Acid–Base Properties of *N*-Methylhistamine [4-(2-Methylaminoethyl)-imidazole] and *NN*-Dimethylhistamine [4-(2-Dimethylaminoethyl)imidazole] and their Complexing Capacity with Cobalt(II), Nickel(II), Copper(II), and Zinc(II)

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Equilibria of *N*-methylhistamine [4-(2-methylaminoethyl)imidazole] and *NN*-dimethylhistamine [4-(2-dimethylaminoethyl)imidazole] with protons and bivalent metals (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}), in aqueous solutions at 25·0 °C and ionic strength 0·1M-KCl, have been investigated potentiometrically. The ligands behave as bivalent bases with $\log K_1 = 9{\cdot}904(4)$, $\log K_2 = 5{\cdot}874(6)$ for *N*-methylhistamine and $\log K_1 = 9{\cdot}334(2)$, $\log K_2 = 5{\cdot}821(4)$ for *NN*-dimethylhistamine, corresponding to the basic sites amino-group and tertiary imidazole nitrogen atom, respectively. The stabilities of the metal complexes are in accord with the Irving–Williams series. With respect to variation of the ligand with the same metal ion, the stability decreases in the series histamine > *N*-methylhistamine > *NN*-dimethylhistamine. The copper(II) ion forms hydrogen complexes with the *N*-methylated ligands, whose stabilities follow the order *N*-methylhistamine < *NN*-dimethylhistamine.

N-METHYLHISTAMINE [4-(2-METHYLAMINOETHYL)IMIDAZOLE], mha, and *NN*-dimethylhistamine [4-(2-dimethylaminoethyl)imidazole], dmha, are more potent stimulators of acid gastric secretion than simple histamine [4-(2-aminoethyl)imidazole], ha,[1] whereas the latter is more effective than the *N*-methylated compounds in their pharmacological action on smooth muscle contraction and vascular effects.[2] In order to contribute to a possible clarification of the chemical causes of such behaviour, we have undertaken the determination of the acid–base strength of these compounds and of their ability to form complexes with bivalent metals.

EXPERIMENTAL

Reagents.—The dihydrochlorides of both *N*-methylhistamine (mha) and *NN*-dimethylhistamine (dmha) were supplied by Professors T. Vitali and F. Mossini.[1,2] Their purity was checked by chemical analysis [Found: C, 39·8; H, 7·15; N, 19·85. Calc. for $C_7H_{13}N_3,2HCl$ (dmha): C, 39·65; H, 7·15; N, 19·8. Found: C, 36·5; H, 6·65; N, 21·15. Calc. for $C_6H_{11}N_3,2HCl$ (mha): C, 36·5; H, 6·60; N, 21·2%]. Standard solutions of the reagents were prepared following the procedure previously described.[3]

Potentiometric measurements, using a digital potentiometer Radiometer PHM52, were carried out as described previously [3,4] at 25·0 ± 0·1 °C and ionic strength 0·1M-KCl. Initial concentrations, pH, and $\bar{n}$ intervals of the solutions employed at the chosen ionic strength are reported in Tables 1 and 2.

Calculations.—Protonation and complex-formation constants, except for copper(II) and for nickel(II) were determined from the formation function $\bar{n}$ and then refined by the computer program Gauss Z.[5] In this program the function to be minimised is $\bar{n}_c - \bar{n}_o$, *i.e.* the calculated (c) and observed (o) formation function. Typical titrations of solutions of mha are represented in Figure 1, and of solutions of dmha in Figure 2. For equilibria involving copper(II) and nickel(II) the modified program Scogs,[6] where the minimised function is $v_c - v_o$, was applied (v = volume of titrant added).

The assessment of the existence of dubious complex species has been made in various ways. First, as usual, the formation functions $\bar{n}_o$ were calculated and plotted against

