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Determination of Acid Dissociation Constants of 4-(2′-Benzimidazolyl)-3-thiabutanoic Acid and Related Compounds and Stability Constants of Their Divalent Metal Complexes with Copper, Nickel, and Zinc

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The acid dissociation constants (K_a) of 4-(2′-benzimidazolyl)-3-thiabutanoic acid and related substances were determined by potentiometric titration in 0.1 mol dm^{-3} $(CH_3)_4NCl$ at 25 °C. pK_a values found were 3.33, 5.46, and 11.32. Stability constants were found for ML_2, MHL_2, MH_3L_2, MH_4L_2, $MH_{-1}L_2$, $MH_{-2}L_2$ complexes for copper, nickel, and zinc.

Introduction

The imidazole ring plays an important role in biochemistry.[1,2] In peptides and proteins, the imidazole ring of histidine residues changes with pH change in most biological fluids, thus providing intermolecular binding sites for histidine-containing biopolymers. Also, imidazole nitrogens are electron pair donor groups to metal ions, and their Lewis basicity depends on the protonation level of the molecule. The presence of the imidazole and amino groups in histidine, imidazolyleacetic acid, and benzimidazolylthiabutanoic acid shows some similarities in binding with other biomolecules and metal ions because of their similar chemical structures.

Benzimidazole is an amphiprotic molecule, like imidazole,[3] with weak basic and weak acidic character and its acidity constants have been measured by a number of workers,[4] but there is disagreement about the values of the acid dissociation constants of the imino group.[3,5]

4-(2-Benzimidazolyl)-3-thiabutanoic acid (BTBA) has been synthesized for biomimicry involving cyclodextrins with two imidazoles in the cavity.[6] The acid dissociation constants of this and of benzimidazole (BNZ) and some related substances, 3-(2′benzimidazolyl) propionic acid (BPA), 2-amino-3-(4-imidazolyl)propionic acid (DL-histidine) (HIS), methylbenzimidazole (MB), and imidazole (IMZ), together with the stability constants of their copper, nickel, and zinc complexes, which are important in biochemistry, were determined by potentiometric titration and compared with literature values.

Experimental Section

Chemicals. 4-(2′Benzimidazolyl)-3-thiabutanoic acid was thrice recrystallized before use in titrations, which showed that the sample was above 98% pure by ligand. BNZ, BPA, HIS, MB, and IMZ were obtained from Fluka, and 0.01 mol dm^{-3} solutions of each were made up without purification. Solutions of 0.01 mol dm^{-3} were prepared from Analar $Cu(NO_3)_2{\cdot}3H_2O$, $ZnCl_2$ and $Ni(NO_3)_2{\cdot}6H_2O$ (BDH). To calibrate the glass-reference electrode pair, a 0.05 mol dm^{-3} potassium hydrogen phthalate (KHP) buffer solution was prepared from AnalaR reagent. A solution of 0.1 mol dm^{-3} $(CH_3)_4NOH$ was prepared from 25% solution (Aldrich) and standardized with 0.1 mol dm^{-3} HCl (BDH ConvoL). NaCl and $(CH_3)_4NCl$ solutions (each 1.0 mol dm^{-3}) were used as background electrolytes.

Table 1. pK_a Values of BTBA in NaOH or $(CH_3)_4NOH$ at 25.0 ± 0.5 °C

	NaOH	$(CH_3)_4NOH$	ΔpK_a
pK_1	3.27	3.33	0.06
pK_2	5.52	5.46	0.06
pK_3	11.60	11.32	0.28

Titration Procedure. The automatic titration system (Molspin,[8] Newcastle upon Tyne), interfaced to a PC, was used with a motor-driven, 10 cm^3 syringe and a glass and calomel reference electrode (Russell pH, Auchtermuchty). The titration cell (100 cm^3) was controlled at 25 ± 0.5 °C, stirred by a magnetic follower, and purged with nitrogen gas. Before use in titration, electrodes were calibrated with KHP at pH 4.008. Then the test solution (100 mL) was put into the cell, and 10 mL of 0.1 mol dm alkali ($(CH_3)_4NOH$ or NaOH) was put into the motor-driven syringe (incremental volume 0.03−0.05 mL). During experiments, nitrogen gas was passed into the titration cell. For every volume increment, the pH of the test solution was read from the pH meter. About 360 titration data points were collected, and the data were analyzed using SUPERQUAD.[7]

