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Stability of the Histamine Chelates[1]

BY B. L. MICKEL AND A. C. ANDREWS

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The structural requirements for histaminic activity have been summarized by Hofmann.[2] The majority of active compounds are those capable of forming a six-membered ring between a 2-amino side chain nitrogen, a tertiary nitrogen of an aromatic nucleus, and some polar center. Niemann and Hays[3] suggested that one characteristic of the histamine-active molecule was its ability to undergo hydrogen bonding between basic nitrogen atoms. A related consideration is that of metal chelate formation. The histamine-active structure also is capable of forming a six-membered ring about a metal ion such as that of a metal–protein or metal activated enzyme.

In order to act as a mediator of binding between small molecules and proteins, a metal ion must be capable of forming an independent complex with the small molecule.[4] Preliminary to mediation binding studies, the nature and stabilities of the Cu^{II}, Ni^{II} and Co^{II} chelates of histamine, 4(5)-(2-aminoethyl)-imidazole, were investigated. The consecutive formation constants for these chelates, at 25°, were reported previously.[5] A maximum of three histamine molecules was indicated to be bound by nickel and cobaltous ions in contrast to copper which added two histamine ligands. The separate contributions to chelate stability of the imidazole and amino nitrogen atoms are reported in this paper. The structures and stabilities of the chelates have been considered in terms of the successive formation constants and the thermodynamics of complex formation.

Experimental

The potentiometric technique of Bjerrum[6] was used. Final values of the formation constants were obtained by successive approximation. In solving for the constants of imidazole, temporary constants were chosen which were small for k_N; this is necessary since the approximation equations for the first and last constants are limiting expressions, only.

Imidazole was obtained from the Eastman Kodak Co., Rochester, N. Y., and was purified by recrystallization from benzene. Recrystallization yielded a product of m.p. 89.0–89.5° (lit. 90°). Nitrogen analysis indicated a purity of 98.4%. Approximately 3 M solutions were made up in 0.1 N KCl and were standardized potentiometrically.

Results

Logarithmic values of the successive formation constants, k_n, are listed in Table I. All constants were determined at ionic strength 0.135.

TABLE I

SUCCESSIVE CONSTANTS FOR THE REACTIONS OF HISTAMINE AND RELATED COMPOUNDS WITH VARIOUS CATIONS, 0 AND 25°

Base	Cation	log k_n			
	n =	1	2	3	4
Ethylamine	H^+	10.8[a]			
		11.4			
Imidazole	H^+	7.09			
		7.63			
	Cu^{II}[b]	4.20	3.47	2.84	2.0
		4.72	3.90	3.28	2.3
	Ni^{II}[c]	2.94	2.41	1.99	1.3
		3.36	2.79	2.24	1.3
Histamine[d]	H^+	9.88	6.13		
		10.5	6.63		
	Cu^{II}	9.55	6.48		
		10.1	6.90		
	Ni^{II}	6.88	5.03	3.09	
		7.24	5.25	3.26	
	Co^{II}	5.27	3.68	2.03	
		5.37	3.81	2.07	

[a] Upper values at 25°, lower values at 0°. [b] These values compare to 4.36, 3.57, 2.85 and 2.05 at 22.5° as converted from the intrinsic constants of J. T. Edsall, G. Felsenfeld, D. S. Goodman and F. R. N. Gurd, THIS JOURNAL, **76**, 3054 (1954). [c] It is not possible to determine whether n_{max} = 4 or 6 for nickel–imidazole by means of the Bjerrum technique. Recent polarographic data of N. C. Li, T. L. Chu, C. T. Fujii and J. M. White, *ibid.*, **77**, 859 (1955), indicate that the hexacovalent complex is formed. Values of 3.27, 2.68, 2.15 and 1.65 were published for the first four constants at 25°. [d] A. Albert, *Biochem. J.*, **50**, 693 (1952), has cited log k_1k_2 values for the copper, nickel and cobaltous chelates of 16.2, 11.7 and 8.7, respectively. Values of about 8.6 were calculated for the histamine–Co^{II} system by J. Z. Hearon, D. Burk and A. L. Schade, *J. Natl. Cancer Inst.*, **9**, 337 (1949). No constants were listed for uptake of the third histamine ligand by hexacovalent ions.

Enthalpy and entropy changes for the ionization of ethylamine, imidazole and the corresponding groups of histamine are similar. The heat of formation of primary aminium ion is -9 kcal. mole^{-1} in both histamine and ethylamine; the corresponding entropy changes are approximately 15 and 19 e.u. Heats and entropies for the protonation of imidazole nitrogen are -8 to -7 kcal., and about 4 e.u. in the mono- and diacidic bases.

The probable structures of the histamine chelates may be described in terms of the successive formation constants. The difference between these consecutive constants is much larger for bis-histamine–Cu(II) ion than in the corresponding chelates of nickel and cobalt. This indicates the expected steric opposition to formation of the square planar copper bonding configuration. In bis-trimethylenediamine–Cu(II), the difference between log k_1 and log k_2 is 2.60.[7] If log k_2 for the trimethylenedia-

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[1] Portion of a dissertation presented by B. L. Mickel as partial fulfillment of the requirement for the degree Doctor of Philosophy in chemistry at Kansas State College, 1955. This investigation was supported by a research grant G 3920 from the National Institutes of Health, Public Health Service.

[2] Klaus Hofmann, "Imidazole and its Derivatives," Interscience Publishers, New York, N. Y., 1953.

[3] C. Niemann and J. T. Hays, THIS JOURNAL, **64**, 2288 (1942).

