

N-CARBOXYMETHYLAMINOACETO-N'-METHYLHYDROXAMIC ACID: ACID-BASE AND CHELATING PROPERTIES

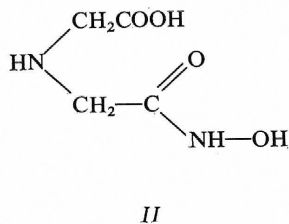
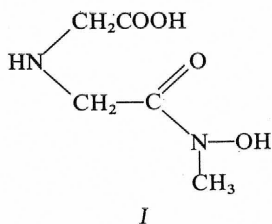
Rolf KARLÍČEK, Miroslav POLÁŠEK and Vladimír JOKL

*Department of Analytical Chemistry,
Faculty of Pharmacy, Charles University, 501 65 Hradec Králové*

Received October 10th, 1977

The preparation of N-carboxymethylaminoaceto-N'-methylhydroxamic acid is described. The dissociation constants of this compound were determined potentiometrically and spectrophotometrically. The reaction of the reagent with copper(II) ions was studied spectrophotometrically and the stability constants of the chelates formed were determined. The properties of the compound under study are discussed in comparison with the analogous hydroxylamine derivative.

This work is a continuation of our previous study of aminopolycarboxylic acid derivatives with the hydroxamic functional group^{1,2}. The objectives of this work were the preparation and study of the properties of a reagent derived from iminodiacetic acid, *viz.* N-carboxymethylaminoaceto-N'-methylhydroxamic acid (*I*). This reagent was deliberately prepared in order to contribute to the investigation of the structure of hydroxamic acid metal chelates from the aspect of the keto-enol tautomerism of the carbohydroxamic functional group. In contrast to N-carboxymethylaminoaceto-N'-methylhydroxamic acid³ (*II*), in the reagent *I* tautomerization of the chelating hydroxamic functional group cannot occur, and thus it reacts only in the keto form.



EXPERIMENTAL

Apparatus and Chemicals

Spectrophotometric measurements were performed on a recording spectrophotometer Unicam SP 1700 with a printer DR-16 using 1 cm and special 100 ml quartz cells for a current adjusting

and monitoring of the pH of the solution measured². The infrared spectra were measured in potassium bromide disks on a spectrophotometer Perkin-Elmer 577. For the measurement of the pH values of the solutions served a pH-meter PHM-52 with a combined electrode GK 2331 C (Radiometer); the latter was calibrated by means of phthalate, phosphate, and borate buffers, pH 4.002, 7.429, and 9.225, respectively, at 20°C. The potentiometric titrations were performed in 0.100M sodium perchlorate employing a plunger microburette ABU-12 (Radiometer). The concentration constants were calculated from the experimental pH values by using the γ_{H^+} parameter⁹; for 0.100M-NaClO₄, γ_{H^+} was determined to be 0.803.

The copper(II) perchlorate solution was prepared from the corresponding crystalline salt (Fluka) and standardized chelometrically. The other chemicals were reagent grade purity.

In order to adjust the pH of the solutions, 0.1M or 1M-NaOH, or 0.1M or 1M-HClO₄ was added by means of a plunger microburette. In all the solutions measured, the ionic strength was adjusted with 1M-NaClO₄ to $I = 0.1$.

Synthesis of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid

5.2 g (30 mmol) of iminodiacetic acid monomethyl ester³ is dissolved in 25 ml of a 2M methanolic solution of N-methylhydroxylamine and stirred at 20–25°C for 5 days. The reaction mixture is evaporated at a reduced pressure almost to dryness, the residue is dissolved in a small volume of methanol, and the crude product is precipitated with an addition of ethanol. After double crystallization from 90% ethanol, the compound forms fine colourless crystals stable on air, m.p. 170–172°C. It is very well soluble in water, soluble in methanol, low soluble in ethanol, and insoluble in ether. For C₅H₁₀N₂O₄ (162.1) calculated: 37.03% C, 6.22% H, 17.28% N; found: 37.18% C, 6.38% H, 17.05% N.

Dissociation Constants

The dissociation constants of the reagent *I* were determined in the same manner as previously¹. The calculation of the constants from the individual buffer zones of the potentiometric titration curve was performed on a digital computer ODRA 1204 using the program POT-3 (ref.⁴). From the spectrophotometric data, the constants were calculated employing the program by Albert and Serjeant⁵.