Results and Discussion

Acidity Constants and Titration End Points for Ligands. Experiments for the determination of pK_a values were performed in duplicate with $(CH_3)_4NOH/(CH_3)_4NCl$ and once at the same concentration with NaOH/NaCl. The differences were small but not negligible (Table 1). Three pK_a values were found for both BTBA and BPA in the pH range of 2.5−11.5. The first pK_a value (3.3) belongs to the −COOH group of BTBA, and the second (5.5), to the −N= of the benzimidazolyl group, whereas the third arises from the pyrrole proton ionizing to give the anion [L^{2-}]

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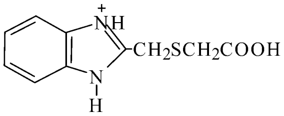
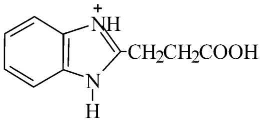
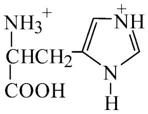
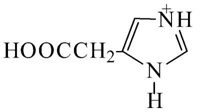
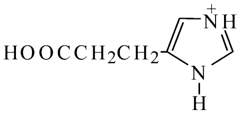
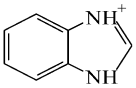
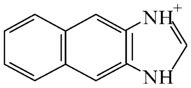
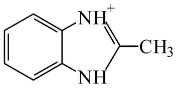
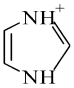
Table 2. Chemical Structures of Ligands and pK_a Values

names of ligands	chemical structure of fully protonated form	pK_a values
4-(2′benzimidazolyl)-3-thiabutanoic acid		3.33, 5.46, 11.32
3-(2′benzimidazolyl)propionic acid		3.75, 6.37, 11.71
2-amino-3-(4-imidazolyl)propionic acid		2.02, 6.10, 9.19, 11.16
4-imidazoleacetic acid		3.30, 7.44, 11.23
4-imidazolylpropanoic acid		3.88, 7.40
benzimidazole (BNZ)		5.59, 12.17
naphthimidazole (NBNZ)		5.24[11]
2-methylbenzimidazole (MB)		6.40, 12.00
imidazole (IMZ)		7.13, 12.70

For IAC, three pK_a values of 3.30, 7.44, and 11.23 were found. The pK_1 and pK_2 values are similar to those of Andrews et al.[9] Although pK_1 for IAC is 3.30, the value for IPA is 3.88 [10] because of the additional carbon in its chain. pK_1 of BTBA is similar to that of IAC. The second pK_a of BTBA is smaller than that of IAC and larger than that of NBNZ (5.24)[11] because of its benzene ring. This confers an acidic property to $-N=$ of imidazole because of the inductive effect. The electron pair of N is shifted through the benzene ring, and N is thus partially positive, providing some acidity to N of imidazole. Likewise, the N of benzimidazole is protonated in the weak acid region. The pK_a values of IMZ were 7.13 and 12.70. These values are similar to those of Vasconcelos and Machado[3] but were rejected by Sjöberg[5] because a glass electrode was used, which he reckoned was not sensitive enough in higher-concentration alkali solutions because of the sodium error. The pK_1 value is very close to that of Chacrovorty[10] and Walba[12] et al.; however, the second values are not close. Walba's spectroscopically determined value was 14.52. There is a 1.74 pK difference between this work and Walba's value for pK_2 for IMZ. Differences probably arise from the conditions of titration such as the background as well as the methods used.