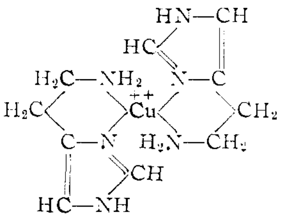
[4] Irving M. Klotz and W. C. Loh Ming, *ibid.*, **76**, 805 (1954).

[5] B. L. Mickel and A. C. Andrews, *ibid.*, **77**, 323 (1955).

[6] J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941, pp. 198–219.

[7] H. Irving, R. J. P. Williams, D. J. Ferrett and A. E. Williams, *J. Chem. Soc.*, 3494 (1954).

mine chelate is reduced by log 2, the statistical correction if only a *trans* species were formed, then log k_1 minus log k_2 becomes 2.90. This compares to 3.07 as observed for the histamine–copper system. The large difference between constants suggests that, in bis-histamine–Cu(II), the imidazole groups are *trans* to one another.



In contrast to copper, differences between constants are small for the tetracovalent nickel and cobaltous chelates. These intermediate complexes must exist in an ionic bonding configuration.

The contributions to chelate stability of ring and side-chain nitrogen atoms were estimated in terms of the corresponding metal ammines and imidazole complexes. The stabilities of the methylamine–cadmium complexes and the cadmium ammines are nearly identical.[8] The same relationship has been observed in the case of silver–ethylamine.[9] Formation constants for the metal ammines[6] were used in estimating the binding energy of histamine side-chain nitrogen. The gain in stability through formation of the n^{th} chelate ring, $\Delta(\Delta F)_n$, was calculated as

$$\Delta(\Delta F)_1 = \Delta F_1^{\text{hn}} - [\Delta F_1^{\text{im}} + \Delta F_2^{\text{NH}_3}] \qquad (1)$$

$$\Delta(\Delta F)_2 = \Delta F_2^{\text{hn}} - [\Delta F_3^{\text{im}} + \Delta F_4^{\text{NH}_3}] \qquad (2)$$

In the above, hn and im designate the energies of formation of the n^{th} histamine or imidazole species. The free energy values for imidazole and ammonia were chosen such that $\Delta(\Delta F)_n$ was minimized. For copper–histamine at 25°, $\Delta(\Delta F)_1$ is -2.7 kcal. mole^{-1}, and $\Delta(\Delta F)_2$ is -2.3 kcal. Corresponding values for nickel–histamine are -2.5 and -2.7 kcal. mole^{-1}.

Thermodynamic quantities, calculated from temperature data, may be of principal significance in a comparative sense. The increased stability of the histamine chelates is indicated to be in consequence of the more positive entropy term. Average values of -7 kcal. mole^{-1} and 12 e.u. were calculated for the heats and entropies in the stepwise formation of $Cu^{++}(hn)_2$; these quantities are -4 kcal. and 10 e.u. for $Ni^{++}(hn)_3$. Under the same conditions, the averages for $Cu^{++}(im)_4$ were -6 kcal. and about -7 e.u. Corresponding values for $Ni^{++}(im)_4$ were -4 kcal. and -4 e.u. In general, small negative entropies of formation are reported for the various metal ammines.

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The Magnetic Susceptibilities of Chlorine Trifluoride, Bromine Trifluoride, Bromine Pentafluoride and Iodine Pentafluoride[1]

BY MAX T. ROGERS, MORTON B. PANISH AND JOHN L. SPEIRS

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As part of a general study of the physical properties of the halogen fluorides we have determined the magnetic susceptibilities of chlorine trifluoride, bromine trifluoride, bromine pentafluoride and iodine pentafluoride. These substances were investigated in the liquid phase at room temperature using the Gouy method. They are all diamagnetic and the measured gram susceptibilities are shown in Table I at several field strengths. The average value, expressed as a molar susceptibility, is shown for each compound along with the molar susceptibility calculated from the theoretical ionic susceptibilities of Angus.[2] The compounds are somewhat less diamagnetic than calculated, as noted also for other polyfluorides which have been investigated.[3] The differences may result from the fact that the bonds are partly covalent in character and the paramagnetic term of the Van Vleck equation for the diamagnetic susceptibility of a polyatomic molecule[4] has become significantly large in these molecules.

TABLE I

SPECIFIC AND MOLAR SUSCEPTIBILITIES OF SOME HALOGEN FLUORIDES AT ROOM TEMPERATURE

H, oersteds	$X \times 10^6$			
	ClF_3	BrF_3	BrF_5	IF_5
4,770	......	−0.267	−0.256	−0.266
7,360	−0.289	.250	.257	.262
9,070	.284	.246	.259	.265
10,500	.286	.236	.258	.261
11,600	.287	.240	.260	.257
X_{gm} (av.)	−0.287	−0.248	−0.258	−0.262
X_{M} (obsd.)	−26.5	−33.9	−45.1	−58.1
X_{M} (calcd.[2])	−30.1	−39.4	−48.1	−58.4

Experimental

Apparatus.—The Gouy balance, the electromagnet and the technique used have been described.[5] A susceptibility tube of the compensated type was constructed of Vycor, which resists the corrosive action of the halogen fluorides fairly well for short periods. Fluorothene tubes were unsuccessful since they absorbed halogen fluorides to too great an extent. The compounds were distilled directly into the susceptibility tube by use of auxiliary apparatus also constructed of Vycor. The tube was closed with a Vycor ground joint while measurements were made. The distillation in Vycor apparatus was found to be necessary in order to eliminate ferromagnetic impurities. All measurements were made at room temperature (25–30°).

Materials.—The apparatus used for purification and handling of halogen fluorides has been described and the purity of the bromine pentafluoride and iodine pentafluoride

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(1) Physical properties of the halogen fluorides. III. For preceding article see M. T. Rogers, H. B. Thompson, Jr., and J. L. Speirs, THIS JOURNAL, **76**, 4841 (1954).

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