[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME, NOTRE DAME, INDIANA]

Chelate Stabilities of Certain Oxine-type Compounds.[1,2] I.

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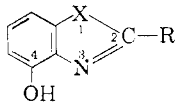
The acid dissociation constants for 4-hydroxybenzimidazole, 4-hydroxy-2-methylbenzimidazole. 4-hydroxy-2-ethylbenzimidazole, 4-hydroxybenzoxazole and 4-hydroxy-2-methylbenzoxazole have been determined in 50% v./v. 1,4-dioxane-water at 25° and chelate stability constants of these ligands with Cu(II), Pb(II), Cd(II), Zn(II), Ni(II) and Co(II) (ligand to metal ratio 8:1 and 4:1) have been obtained by Calvin–Bjerrum potentiometric titration method. The basicity of the ligands have been compared among themselves and with that of 8-hydroxyquinoline and the differences in values have been accounted for. 4-Hydroxybenzimidazole chelates were found to be more stable than those of the 4-hydroxybenzoxazoles, the order of stability constants being Cu(II) > Pb(II) > Cd(II) > Zn(II) > Ni(II) > Co(II). The metal chelates of the 4-hydroxybenzimidazoles and the 4-hydroxybenzoxazoles were less stable than those of 8-hydroxyquinoline and 2-(*o*-hydroxyphenyl)-benzimidazole. The differences have been explained by the greater distance between the chelating atoms, by the orientation of the donor electrons on the nitrogen and by resonance contribution.

This investigation was undertaken to determine the stability constants of the metal chelates of a series of oxine-type compounds having the general formula



where X = NR, O, S, Se, CH_2 and R = H, CH_3, C_2H_5, C_6H_5. Only the stability constants of the benzimidazoles and the benzoxazoles are discussed in this paper.

The high reactivity of 8-hydroxyquinoline has been attributed by Hata[3] to the favorable combination of the reactive pyridine nitrogen and the phenolic 'OH' in one condensed ring. The compounds under investigation are structural analogs of 8-hydroxyquinoline and hence could be biologically and analytically important.

Experimental

Materials.—4-Hydroxybenzimidazole was prepared by a slight modification of Phillips' method.[4] 2,3-Dinitroanisole, obtained by the nitration of *o*-nitroanisole, was reduced to 2,3-diaminoanisole[5] by tin(II) chloride and hydrochloric acid. An equimolecular mixture of 2,3-diaminoanisole and sodium formate was refluxed in 4 *N* HCl for 2 hr.[6,7] and then neutralized with concentrated ammonia under nitrogen precipitating 4-methoxybenzimidazole. On hydrolyzing this compound with 48% HBr and neutralizing with sodium hydrogen carbonate, 4-hydroxybenzimidazole was obtained. The final product was recrystallized several times from aqueous ethanol.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.48; N, 20.9. Found: C, 62.7; H, 4.67; N, 20.5.

2-Methyl and 2-ethyl-4-hydroxybenzimidazoles were prepared in an analogous manner by using sodium acetate and sodium propionate, respectively, in the place of sodium formate.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.9; H, 5.41; N, 18.3. Found: C, 64.6; H, 5.39; N, 18.7. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.17; N, 17.3. Found: C, 66.7; H, 6.26; N, 16.4.

4-Hydroxybenzoxazole was prepared according to the method of Lane and Williams[7] with slight modifications. An equimolecular mixture of 2-aminoresorcinol hydrochloride and formamide was refluxed for 15 minutes. The product was extracted with ethanol, evaporated and purified by sublimation under vacuum at 120°.

Anal. Calcd. for $C_7H_5NO_2$: C, 62.2; H, 3.70; N, 10.4. Found: C, 61.9; H, 3.96; N, 10.7.

2-Methyl-4-hydroxybenzoxazole was prepared similarly by using acetamide in the place of formamide.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.4; H, 4.70; N, 9.40. Found: C, 64.3; H, 4.92; N, 9.40.

The dioxane used as solvent was purified according to the method described by Vogel,[8] kept over sodium and distilled as needed. Stock solutions of 0.01 *M* in metallic ions were prepared and standardized by accepted methods of analysis. Fisher reagent grade sodium hydroxide (0.1 *N*) was standardized against reagent grade potassium acid phthalate. 0.01 *N* perchloric acid was prepared from Fisher reagent grade acid and standardized against the sodium hydroxide.

