[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Interaction of Metal Ions with Amidoximes[1a]

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A series of amidoximes was investigated with respect to the reactivity toward transition metal ions. Benzamidoxime, α-phenylacetamidoxime, *o*- and *p*-toluamidoxime, 2- and 4-pyridine amidoxime, oxamidoxime, malonamidoxime and succinamidoxime were prepared together with hydrochloride and perchlorate derivatives. Copper and nickel salts of benzamidoxime, α-phenylacetamidoxime and oxamidoxime were prepared and analyzed. The ultraviolet spectra of the reagents were studied. Results showed that all of the compounds investigated undergo a bathochromic shift with increasing *p*H. The pK_a values for seven amidoximes were determined. The soluble blue complex formed between cobalt and monoamidoximes under extremely basic conditions was investigated.

Introduction

The preparation of amidoximes by the reaction of hydroxylamine on nitriles was first reported by Tiemann.[2] Subsequently, many investigators studied the effect of substituent groups in these compounds. Krug[3a] reported the formation of a red color on addition of ferric chloride to an amidoxime solution, and the first solid copper salt was reported by Werner.[3b] Dubsky and Trtilek[4] determined the formulas of certain solid copper and nickel complexes. Kuras and Ruzicka[5] proposed α-hydroxyisobutyramidoxime for the detection of mercury(I) ion. Other investigators have been interested in amidoximes as anti-tuberculants and as rust inhibitors.

Present interest in amidoximes was concerned with the reactivity of these compounds toward metal ions. Specifically, absorptimetric and potentiometric studies were carried out on transition metal ion systems. In addition, a number of solid metal–ligand reaction products were isolated and characterized.

Experimental Part

Reagents.—The amidoximes used in this study were prepared by the reaction of the nitrile with hydroxylamine. The following compounds, prepared according to reported procedures, yielded expected analyses and physical properties: benzamidoxime, BAO,[6] -α-phenylacetamidoxime, α-PAO,[7] *o*-toluamidoxime, *o*-TAO,[8] *p*-toluamidoxime, *p*-TAO,[8] 2-pyridineamidoxime, 2-pyAO,[9] 4-pyridineamidoxime, 4-pyAO,[9] malonamidoxime, MAO,[10] and succinamidoxime, SAO.[11] Oxamidoxime, OAO, was prepared by treating one mole of hydroxylamine with 0.5 mole of dithiooxamide (rubeanic acid) in an ethanolic solution. The hydroxylamine solution was prepared by neutralizing hydroxylamine hydrochloride with an equivalent amount of sodium carbonate. The reaction mixture was refluxed for 25 minutes and concentrated by vacuum distillation. The oxamidoxime, which precipitated as white needles, was recrystallized from water, and had a melting point of 203°. The yield was 75% compared to 40% for the cyanogen gas reaction described by Fischer.[12]

The hydrochloride derivatives of the amidoximes were prepared by dissolving the amidoxime in glacial acetic acid and passing dry hydrogen chloride gas through the solution. The precipitated hydrochloride was filtered, recrystallized from acetonitrile, and dried *in vacuo*.

Crystalline copper amidoxime salts were prepared by adding with stirring a saturated solution of copper(II) acetate to an aqueous solution of the ligand. The precipitate was washed, filtered and air-dried. These compounds were analyzed for copper content by electrodeposition. The compounds, dried at 0.1 mm. over phosphorus pentoxide for three days, were also analyzed.

The nickel salts of BAO, α-PAO, and OAO were prepared by the dropwise addition of a concentrated solution of ammonia to an aqueous solution containing the amidoxime and nickel(II) ion until a *p*H of 9 was established. These nickel salts were analyzed by the standard dimethylglyoxime procedure.

Acetonitrile was obtained from the Matheson, Coleman, and Bell Division of the Matheson Co. and was purified by standard methods.[13] The nitriles used in the synthesis of the corresponding amidoximes were obtained from Eastman Kodak Chemical Co. and used without further purification. The dithioöxamide was obtained from the Mallinckrodt Chemical Works and was used as received. The metal perchlorate salts were used as received from the G. Frederick Smith Chemical Co.

