyclopentylamine and cyclohexylamine have maximum solubilities of 100 mM; (ii) the complexing reactions are seriously challenged by hydrolysis producing insoluble complexes [with the exception of $Zn(pent)_2(OH)_2$ for which we were able to derive a constant in solution] (see Table).

The solubility problems preclude *pro tem.* mixed ligand, ternary complex, studies related to anticancer drugs. Nevertheless there are two points pertinent to this subject that arise from our results. (i) The most soluble systems are the cobalt- and copper–cyclohexylamine. (ii) Log β_1 values obey the Irving–Williams series, *i.e.* apart from a general enhancement of the stability of all complexes compared to ammonia, the cyclic rings introduce nothing unusual into the expected complexing order.

Model Studies.—*cis*-Dichlorodicyclopentylamineplatinum(II) is a superior anticancer drug to *cis*-dichlorodicyclohexylamineplatinum(II) (as far as side reactions in animals are concerned) which in turn is far superior to *cis*-dichlorodiammineplatinum(II) (in terms of therapeutic indices). For the reasons already stated, formation constants for chloro complexes are not available, nevertheless we set up a COMICS computer model [11] of the equilibria involved when $Ni(amine)_2^{2+}$ (total concentration = 10 μM) was allowed to equilibriate at various pHs. The results are plotted in the Figure. It is important to note that the order of apparent drug effectiveness pentylamine > hexylamine > ammonia coincides with the amount of mono and bis nickel complexes present at physiological pHs. However, more evidence would be desirable before one can be justified in making the sweeping assumption that platinum complexes *in vivo* have solution equilibria analogous to nickel complexes *in vitro*. Further, it must be remembered that our model calculations are only pertinent when the platinum complexes have reached equilibrium



COMICS model of distribution of cyclopentylamine, cyclohexylamine, and ammonia (20 μM) between H^+ and Ni^{2+} (10 μM) at 37 °C, I = 150 mM (Na)ClO_4; lower curves = NiA^{2+}, upper curves = NiA_2^{2+}, —— pentylamine, — — — hexylamine, +++ = ammonia

concentrations [platinum(II) is kinetically more inert than palladium(II) or nickel(II)]. Clearly there is a need for more ternary complex studies of amines which are more soluble and more strongly complexing than cyclopentylamine and cyclohexylamine.

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