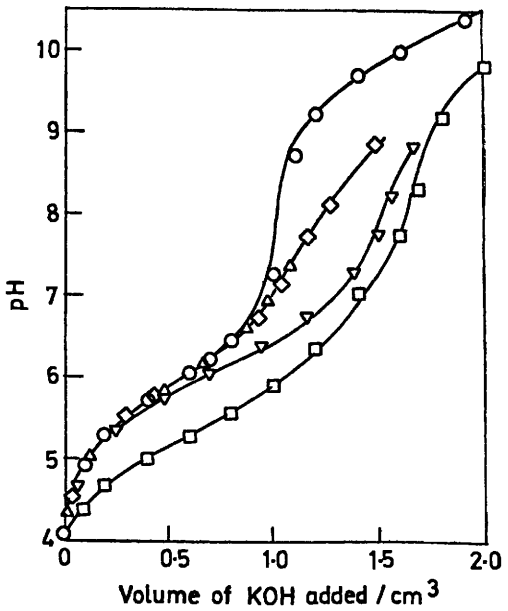


FIGURE 1 Titration curves calculated by the Haltafall [7] program. Experimental points refer to titrations in Table 1: expt. no. 4 (○, ligand); 7 (◇, Co^{2+}); 20 (△, Zn^{2+}), 11 (▽, Ni^{2+}); and 14 (□, Cu^{2+})

pL. For cobalt(II) and zinc(II) solutions $\bar{n}_o$ was independent of c_M (total metal concentration), thus indicating that only simple complexes, ML^{2+} and ML_2^{2+}, have to be considered. On the other hand, for copper(II) and nickel(II) the formation functions were indicative of the presence of complexes other than simple. Therefore several hydrogen, hydroxo-, and binuclear complexes were searched for. Several of them,

[1] C. F. Code, S. M. Maslinki, F. Mossini, and H. Navert, *J. Physiology USSR*, 1971, **217**, 557.
[2] G. Bertaccini and T. Vitali, *J. Pharm. Pharmacol.*, 1964, **16**, 441.
[3] A. Braibanti, F. Dallavalle, E. Leporati, and G. Mori, *J.C.S. Dalton*, 1973, 323.
[4] A. Braibanti, G. Mori, F. Dallavalle, and E. Leporati, *Inorg. Chim. Acta*, 1972, **6**, 106.
[5] R. S. Tobias and M. Yasuda, *Inorg. Chem.*, 1963, **2**, 1307.
[6] I. G. Sayce, *Talanta*, 1968, **15**, 1397; statement number 150 of the Scogs program is amended.

TABLE 1

Protonation and complex-formation constant determinations. Initial concentrations [c/mmol, initial volume (V_0) = 99·65 cm³], pH, and $\bar{n}$ ranges for titrations of *N*-methylhistamine with H^+ and bivalent metal ions

Expt. no.	Ion	c_M	c_L	c_H	pH	$\bar{n}$
1	H^+		0·2296	0·4591	4·223—10·50	1·98—0·20
2			0·2981	0·5963	4·123—10·81	1·98—0·11
3			0·2984	0·5968	4·120—10·63	1·98—0·16
4			0·3214	0·6427	4·106—10·60	1·98—0·17
5	Co^{2+}	0·0803	0·3211	0·6422	4·091—9·441	0·02—1·00
6		0·1066	0·3211	0·6422	4·094—9·076	0·01—1·00
7		0·1507	0·3214	0·6427	4·104—8·939	0·01—0·94
8		0·2550	0·2755	0·5509	4·138—8·523	0·01—0·58
9	Ni^{2+}	0·0748	0·2984	0·5968	4·098—9·904	0·02—1·80
10		0·0935	0·2755	0·5509	4·114—9·825	0·02—1·71
11		0·1584	0·3214	0·6427	4·062—9·656	0·01—1·56
12		0·2374	0·2981	0·5963	4·065—8·555	0·01—1·06
13	Cu^{2+}	0·0806	0·3211	0·6422	3·898—9·931	0·06—1·00 [a]
14		0·1058	0·3214	0·6427	3·871—9·980	0·04—1·00 [a]
15		0·3024	0·3211	0·6422	4·475—8·324	0·17—1·00 [a]
16		0·1813	0·3211	0·6422	3·824—9·717	0·04—1·00 [a]
17	Zn^{2+}	0·0819	0·3214	0·8424	2·696—7·544	0·01—0·51
18		0·1105	0·3214	0·9123	2·564—7·634	0·01—0·54
19		0·1596	0·3214	1·0321	2·414—7·707	0·02—0·53
20		0·0819	0·3214	0·6427		

[a] Calculated from complex-formation constants.