Apparatus, Procedure and Calculations.—The stability constants were determined at 25° by the Bjerrum method[9] of potentiometric titration in 50% v./v. dioxane–water. The titration apparatus and procedure have been described previously.[10] Titrations were carried out using ligand to metal ratios of 8:1 and 4:1.

Stability values were calculated by the method described by Freiser, *et al.*[10] Since the *p*H value at which a metal ion begins to hydrolyze sets an approximate upper limit for the calculation of formation constants, the $\bar{n}$ values in metal hydrolysis regions were obtained by extrapolation from lower values.

Results

Acid dissociation constants of the various ligands and previously reported values for 8-hydroxyquinoline[11] and for benzimidazole[12] are given in Table I. A summary of the formation constants of the ligands with various metal ions appears in Table II.

Discussion

Acid Dissociation Constants.—The pK_{NH} of 4-hydroxybenzimidazole is 4.92 while that of 8-hydroxyquinoline is 3.97. The increase in value is probably due to the base-strengthening resonance of the symmetrically protonated benzimidazole species as has been discussed by Albert, *et al.*[13]

The slight increase in the pK_{NH} of the 4-hydroxy derivative compared to that of benzimidazole can

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[2] Based partly on a thesis submitted by Rev. A. J. Kandathil to the Graduate School of the University of Notre Dame in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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[9] J. Bjerrum, "Metal-Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941.

[10] H. Freiser, R. G. Charles and W. D. Johnston, THIS JOURNAL, **74**, 1383 (1952).

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TABLE I

SUMMARY OF THE ACID DISSOCIATION CONSTANTS OF THE LIGANDS

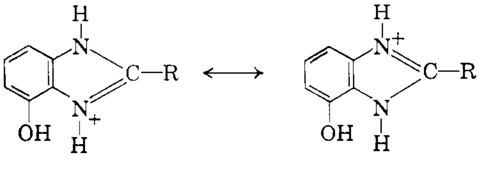
	pK_{NH}	pK_{OH}
8-Hydroxyquinoline	3.97	11.54
Benzimidazole	4.71	
4-Hydroxybenzimidazole	4.92	10.95
2-Methyl-4-hydroxybenzimidazole	5.85	11.05
2-Ethyl-4-hydroxybenzimidazole	5.85	11.15
4-Hydroxybenzoxazole	<2	10.24
2-Methyl-4-hydroxybenzoxazole	$\cong 2$	10.43

TABLE II

SUMMARY OF THE METAL CHELATE FORMATION CONSTANTS FOR THE LIGANDS

	Ligand: Metal = 8:1			Ligand: Metal = 4:1		
	Log K_1	Log K_2	2 Log $K_{av.}$	Log K_1	Log K_2	2 Log $K_{av.}$
4-Hydroxybenzimidazole						
Cu(II)	8.10	6.74	14.84	8.73	(7.13)	(15.86)
Pb(II)	7.11	(4.52)	11.63	7.21	(4.40)	11.61
Zn(II)	6.48	(6.24)	(12.72)	(6.65)	(6.54)	(13.18)
Cd(II)	6.26	(4.51)	10.77	6.32	(4.61)	10.93
Ni(II)	6.08	(4.68)	10.76	6.26	(4.76)	11.01
Co(II)	(5.72)	(4.27)	(9.99)	(5.74)	(4.25)	(9.99)
2-Methyl-4-hydroxybenzimidazole						
Cu(II)	8.85	7.98	16.83	9.22	7.87	17.09
Pb(II)	7.64	(4.32)	11.96	7.49	(4.51)	12.00
Zn(II)	6.22	(5.58)	(11.80)	(6.38)	(5.91)	(12.29)
Cd(II)	6.40	(4.58)	10.98	6.47	4.69	11.16
Ni(II)	5.76	(4.24)	10.10	5.91	(4.84)	10.75
Co(II)	(5.58)	(4.05)	(9.63)	(5.71)	(4.76)	(10.57)
2-Ethyl-4-hydroxybenzimidazole						
Cu(II)	9.05	8.07	17.12	9.13	8.41	17.54
Pb(II)	7.19	(5.21)	12.40	7.79	(4.64)	12.43
Cd(II)	7.05	(4.17)	11.22	6.60	(4.85)	11.45
Zn(II)	6.51	(5.37)	(11.88)	6.53	(6.10)	12.63
Ni(II)	5.77	(4.43)	10.20	5.84	(4.82)	10.65
Co(II)	(5.93)	(4.28)	(10.21)	(5.75)	(5.05)	(10.80)
4-Hydroxybenzoxazole						
Cu(II)	6.40	5.85	12.27	6.56	(6.18)	12.74
Pb(II)	5.38	(4.33)	9.71	5.48	(4.53)	10.01
Zn(II)	(4.78)	(4.28)	(9.06)	..	..	...
Ni(II)	4.05	3.28	7.33	4.07	(3.62)	7.68
Co(II)	(3.81)	(3.22)	(7.03)	..	..	...
2-Methyl-4-hydroxybenzoxazole						
Cu(II)	6.21	5.64	11.89	6.46	6.08	12.53
Pb(II)	5.79	(5.02)	10.81	..	..	...
Ni(II)	4.61	(3.39)	8.00	..	..	...
Co(II)	(4.43)	(3.58)	(7.76)	..	..	...