pK_a values of BNZ obtained were 5.59 and 12.17. pK_1 values of 5.58, 5.56, 5.43, and 5.55 were reported by Thomas et al.,[13] Notario et al.,[14] Pavlova,[15] and Davies et al.[16], respectively. The new value is very close to the literature values for pK_{a1} of BNZ. Values of pK_{a2} of BNZ have been reported as 11.70,[15] 12.30,[16] 12.30,[17] 12.78,[12] and 12.86.[18] The present value of 12.17 is within this range. When a methyl group binds to 2-benzimidazolyl, pK_{a1} rises by 0.81. However, pK_{a2} decreased by 0.17. Pavlova[15] found pK_a values for MB of 6.15 and 11.48, respectively. Lane's value[19] was 6.29. The pK_a values of BTBA compared with those of BPA are slightly smaller, suggesting that the $-S-$ group in BTBA confers lower acidity. The N$-$H bond of the benzimidazole of BTBA might be that protonated at pH 11.32. Its value is similar to those of HIS and IAC. The pK_{a2} values of the N in IAC and IPA (7.45 and 7.40[10]) are almost the same because neither has a benzene ring.

HIS has four pK_a values, 1.98, 6.10, 9.19 and 11.16, which is one more than BTBA or IAC because of the presence of an amino group ($-NH_2$). For the first three pK_a values of HIS, there is agreement with literature data.[20−22] A fourth (pK_{4a}) of HIS has not previously been reported. The values for the first three in the present work are very close to Attaelmannan's values,[21] possibly because of the use of the same analysis program for the calculation of the constants.

Stability Constants of Species. Table 3 shows stability constant values determined for the ligands studied.

[ML_2], [MHL_2] [MH_2L_2], [$M(OH)L_2$], and [$M(OH)_2L_2$] complexes were formed with each ligand with copper, nickel, and zinc ions. In the M$-$HIS and M$-$BTBA systems, [MH_3L_2] and [MH_4L_2] complexes were found. Stability constants of ML_2 were in the order $Ni^{2+} > Zn^{2+} > Cu^{2+}$. The stability constants of BPA and BTBA decreased from nickel to copper. However, in the M$-$HIS and IAC systems,

Table 3. Stability Constants of BTBA, BPA, IAC, and HIS with Cu^{2+}, Ni^{2+}, and Zn^{2+} in 0.1 mol dm^{-3} $(CH_3)_4NCl$ at 25 °C ± 0.5

ligands	log β	Cu^{2+}	Ni^{2+}	Zn^{2+}	ref
BTBA	ML_2	8.63 ± 0.062	11.47 ± 0.05	9.74 ± 0.12	this work
	MHL_2	14.80 ± 0.06	17.54 ± 0.01	19.41 ± 0.01	
	MH_2L_2	20.03 ± 0.07	22.45 ± 0.10	25.60 ± 0.02	
	MH_3L_2	24.59 ± 0.10	27.54 ± 0.03	30.71 ± 0.05	
	MH_4L_2		32.16 ± 0.03	35.69 ± 0.14	
	$MH_{-1}L_2$	−0.03 ± 0.05	2.15 ± 0.03	1.98 ± 0.01	
	$MH_{-2}L_2$	−9.41 ± 0.04	−8.19 ± 0.03	−8.67 ± 0.02	
	$MH_{-3}L_2$	−19.66 ± 0.03			
BPA	ML_2	6.91 ± 0.02	10.49 ± 0.06		this work
	MHL_2	14.99 ± 0.01	17.22 ± 0.05		
	MH_2L_2	20.08 ± 0.01	20.62 ± 0.05		
	$MH_{-1}L_2$	−0.27 ± 0.011	0.70 ± 0.09		
	$MH_{-2}L_2$	−10.11 ± 0.04	−8.70 ± 0.06		
IAC	ML_2	12.59 ± 0.07	8.77 ± 0.03	7.38 ± 0.02	this work
	MHL_2	17.64 ± 0.05	15.30 ± 0.04	14.55 ± 0.03	
	$MH_{-1}L_2$	2.98 ± 0.06	1.83 ± 0.13	−0.02 ± 0.03	
	$MH_{-2}L_2$	−8.21 ± 0.04	−6.46 ± 0.07	−9.19 ± 0.06	
	ML	7.00	4.70	3.86	10
	ML_2	12.69	8.25	7.10	
HIS	ML_2	17.93 ± 0.07	14.88 ± 0.04	12.60 ± 0.03	this work
	MHL_2	23.40 ± 0.05	20.91 ± 0.03	19.07 ± 0.03	
	MH_2L_2	28.36 ± 0.03	26.60 ± 0.01	25.16 ± 0.03	
	MH_3L_2	32.75 ± 0.02	30.81 ± 0.16	30.39 ± 0.16	
	$MH_{-1}L_2$	7.61 ± 0.03	5.15 ± 0.02	2.69 ± 0.05	
	$MH_{-2}L_2$	−2.96 ± 0.03	−5.05 ± 0.02	−7.96 ± 0.02	
	ML	10.16, 10.10	8.53	6.62, 6.26	20−24
	ML_2	18.11, 19.15	15.10	12.03, 11.45	
	MHL	14.11, 13.94	12.91	10.38	22−24
	MHL_2	23.81, 24.05	20.81	16.67	23, 24
	MH_2L_2	27.2, 28.02			
	$MH_{-1}L$	2.0			
	$MH_{-1}L_2$	11.81			
	$MH_{-2}L_2$	7.9			