TABLE 2

Proton and complex-formation constant determinations. Initial concentrations [c/mmol, initial volume (V_0) = 99·65 cm³], pH, and $\bar{n}$ ranges for titrations of *NN*-dimethylhistamine with H^+ and bivalent metal ions

Expt. no.		c_M	c_L	c_H	pH	$\bar{n}$
1	H^+		0·3186	0·6371	4·137—11·24	1·98—0·01
2			0·3182	0·6365	4·131—10·82	1·98—0·03
3			0·2864	0·5728	4·165—10·68	1·98—0·04
4			0·2548	0·5096	4·191—10·87	1·98—0·03
5	Co^{2+}	0·0796	0·3185	0·6371	4·120—8·684	0·01—0·33
6		0·1059	0·3185	0·6371	4·130—8·657	0·01—0·28
7		0·1546	0·3185	0·6371	4·136—8·461	0·00—0·20
8	Ni^{2+}	0·0741	0·3185	0·6371	4·120—8·723	0·01—0·82
9		0·0997	0·3182	0·8580	2·639—8·591	0·04—0·77
10		0·1426	0·3185	0·6371	4·123—8·357	0·00—0·63
11		0·2374	0·3182	0·6365	4·169—8·320	0·00—0·58
12	Cu^{2+}	0·1008	0·3949	0·7900	3·962—9·449	0·03—1·00 [a]
13		0·1059	0·3185	0·6371	3·991—9·319	0·03—1·00 [a]
14		0·1586	0·3182	0·6365	3·944—8·148	0·02—1·00 [a]
15		0·2845	0·3182	0·6365	3·869—6·172	0·03—1·00 [a]
16	Zn^{2+}	0·0778	0·3185	0·8268	2·706—7·732	0·04—0·22
17		0·1064	0·3185	0·8967	2·586—7·543	0·00—0·12
18		0·1595	0·3182	1·0254	2·412—7·653	0·00—0·25
19		0·2292	0·3185	1·1962	2·250—7·536	0·00—0·14
20		0·0778	0·3185	0·6371		

[a] Calculated from complex-formation constants.

TABLE 3

Overall stability constants for equilibria involving *N*-methylhistamine and *NN*-dimethylhistamine

	N-Methylhistamine					*NN*-Dimethylhistamine				
	H^+	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	H^+	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
$\log \beta_{101}(\sigma)$	9·904(4)					9·334(2)				
$\log \beta_{201}(\sigma)$	15·778(5)					15·155(3)				
$\log \beta_{111}(\sigma)$				12·977(41)					12·357(14)	
$\log \beta_{011}(\sigma)$		4·453(8)	5·855(6)	8·345(8)	4·829(7)		2·821(18)	3·877(5)	6·558(7)	3·400(22)
$\log \beta_{012}(\sigma)$		7·248(40)	9·421(23)							
$\log \beta_{-111}(\sigma)$				1·159(11)					−0·819(13)	
$\log \beta_{023}(\sigma)$			18·151(61)							

both singly and in conjunction, produced a remarkable increase in the sum of the residuals $U = \Sigma(v_c - v_o)^2$. The best sets of complexes were $[HCuL]^{3+}$, CuL^{2+}, and $[Cu(OH)L]^+$, both for mha and dmha, and NiL^{2+}, NiL_2^{2+}, and $Ni_2L_3^{4+}$, for mha. The reliability of the complexes $[HCuL]^{3+}$ was checked by calculating the function (1) at those zones

$$\eta = \frac{[(\overline{\Delta_{NO} - \Delta_{YES}})^2]^{\frac{1}{2}} - [(\overline{\Delta_{YES}})^2]^{\frac{1}{2}}}{[(\overline{\Delta_{YES}})^2]^{\frac{1}{2}}} \cdot 100 \qquad (1)$$

where the concentration of $[HCuL]^{3+}$ is or should be appreciable [Δ_{NO} = the residual ($v_o - v_c$) at each point in the absence of the complex, Δ_{YES} the residual in its presence]. The quantity η was taken as a measure of the excess over average deviations; values of +48·8% for $[HCu(mha)]^{3+}$ and +111·7% for $[HCu(dmha)]^{3+}$ were obtained; these figures are considered to confirm the 'YES' hypothesis.