Spectrophotometric Measurements.—A Cary model 11 recording spectrophotometer was used to obtain absorptimetric data. The absorption spectra of the pure reagents and the metal ion–ligand systems under varying conditions of *p*H were determined. All measurements were made in 1-cm. silica cells at 25°.

Formulas for the cobalt monoamidoxime complexes were determined by the method of continuous variations.[14] Stock solutions of 1×10^{-3} *M* cobalt(II) ion and the reagent were prepared and aliquots were mixed in the appropriate ratios. Absorption measurements were made at selected wave lengths. Formulas were determined from plots of absorbance *versus* the mole fraction of metal ion in conjunction with the data obtained from the migration studies.

Potentiometric Measurements.—A Beckman model G *p*H meter equipped with a general purpose glass indicator electrode and a saturated calomel reference electrode was used to obtain potentiometric data. The meter was standardized at 25° with commercially available buffer solutions. Aqueous solutions containing 1.0–1.2 mmoles of the reagent, 2.75 mmoles of hydrochloric acid and 3.0 mmoles of potassium chloride were titrated potentiometrically with standard sodium hydroxide. The pK_a values for the amidoximes were calculated from measured *p*H values and from known concentrations of total acid and reagent in the usual manner.

Extraction Studies.—A study of the extractability of the blue complex resulting from the reaction of cobalt(II) ion with monoamidoximes in highly alkaline solutions was carried out. Common solvents immiscible with water were added to aqueous solutions containing the colored complex. The stability of the colored complex in the non-aqueous medium was compared to that in the aqueous medium.

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(1) (a) Presented before the Division of Analytical Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill. (b) An abstract of a thesis submitted by George A. Pearse, Jr., to the Graduate College of the State University of Iowa, 1959, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) F. Tiemann, *Ber.*, **17**, 126 (1884).

(3) (a) P. Krug, *ibid.*, **17**, 128 (1884); (b) A. Werner, *ibid.*, **41**, 1069 (1908).

(4) J. Dubsky and J. Trtilek, *Coll. Czech. Chem. Comm.*, **5**, 310 (1933).

(5) M. Kuras and E. Ruzicka, *ibid.*, **15**, 147 (1950).

(6) F. Tiemann, *Ber.*, **17**, 1685 (1884).

(7) P. Knudsen, *ibid.*, **18**, 1070 (1885).

(8) L. Schubert, *ibid.*, **22**, 2433 (1889).

(9) L. Michaelis, *ibid.*, **24**, 2439 (1891).

(10) H. Schmidtmann, *ibid.*, **29**, 1169 (1896).

(11) F. Sembritzki, *ibid.*, **22**, 2958 (1889).

(12) E. Fischer, *ibid.*, **22**, 1931 (1889).

(13) S. Wawzonek and M. Runner, *J. Electrochem. Soc.*, **99**, 457 (1952).

(14) P. Job, *Ann. chim.*, **9**, 113 (1928).

Transference Studies.—A Hittorf-type transference cell with platinum electrodes was used to investigate the influence of an electric potential on the cobalt benzamidoxime complex. A colored solution containing 0.1 *M* potassium chloride and the complex was introduced into the center compartment, and 0.1 *M* potassium chloride was placed in the electrode compartments. An average current of 0.5 amp. was applied for 30 minutes. The tris-1,10-phenanthroline-iron(II) complex was studied under identical conditions as a reference system.