be attributed to the mesomeric effect of the 'OH' group in the 4-position causing an increase in the electron density of the benzene ring and of the adjacent nitrogen atom.



The 2-methyl and the 2-ethyl derivatives show higher basicity (Table I) due to the inductive effect of the alkyl substituents. Their pK_{NH} values indicate that the inductive effect is practically the same in these two ligands.

The low basicity of the benzoxazoles (<2) is consistent with the higher electronegativity of the oxygen atom in the 1-position which tends to reduce the electron cloud on the nitrogen.

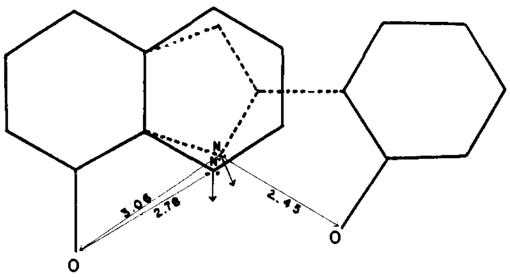


Fig. 1.—Chelation distances in 8-hydroxyquinoline, 4-hydroxybenzimidazole and 2-(*o*-hydroxyphenyl)-benzimidazole.

Lower hydrogen-bonding tendency of a hydroxyl group makes for better proton release resulting in higher acidity and lower pK_{OH}. An infrared investigation of the 'OH' absorption peaks in the 4-hydroxybenzimidazoles shows very little intramolecular hydrogen bonding.[14] This could therefore explain why the pK_{OH} values of these compounds are lower than that of 8-hydroxyquinoline.

Formation Constants.—The 2 log K_{av} values for the copper chelates of the 4-hydroxybenzimidazoles are lower than that of the 8-hydroxyquinoline chelate by a factor of 8 to 11 units (Table II). A corresponding decrease is observed with Pb(II), Cd(II), Zn(II), Ni(II) and Co(II). This difference seems abnormal considering ligand basicities.

Formation constants of the chelates of 4-hydroxybenzimidazole are lower than those of 2-(*o*-hydroxyphenyl)-benzimidazole,[15] although the latter ligand is less basic and should form the less stable 6-membered metal chelates.

In this study the complexes of Pb(II) and Cd(II) show greater stability than those of Ni(II) and Co(II). This is an inversion of the metal orders reported for similar compounds, such as 8-hydroxyquinoline[11] and 2-(*o*-hydroxyphenyl)-benzimidazole.[15]