the trend was $Cu^{2+} > Ni^{2+} > Zn^{2+}$. In the Cu−HIS system, the determined values of lg β_{102}, lg β_{112} and lg β_{122} were 17.93, 23.40, and 28.36, respectively, which agree well with literature values.[20−22] However, lg β_{112} and lg β_{122} values are lower. From the literature, lg β_{132} is 32.75. Also, values of lg β_{102} of 14.88 for Ni−HIS and 12.60 for Zn−HIS are similar to literature values.[22−24] As seen in Table 3, El-Ezaby et al.[22] obtained 15.10 for Ni−HIS, and Gockel et al.[23] obtained 12.03 for Zn−HIS. The lg β_{112} and lg β_{122} values for the Zn−HIS complex system are slightly larger than literature values[25] perhaps because of a different titration background (KNO_3). Also, the value of $NiHL_2$ is in good agreement with that of El-Ezaby et al., but no values could be found in the literature for NiH_2L_2, NiH_3L_2, ZnH_3L_2, $ZnH_{-1}L_2$, and $ZnH_{-2}L_2$ complexes. The structures of $Cu(C_6H_8N_3O_2)_2 \cdot 4H_2O$, $(Ni(C_6H_8N_3O_2)_2) \cdot H_2O$, and $(Zn(C_6H_8N_3O_2)_2) \cdot 2H_2O$ at neutral pH have been determined by Camerman et al.,[26] Fraser and Harding[27] and Kistenmacher,[28] and Kretsinger et al.,[29] respectively, and all agreed in the formulation of ML_2 for Ni, Cu, and Zn complexes with HIS. The present potentiometric titration results parallel the X-ray diffraction results.[30]

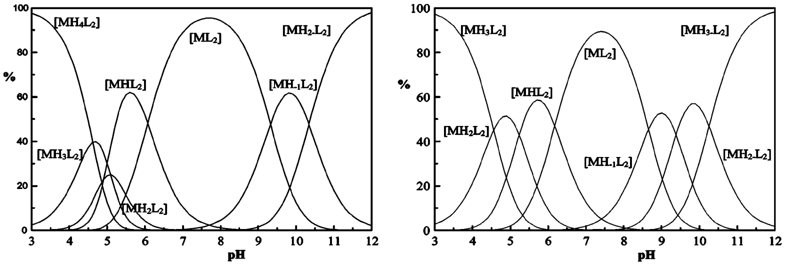
Arising from their similar chemical structures, BTBA, BPA, and IAC all form similar complexes with Ni, Cu, and Zn in aqueous solutions at room temperature. In the M−IAC system, stability constants were in the order Cu > Ni > Zn, like M−HIS. From Table 3, it is clear that the Irving−Williams stability order[31] is satisfied for IAC and HIS. Andrews and Zebolsky[9] obtained ML_2 values of 12.69, 8.25, and 7.10 for Cu, Ni, and Zn, respectively. The present values (12.59, 8.77, and 7.38) are similar, but that for NiL_2 is slightly higher than the literature value.[10] Also, an ML_2 value for IPA of 8.45 was obtained,[10] but although the chemical structure of IPA is similar to that of IAC, this value is smaller than the present value. Stability constants obtained for $[Cu(OH)L_2]$ and $[Cu(OH)_2L_2]$ were 2.98 and −8.21, and no comparative values could be found in the literature.