Results and Discussion

Reagents.—All of the reagents prepared, with the exception of 4-pyAO and of OAO (prepared from dithioöxamide), had been previously synthesized. The preparation of 4-pyAO closely paralleled that of 2-pyAO, but OAO was synthesized utilizing an alternative method of preparation. In this method, dithioöxamide was treated with hydroxylamine in ethanolic solution. The reaction was complete in 25 minutes. This synthesis is much faster, safer, and more efficient than the preparation utilizing cyanogen.[12]

Hydrochloride derivatives of some of the amidoximes were prepared and twice recrystallized from acetonitrile. The compounds are white, high-melting, non-hygroscopic solids. The melting points of these salts are listed in Table I. Analyses of the hydrochlorides were made by gravimetric chloride determination with silver nitrate (Table I). The hydrochloride derivatives of amidoximes serve as a means of solubilizing those compounds which are difficultly soluble in water.

TABLE I

ANALYSES AND MELTING POINTS OF SOME AMIDOXIME HYDROCHLORIDES

Compound	M.p., °C.	Chlorine, % Calcd.	Chlorine, % Found[a]
BAO·HCl	176–177	21.12	21.07
2-pyAO·HCl	167	34.72	34.53
4-pyAO·HCl	209–210	34.72	34.46
OAO·2HCl	150	38.18	38.62
MAO·2HCl	171	35.57	35.84
SAO·2HCl	148	33.29	33.36

[a] Average value of three or more determinations.

The perchlorate salts of amidoximes were obtained as white, slightly hygroscopic, high-melting solids. Because they are somewhat hygroscopic, perchlorate salts are not as easily handled as the hydrochlorides. The perchlorate salts are also more difficult to prepare. They offer no advantages over the hydrochlorides with respect to analysis, solubility and stability.

The copper amidoxime salts were purified by treating the solid with hot water to remove any excess copper(II) salt and then with an appropriate organic solvent to remove any residual amidoxime. The air-dried salts were analyzed for copper by electrodeposition at a platinum electrode. In all cases of copper monoamidoxime salts, the results were consistent with a formula of $CuA(OH)\cdot H_2O$ where A represents the organic ligand. For the oxamidoxime, malonamidoxime and succinamidoxime salts, two molecules of water of hydration are present in the solid compound.

The above copper salts were obtained in anhydrous form upon dehydration *in vacuo* over phosphorus pentoxide. Melting points and analyses are presented in Table II.

TABLE II

ANALYSES AND MELTING POINTS OF SOME COPPER AMIDOXIME SALTS

Compound	M.p., °C.	Copper, % Calcd.	Copper, % Found[a]
Cu(BAO)OH	146–148	29.45	29.73
Cu(α-PAO)OH	143–144	27.66	27.98
Cu_2-OAO$(OH)_2$	213–215	45.85	46.21
Cu_2-MAO$(OH)_2$	Dec.	43.64	43.06
Cu_2-SAO$(OH)_2$	208–209	41.63	41.42

[a] Average value of three or more determinations.

Nickel salts obtained as insoluble red crystals from ammoniacal solutions of nickel(II) ion and the amidoxime were vacuum dried and analyzed by the standard dimethylglyoxime procedure. The nickel salt of benzamidoxime, melting at 126°, contains 20.31% Ni by analysis; the α-phenylacetamidoxime salt, m.p. 113°, contains 18.72% Ni. These results are not consistent with analogous formulations for the copper salts. The assumption can be made that the red material is a mixture of nickel salts. This is in agreement with the findings of Bandyopadhayay.[15]

The nickel salt of oxamidoxime, m.p. 270–272°, contains 20.11% nickel by analysis. This is consistent with the calculated percentage for $Ni(OAO)_2$. Thus it would appear that a normal type inner complex salt is formed between nickel and a diamidoxime ligand.

Effect of *p*H on Amidoxime Spectra.—The investigation of the effect of hydrogen ion concentration on the absorption of the pure reagent was studied by observing the changes in the ultraviolet spectra of the compounds. Absorptimetric data for amidoximes in deionized water are summarized in Table III. As the *p*H of a solution is increased, the wave length of maximum absorption shifts to longer wave lengths and is accompanied by a decrease in absorbance. The spectrum is essentially constant over a fairly wide *p*H range as shown by the study of BAO. From *p*H 1–5, BAO exhibits a maximum at 228 mμ with a molar absorptivity of 12,000. A gradual transition takes place until *p*H 8.5. At this *p*H, the curve shows a peak at 253 mμ with a molar absorptivity of 6,650. These same general bathochromic, hypochromic spectral shifts with increasing *p*H are characteristic of all the amidoximes investigated.