The distance between the chelating atoms and the orientation of the lone pair of electrons on the donor nitrogen in the 4-hydroxybenzimidazoles could explain these anomalies. The nitrogen atom in 8-hydroxyquinoline is part of a regular hexagon with an internal angle of 120°, while that in the benzimidazoles is part of a more or less regular pentagon with an internal angle of about 108°. Due to this difference in the internal angles the donor nitrogen would be farther away from the phenolic oxygen in the 4-hydroxybenzimidazoles than in 8-hydroxyquinoline. Based on the assignment of bond length made by Ingold[16] the nitrogen–oxygen distances in 4-hydroxybenzimidazole, 8-hydroxyquinoline and 2-(*o*-hydroxyphenyl)-benzimidazole could be estimated to be about 3.1, 2.8 and 2.5 Å., respectively (Fig. 1). The large distance in the 4-hydroxybenzimidazoles could hinder strong chelation with metals by making it more difficult for the metal ion to be strongly held between the 'claws' of the chelating atoms. The absence of any appreciable amount of intra-molecu-

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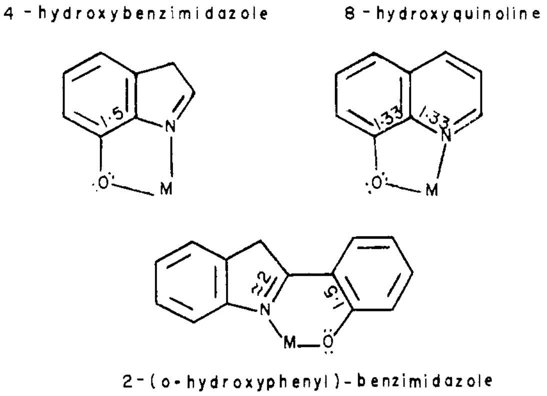

Fig. 2.—Double bond character of the bonds in the chelate rings.

lar hydrogen bonding in the ligands under study also indicates that the distance between the donor atoms is an important contributing factor in the formation of chelates, particularly, with the smaller metal ions.

The distance factor could also explain the inversion in stability values observed with the larger ions like Pb(II) and Cd(II). A comparative study of the log K_1 values (Table II) with the radii of the divalent metal ions shows that except with Cu(II) the decreasing order of stability is practically the same as the decreasing radius of the metal ion.

The difference in the internal angles could, in addition, cause a change in the orientation of the donor electrons on the nitrogen atom. Due to the repulsion from the bonded electrons the donor electrons of the nitrogen atom would be orientated in a direction bisecting the external angle as indicated by arrows in Fig. 1. Both the distance factor and the electron orientation, while appreciably hindering strong chelation in the 4-hydroxybenzimidazoles, would favor the formation of more stable chelates with 8-hydroxyquinoline and with 2-(*o*-hydroxyphenyl)-benzimidazole.

Calvin[17] showed that resonance contribution which depends on the double bond character of the bonds is an imporatnt factor contributing to the stability of a chelate ring. Based on the method of Pauling[18] and Branch and Calvin,[19] the "double-bondedness" of the bonds in 2-(*o*-hydroxyphenyl)-benzimidazole, 8-hydroxyquinoline and 4-hydroxybenzimidazole was assigned and, as seen in Fig. 2, decrease in the same order. This may be an additional factor contributing to the abnormally low stability values of the 4-hydroxybenzimidazoles.

The increase in stability values observed with the 2-methyl and the 2-ethyl derivatives of 4-hydroxybenzimidazole can be explained by the increase in ligand basicity and by the shielding effect of the alkyl groups in the 2-position. The shielding effect could partially block the solvent molecules from being tied up to the central metal ion, thus causing an increase in the number of free particles which would result in an entropy increase.

Ordinarily, an alkyl group in a sterically blocking position decreases the stability of the chelates. In this study, however, the formation constants indicate that steric hindrance, if any, is more than compensated by the combined effect of the increase in basicity and in entropy.

The very low formation constants of the 4-hydroxybenzoxazole chelates can be adequately explained by the factors mentioned above and by low ligand basicities. The smaller size of the oxygen atom in the 1-position might also tend to decrease, even if only slightly, the distance between the donor atoms. The same inversion of order for metal stabilities as in the 4-hydroxybenzimidazoles is observed with these ligands.

Introduction of a larger atom, such as sulfur or selenium, in the 1-position might tend to decrease the nitrogen-oxygen distance and change the electron orientation more favorably for chelation. Therefore, the study of the 4-hydroxybenzothiazoles and the 4-hydroxybenzoselenoles is being undertaken.

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