The stability constants of BPA and BTBA have not been reported before. The crystal structures of Ni and Cu BTBA were given by Matthews et al.,[30] who found the formulation $M(BTBA)_2$ for Ni and Cu complexes, which is confirmed by the present potentiometric titrations. Complexes of BTBA with Ni, Cu, and Zn varied from ML_2 to MH_4L_2 for pH values between 3 and 11. Above pH 7.0, $M(OH)L_2$ complexes were found. Values of the stability constants were Ni > Cu for −BTBA and −BPA complexes, the stability constants of the former being slightly larger probably because S behaves as an electron donor when the complexes are formed.

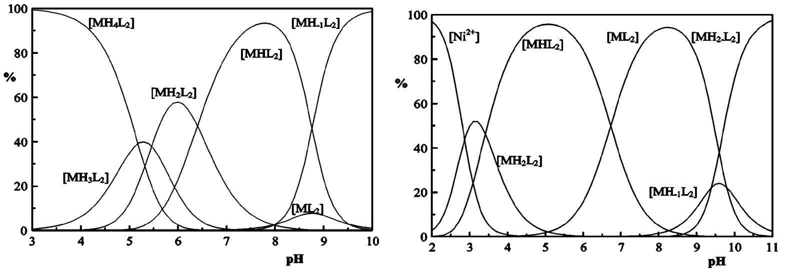
Distribution Curves for Complexes. The species distribution curves for BTBA and its complexes with Cu^{2+}, Ni^{2+}, and Zn^{2+} are shown in Figures 1a−c, and their stability constants are given in Table 3. In all experiments, only low concentrations of M^{2+} were used to avoid the precipitation of metal hydroxides. $[ML_2]$ and $[M(OH)L_2]$ were found for copper and zinc. When 1:1 and 1:3 M/L ratios were studied, M^{2+} ions hydrolyzed strongly, and $M(OH)_2$ was precipitated.

Figure 1a shows the species distribution diagram of the Ni−BTBA system. $[NiL_2]$ exists in a very large range between pH 4.5−11.0 at 95%. Above pH 7.0, Ni^{2+} hydrolyses, forming the species $M(OH)L$ and $M(OH)_2L$. At pH 4−8, MHL_2 is 60%. Below pH 6, MH_2L_2, MH_3L_2, and MH_4L_2 complexes are present.

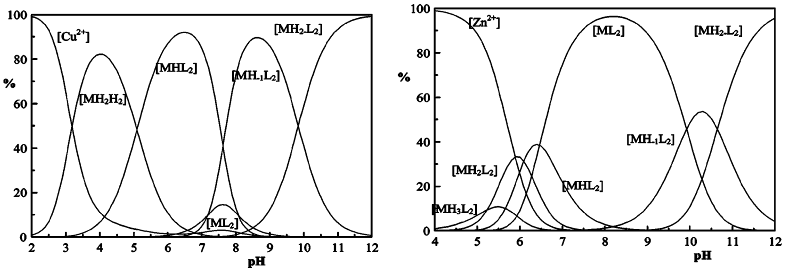
The species distribution diagram of the Cu−BTBA system (Figure 1b) is similar to that of Ni^{2+} for all species except $[MH_4L_2]$, but $[Cu(OH)_3L_2]$ is curved above pH 9.0. The stability constants are only slightly different from those for nickel.