It was also found that the wave length of maximum absorption decreases with increasing chain length for aliphatic diamidoximes. No comparison could be made for aromatic amidoximes, but it was observed that 2- and 4-pyAO have much higher molar absorptivities than *p*- and *p*-TAO. This is consistent with the molar absorptivities of pyridine and benzene.

Basicity of Amidoximes.—The pK_a values for a series of amidoximes are presented in Table IV. The monoprotonated compounds are listed in order of increasing base strength.

Two interesting conclusions can be drawn from a study of the basicities observed. Firstly, the strength of an amidoxime as a base can be correlated

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(15) D. Bandyopadhayay, *J. Indian Chem. Soc.*, **30**, 119 (1953).

TABLE III

ABSORPTIMETRIC DATA FOR SOME AMIDOXIMES IN DEIONIZED WATER

Compound	λ_{max}, mμ	a_m
Benzamidoxime	250	5,400
o-Toluamidoxime	263	1,150
p-Toluamidoxime	257	5,700
2-Pyridineamidoxime	277	25,000
4-Pyridineamidoxime	268	22,500
α-Phenylacetamidoxime	258	400
	262	170
	267	120
Oxamidoxime	233	10,500
Malonamidoxime	228	11,000
Succinamidoxime	210	....

TABLE IV

BASICITY VALUES OF SOME AMIDOXIMES

Compound		pK_a
Oxamidoxime		3.02
o-Toluamidoxime		4.03
Benzamidoxime		4.99
p-Toluamidoxime		5.14
α-Phenylacetamidoxime		5.24
Malonamidoxime		~4.77
Succinamidoxime	pK_1	3.11
	pK_2	5.97

to the strength of the parent carboxylic acid. Thus if one plots the *pK*'s of amidoximes *versus* the *pK*'s of the parent acids, *i.e.*, benzamidoxime *versus* benzoic acid, *o*-toluamidoxime *versus* *o*-toluic acid, etc., a straight line relationship is obtained with the strongest acid yielding the amidoxime which acts as the weakest base. The same relationship can be observed in the data of Wise and Brandt[16] on the strengths of hydroxamic acids. From their data, it can be seen that the replacement of the carbonyl oxygen of an acid with an oxime group results in a hydroxamic acid which is approximately 4.6 *pK* units weaker than the original carboxylic acid. Further replacement of the hydroxyl group of the hydroxamic acid with an amino group to form the amidoxime results in a basic compound.

Secondly, whereas oxamidoxime is a diamidoxime, only one proton appears to be associated with the compound in solution. This is in agreement with the conclusions of Wenger, *et al.*,[17] who reported that the di-protonated reagent did not exist in aqueous solution. These authors calculated values of 2.95 ± 0.05 and 2.96 ± 0.05 for the pK_a of oxamidoxime from potentiometric and from spectrophotometric data, respectively. In the case of malonamidoxime, only an approximate value for the second dissociation constant for the protonated reagent could be calculated. Succinamidoxime, however, is derived from a weaker acid and it was possible to calculate the constants for the correspondingly stronger base.

Reaction of Metal Ions with Amidoximes.—The reactivity of amidoximes toward metal ions was studied. Iron(III) gives a strong red color with all of the amidoximes. This reaction can be used as a qualitative identification of these compounds, quite analogous to the iron hydroxamic acid test for the identification of organic esters. Of the metal ions studied, iron(III), cobalt(II), nickel(II), and copper(II) were of prime interest due to the colored complexes they form in both acetonitrile and in aqueous media. These systems were studied and it was found that the main advantage of acetonitrile as a solvent was the solubilization of the colored complexes formed. Figure 1 shows representative curves of copper(II), cobalt(II) and iron(III) with benzamidoxime in acetonitrile. The same low molar absorptivities were observed with other monoamidoximes. Nickel complexes exhibit very little absorption in the visible region of the spectrum. Diamidoximes likewise form metal ion complexes of low absorptivity in this region.