A further check of the reliability of dubious species was given by a comparison of the observed pH_o with pH_c as

calculated with and without the complex $[HCuL]^{3+}$, the latter quantity being calculated with the program Haltafall.[7] Both these procedures confirmed that the complex

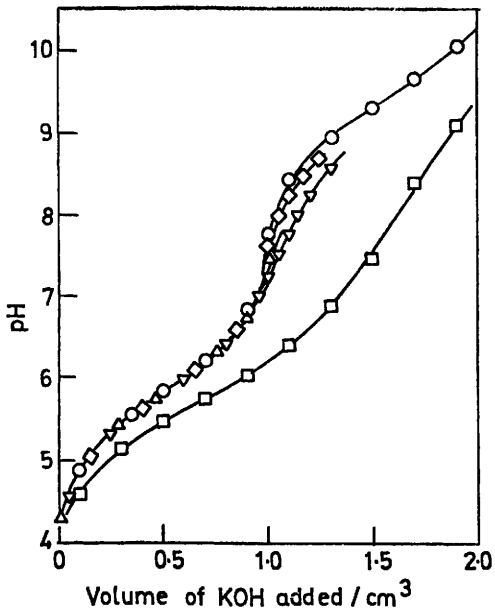


FIGURE 2 Titration curves calculated by the Haltafall [7] program. Experimental points refer to titrations of Table 2: expt. no. 1 (○, ligand); 5 (◇, Co^{2+}); 20 (△, Zn^{2+}); 8 (▽, Ni^{2+}); and 13 (□, Cu^{2+})

The complete sets of stability constants are reported in Table 3. All the calculations were performed on the computer CDC 6600 of Consorzio Interuniversitario dell'Italia Nord-Orientale, Bologna. A complete list of the experimental data is available in Supplementary Publication No. SUP 20815 (39 pp., 1 microfiche).*

DISCUSSION

Protonation Equilibria.—Sites on the molecules *N*-methylhistamine and *NN*-dimethylhistamine suitable for protonation are the same as for histamine,[8] namely the amino-group and the tertiary nitrogen atom of the imidazole ring. The protonation constants are compared in Table 4. Values of log *K* show how the trend in base strength of the amino-group is in accord with that of primary, secondary, and tertiary amines, whereas protonation constants of the imidazole ring are practically constant.

Metal Complexes.—Stability constants of the complexes formed by histamine,[8] *N*-methylhistamine, and *NN*-dimethylhistamine are compared in Table 5. The stability constants of complexes ML^{2+}, for each ligand with various metal ions, follow the Irving–Williams sequence Co < Ni < Cu < Zn. This demonstrates that the complexes are of the same type for every metal ion considered. The participation of the nitrogen atom of the imidazole ring implies that six-membered chelate rings are formed, as that for histamine in structure (I).

TABLE 4

Comparison between stability constants of protonation processes in related compounds

Equilibrium	ha	mha	dmha	spam	spac
$L + H^+ \rightleftharpoons HL^+$	$\log \beta_1 = 9{\cdot}826(2)$	$\log \beta_1 = 9{\cdot}904(4)$	$\log \beta_1 = 9{\cdot}334(2)$	$\log \beta_1 = 8{\cdot}904(1)$	$\log \beta_1 = 8{\cdot}663(4)$
$L + 2H^+ \rightleftharpoons H_2L^{2+}$	$\log \beta_2 = 15{\cdot}884(2)$	$\log \beta_2 = 15{\cdot}778(5)$	$\log \beta_2 = 15{\cdot}155(3)$	$\log \beta_2 = 13{\cdot}799(2)$	$\log \beta_2 = 13{\cdot}599(5)$
$HL^+ + H^+ \rightleftharpoons H_2L^{2+}$	$\log K_2 = 6{\cdot}058(2)$	$\log K_2 = 5{\cdot}874(6)$	$\log K_2 = 5{\cdot}821(4)$	$\log K_2 = 4{\cdot}895(2)$	$\log K_2 = 4{\cdot}936(6)$

ha = Histamine [4-(2-aminoethyl)imidazole], mha = *N*-methylhistamine [4-(2-methylaminoethyl)imidazole], dmha = *NN*-dimethylhistamine [4-(2-dimethylaminoethyl)imidazole], spam = spinaceamine {1*H*-imidazo-4,5,6,7-tetrahydro[4,5-*c*]pyridine}, and spac = spinacine {4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine-6-carboxylic acid}.