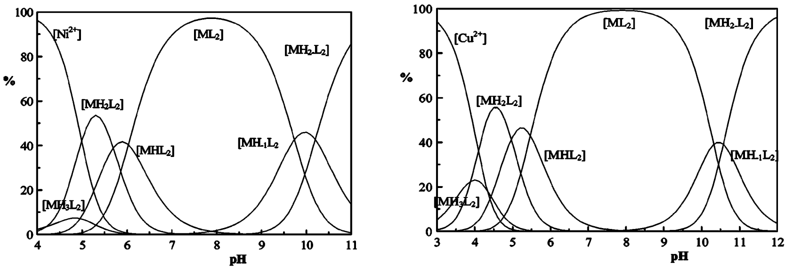
(a) Ni-BTBA (b) Cu-BTBA



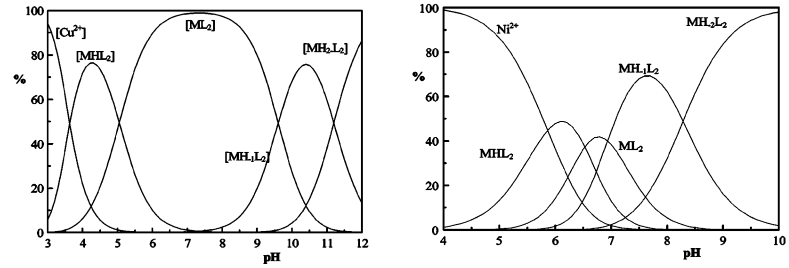
(c) Zn-BTBA (d) Ni-BPA



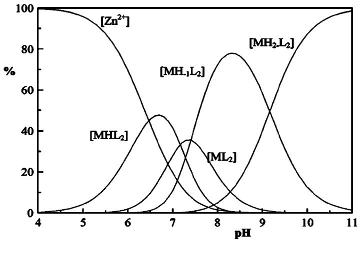
(e) Cu-BPA (f) Zn-HIS



(g) Ni-HIS (h) Cu-HIS



(i) Cu-IAC (j) Ni-IAC



(k) Zn-IAC

Figure 1. Species Distribution Curves for BTBA, BPA, HIS, and IAC with Ni, Cu, and Zn Complexes.

The species distribution diagram of the Zn−BTBA system is shown in Figure 1c. Zn^{2+} forms in the range of pH 3−7 the complex $[MH_3L_2]$, in the range of pH 4−8.5 $[MH_2L_2]$, and in the range of 5−10 $[MH\ L_2]$, whereas $[ML_2]$ is present at only 10% at pH 7−10 and $[MH_4L_2]$ occurs below pH 6.5. $[Zn(OH)L_2]$ was seen above pH 7.

Species distribution curves for Ni−Cu−BPA systems are shown in Figure 1d and e. As seen in Figure 1d, $[MHL_2]$ occurs over the pH range of 2−9, and $[ML_2]$ occurs over the pH range of 4−11 at 90%. $[MH_2L_2]$ is present at 20% between pH 2−6. Above pH 7, $[Ni(OH)L_2]$ and $[Ni(OH)_2L_2]$ exist, but $[Ni(OH)L_2]$ is only 20%. Cu−BPA is similar to Ni−BPA, but only a very low percentage of $[ML_2]$ is present in this system.

Parts f−h of Figure 1 relate to Zn−, Ni−, or Cu−HIS systems. For these three systems, the main complex is $[ML_2]$ over pH 5−11 present at the highest concentration. $[M(OH)L_2]$ and $[M(OH)_2L_2]$ exist above pH 7, and the others, below pH 7. In all systems, $[MH_3L_2]$ exists at only low concentration (10%).

Parts i−k of Figure 1 shows distribution curves of Cu−Ni Zn−IAC systems. As for the HIS system, $[M(OH)L_2]$ and$[M(OH)_2L_2]$ are located in the range above pH 7. $[ML_2]$ is the dominant complex in the Cu−IAC system. $[MHL_2]$ species exist over pH 4−8 in the Ni− and Zn−IAC systems but at pH 3−7 in the Cu−IAC system.

Acknowledgment

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