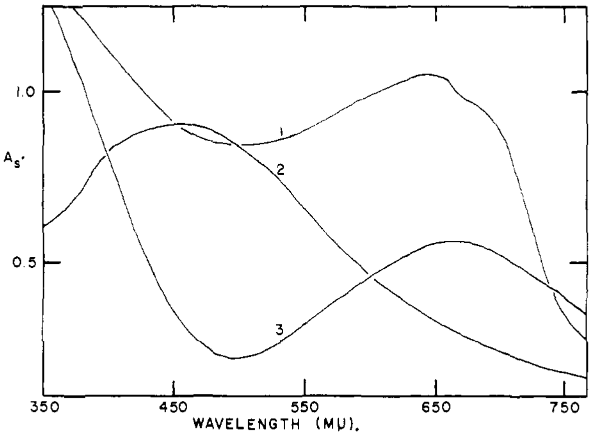

Fig. 1.—Absorption spectra of benzamidoxime–metal ion systems in acetonitrile: curve 1, cobalt(II) 1 × 10^{-1} *M*; 2, iron(III) 1 × 10^{-2} *M*; 3, copper(II) 2 × 10^{-1} *M*.

The above systems were investigated in aqueous media to determine the effect of hydrogen ion concentration on the complexes formed. Nickel, copper and iron form *p*H dependent colored complexes in the *p*H range of 1 to 7. The respective hydrous metal oxides precipitate at higher *p*H values. Cobalt forms a deep blue complex which is soluble in alkaline medium. The molar absorptivity of this complex increases with increasing *p*H.

Cobalt Amidoxime Systems.—Because of the uniqueness of the reaction of cobalt(II) ion with amidoximes, further study was limited to this system. The blue cobalt benzamidoxime complex was investigated fully to determine its physical properties and formula. The absorption due to the cobalt monoamidoxime complex is *p*H dependent and the system does not attain maximum color development until *p*H 12.5. It was also noted that only alkali metal hydroxides cause color formation. Coördinating amines interfere in the color development due to the formation of the cobalt amine complex. The blue benzamidoxime complex exhibits a wave length of maximum absorption at 580 mμ with a molar absorptivity of 2000.

Mole ratio studies on the effect of reagent concentration showed that maximum color formation resulted in solutions containing a 20:1 ratio of reagent to cobalt. The apparent instability of the

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[16] W. M. Wise and W. W. Brandt, THIS JOURNAL, **77**, 1058 (1955).

[17] P. E. Wenger, D. Monnier and I. Kapetanidis, *Helv. Chim. Acta*, **40**, 1456 (1957).