TABLE 5

Comparison between step-wise formation constants for metal complexes with histamine, *N*-methylhistamine, and *NN*-dimethylhistamine

M	Co^{2+}			Ni^{2+}			Cu^{2+}			Zn^{2+}		
Equilibrium	ha	mha	dmha	ha	mha	mdha	ha	mha	dmha	ha	mha	dmha
$ML^{2+} + H^+ \rightleftharpoons [HML]^{3+}$								4·632 [a]	5·799 [a]			
$(HL^+ + H^+ \rightleftharpoons H_2L^{2+})$								(5·874) [a]	(5·821) [a]			
$M^{2+} + L \rightleftharpoons ML^{2+}$	5·025 [b]	4·453 [a]	2·821 [a]	6·76 [b]	5·855 [a]	3·877 [a]	9·56 [b]	8·345 [a]	6·558 [a]	5·15 [c]	4·829 [a]	3·400 [a]
$2ML^{2+} + L \rightleftharpoons M_2L_3^{4+}$					6·441 [a]							
$ML^{2+} + L \rightleftharpoons ML_2^{2+}$	3·742 [b]	2·795 [a]		5·02 [b]	3·566 [a]		6·57 [b]			4·84 [c]		
$ML_2^{2+} + L \rightleftharpoons ML_3^{2+}$				3·11 [b]								
$ML^{2+} + OH^- \rightleftharpoons [M(OH)L]^+$								6·814 [a]	6·623 [a]			
$[M(OH)L]^+ + H^+ \rightleftharpoons ML^{2+}$							7·10 [d]	7·187 [a]	7·377 [a]			
$\log (K_1/K_2)$	1·28	1·66		1·74	2·28		2·99			0·31		

ha = Histamine, mha = *N*-methylhistamine, and dmha = *NN*-dimethylhistamine.

[a] This work. [b] W. J. Eilbeck, F. Holmes, and T. W. Thomas, *J. Chem. Soc.* (*A*), 1969, 113. [c] B. Rao and H. B. Mathur, *J. Inorg. Nuclear Chem.*, 1971, **33**, 809. [d] J. Zarembowitch, *J. Chim. phys.*, 1966, **63**, 420.

$[HCuL]^{3+}$ is probably present. On the same grounds, species such as $[Cu(OH)_2L_2]$ and $[Cu_2(OH)_2L_2]^{2+}$ were excluded. The same procedure was adopted also for acceptance of the species $Ni_2L_3^{4+}$ in the Ni^{II}–mha system.

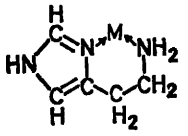
* For details see Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index Issue.

When, for each metal, stability constants of the complexes ML^{2+} of ha, mha, and dmha are compared, the

[7] N. Ingri, W. Kakolowicz, L. G. Sillén, and B. Warnqvist, *Talanta*, 1967, **14**, 1261.

[8] W. J. Eilbeck, F. Holmes, and T. W. Thomas, *J. Chem. Soc.* (*A*), 1969, 113.

order ha > mha > dmha is apparent. Steric hindrance of the methyl group is probably responsible for the gradual weakening of the complexes. The relative importance of the various species at each pH range is shown by distribution diagrams for mha and dmha with



(I)

Ni^{2+} and Co^{2+} (Figure 3). The trend in stability constants with respect to the ligands, at fixed metal ion, parallels the action of the ligands on smooth muscle contraction.[2]

The complex $Ni_2L_3^{4+}$ with L = mha is the only binuclear complex found with these ligands. In this complex a molecule of the ligand bound to nickel(II) is positioned so that the methylaminoethyl group is turned toward the second metal ion. Somewhat different from this is the behaviour of these ligands with respect to Cu^{2+}. With this metal ion, mha and dmha form hydrogen complexes at pH *ca.* 4·0 and hydroxo-complexes at pH *ca.* 6·0. The absence of such hydrogen complexes in equilibria involving ha is in accord with these results because the stability of the hydrogen