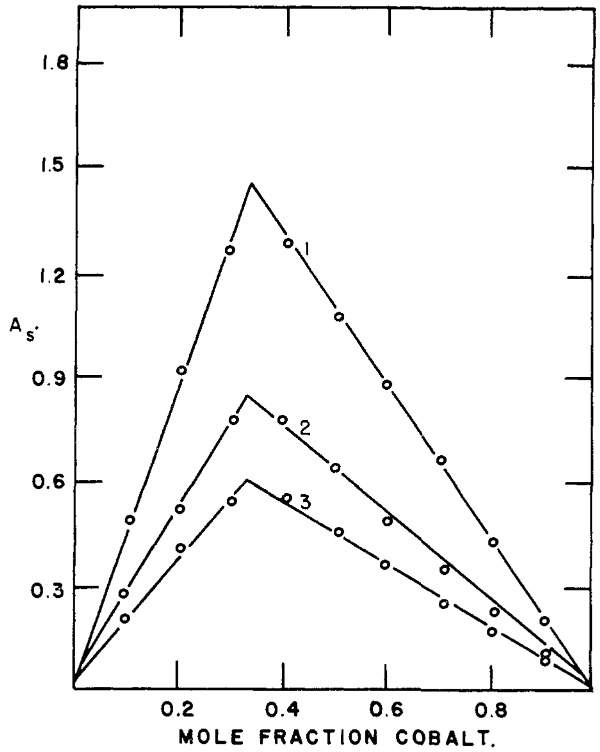


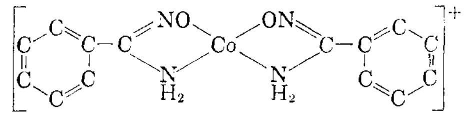
Fig. 2.—Continuous variations cobalt(II) and BAO at *p*H 12.5; curve 1, 573 mμ; 2, 625 mμ; 3, 550 mμ.

complex precluded a determination of the stoichiometry by this method.

In an attempt to stabilize the system, the blue complex was extracted into water-immiscible alcohols. Such an extraction is quite complete in a single volume of extractant. This increases the molar absorptivity of the complex by 50%.

Although all of the monoamidoximes, with the exception of 2-pyAO, form the blue complex, benzamidoxime gives a complex of greater stability and higher molar absorptivity. Continuous variation studies, Fig. 2, show that the complex exists in a two-to-one ratio of ligand to metal ion.

In order to assign a configuration to the blue species, it was necessary to determine if it were a charged complex. Investigations of this property were carried out in a Hittorf cell using tris-1,10-phenanthroline-iron(II) as a reference system. The results showed that the cobalt monoamidoxime complex was positively charged. From all of the data obtained, the blue cobalt benzamidoxime species, which exists in highly alkaline solutions, was assigned the formula



This structure necessitates cobalt being in the tervalent state. This is reasonable in view of the instability of the complex in the presence of reducing agents and the ultimate precipitation of cobaltic hydroxide out of strongly basic solutions.

The addition of alkali metal hydroxides to a solution containing cobalt and a diamidoxime such as oxamidoxime gives rise to a yellow complex. This species is not extractable into water-immiscible alcohols. The complex exhibits a greater stability toward chemical reducing agents than does the cobalt monoamidoxime complex.

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IOWA CITY, IOWA

[CONTRIBUTION NO. 483 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Piperidine Compounds. VII. The Synthesis of Arylpiperidinemethanol and Arylpiperidineëthanol Compounds

BY JACOB FINKELSTEIN AND WARREN SOLODAR

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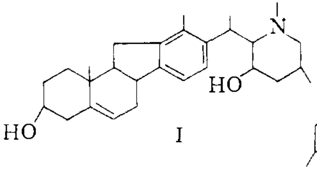
A number of piperidine compounds of potential pharmacological interest was synthesized in a search for hypotensive activity based upon certain structural and biological relationships.

The tertiary veratrum alkaloids have various powerful pharmacological effects, particularly vasodepressor properties,[1] and have been used as effective hypotensive agents in clinical trials.[2] The secondary veratrum bases also lower blood pressure and in addition have a specific antiaccelerator action on the heart and antagonize the effects of epinephrine on the heart.[3]

In a series of publications,[4,5] the structure of



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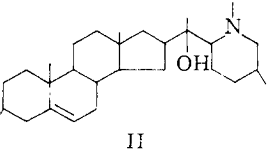

II

veratramine (I) was established as a steroid-like alkanolamine. However, on the basis of a formerly postulated structure, Uhle[6] prepared the synthetic steroid alkaloid II by treating 5-pregnene-3β-ol-20-one with 5-methyl-2-pyridyllithium and

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[1] O. Krayer and Acheson, *Physiol. Rev.*, **26**, 383 (1946).

[2] E. D. Fries and J. R. Stanton, *Amer. Heart J.*, **36**, 725 (1948).

[3] O. Krayer, *J. Pharm. Exp. Therap.*, **96**, 422 (1949).

[4] J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsburg, THIS JOURNAL, **73**, 2970 (1951).

[5] C. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952); O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

[6] F. C. Uhle, *ibid.*, **73**, 883 (1951).