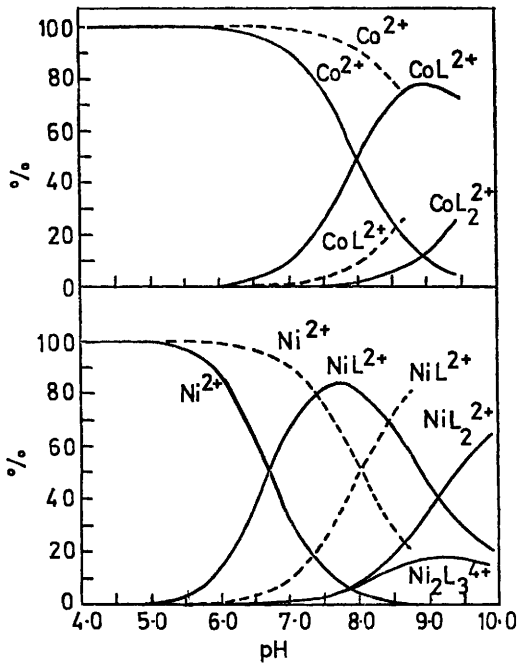


FIGURE 3 Typical distribution diagrams for equilibria of some metal ions with *N*-methylhistamine (——) and *NN*-dimethylhistamine (– – – –). Percentages have been calculated by the Haltafall [7] program from data of titrations 9 and 5 in Table 1 and 5 and 8 in Table 2

complexes varies in a sequence opposite to that of the simple metal complexes, *i.e.* for the hydrogen complexes mha < dmha. For instance in the distribution diagrams (Figure 4) the maximum mol fraction of the complex $[HCuL]^{3+}$ is *ca.* 17% for mha at pH 5·0 and *ca.* 42% for dmha at pH 5·5. By extrapolation of these data to ha, the absence of hydrogen complexes from equilibria involving ha is perfectly justified.

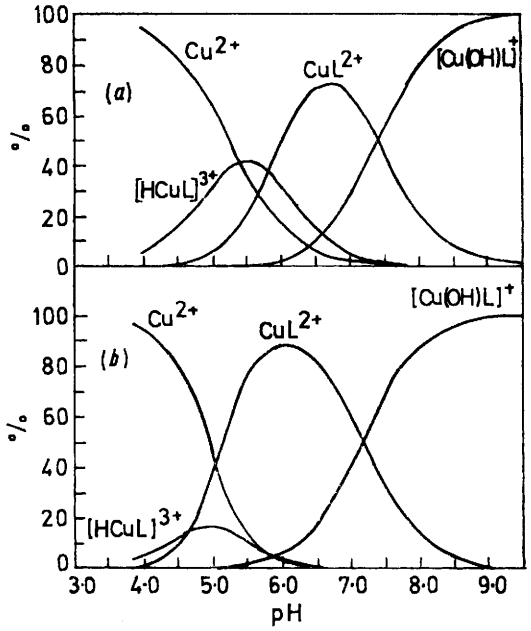


FIGURE 4 Typical distribution diagrams for equilibria of copper(II) with (*a*) *NN*-dimethylhistamine and (*b*) *N*-methylhistamine. Percentages have been calculated by the Haltafall [7] program from data of titration 12 in Table 2 and 14 in Table 1

The formation of the hydrogen complexes can be interpreted as competition between the proton and metal ions in bonding to the nitrogen atom of the imidazole ring. This implies that protonation opposes closure of the chelate ring. It is also worth noting that the base strength of this nitrogen atom, as calculated for equilibrium (2), is the same as that for the free ligand

$$CuL^{2+} + H^+ \rightleftharpoons [HCuL]^{3+} \qquad (2)$$

in Cu^{II}–dmha solutions, and is slightly reduced in Cu^{II}–mha solutions. By extrapolation to ha the base strength of the nitrogen atom becomes very low and cannot be detected.

The formation of hydroxo-complexes $[Cu(OH)L]^+$ has been carefully checked. Species such as $[Cu_2(OH)_2L_2]^{2+}$ and CuL_2^{2+} in the same region gave substantially worse agreement of the experimental and calculated data and their existence, at least in the solutions investigated, can be excluded. The reliability of the formation constant obtained may be assessed also by comparison of the formation constant of equilibrium (3) for ha, with

$$[Cu(OH)L]^+ + H^+ \rightleftharpoons CuL^{2+} \qquad (3)$$

the values for mha and dmha (Table 5). These values, referring to protonation equilibria of the same ligand OH^-, are practically equal.

We thank Professor M. Nardelli, for research facilities, Professors T. Vitali and F. Mossini, for samples of *N*-methylhistamine and *NN*-dimethylhistamine dihydrochlorides, and Consiglio Nazionale delle Ricerche (Rome), for support.

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