Formation of the Chelates

The formation of the copper(II) chelates was studied by measuring the absorption spectra of solutions containing various excess of the reagent in a wide pH region. Very fine measurements were enabled by a modification of the spectrophotometer allowing a continuous change of pH and simultaneous accurate measurement of the absorbance and the pH of the solution². The fundamental equations and the corresponding transformations making possible the evaluation of the found *A*-pH curves by graphical and logarithmic analyses have been given previously¹. The experimental data were also evaluated numerically by employing a computer.

RESULTS AND DISCUSSION

N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid

The potentiometric titration curve of the reagent exhibits an indistinct potential jump for one equivalent and two more pronounced ones for two equivalents of the

hydroxide per a molecule of the compound. The dissociation constants were determined potentiometrically both for fresh solutions and for solutions stored for a fortnight. All the values found are in a very good mutual agreement, which evidences that the reagent in question is stable in aqueous medium. The dissociation constant K_{a0} pertaining to the carboxylic group dissociation was obtained by evaluating the experimental data concerning the titration of a $2 \cdot 10^{-2}M$ solution of the reagent with $1M-HClO_4$. The average values of the concentration constants are given in Table I.

The UV absorption curves of acidic reagent solutions, up to pH 6, are virtually identical, displaying an absorption maximum at 203 nm. The shape of the curves alters on increasing the pH above 6, a new maximum appearing at 232 nm. The experimental values (ϵ) measured at this wavelength for solutions with different concentration of hydrogen ions are shown in Fig. 1, together with the theoretical curve calculated from the obtained dissociation constants and molar absorption coefficients.

In comparison with N-carboxymethylaminoaceto-hydroxamic acid³ and all amino-carbohydroxamic acids which have a single $-CH_2CONHOH$ grouping bound to the amine nitrogen atom¹, the reagent investigated, as a derivative of N-methylhydroxylamine, exhibits a bathochromic shift in the absorption spectra, and particularly, the dissociation of both protons is reflected in the UV spectra (Table II). At the same time, the constants calculated from the spectrophotometric data are equal (in the limits of experimental errors) to those obtained from the potentiometrically.

TABLE I

Dissociation Constants of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (I) and N-Carboxymethylaminoaceto-hydroxamic Acid (II) for the Temperature of 20°C, Ionic Strength 0.1 (NaClO₄)

P values obtained potentiometrically, for the reagent studied from six titrations, total of 204 experimental points; S values obtained spectrophotometrically, for the reagent studied from five sets, total of 125 experimental points; the confidence intervals calculated for the 95% probability.

Equilibrium	Constant	pK_a			
		I		II	
		P	S	P	S
$[H_2L][H]/[H_3L]$	K_{a0}	1.90 ± 0.05		1.75	—
$[HL][H]/[H_2L]$	K_{a1}	7.58 ± 0.02	7.63 ± 0.03	6.99	—
$[L][H]/[HL]$	K_{a2}	9.22 ± 0.02	9.20 ± 0.03	9.09	9.12

metric measurements. In the spectral region examined, all the compounds mentioned exhibit in the HL as well as in the ionized L form a single absorption band, analogously as benzohydroxamic acid N-alkyl and N-aryl derivatives^{6,7}.

The infrared spectra of N-carboxymethylaminoaceto-N'-methylhydroxamic acid (KBr disks, 1 mg of the substance in 400 mg KBr) measured in the region of 4000 to 200 cm^{-1} showed bands as follows (s strong, m medium, w weak; positions in cm^{-1}): 3420 s, 3000 m, 2800 m, 1650 s, 1610 s, 1550 w, 1400 s, 1320 w, 1200 s, 1120 m, 1060 m, 930 m. The band assignment to the significant groups in the reagent is given in Table III.

The results obtained indicate that the reagent under study in the form H_2L is present in an aqueous solution in the form of a dipolar ion, similarly as iminodiacetic acid. The basicities of the various groups of the two reagents compared (Table I)

TABLE II

Spectrophotometric Characteristics of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (I) and N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (II)

Species	I		II	
	λ_{max} nm	ϵ	λ_{max} nm	ϵ
H_3L^+ , H_2L	203	5 550	196	4 700
HL^-	232	4 250	196	4 700
L^{2-}	232	6 140	217	6 140

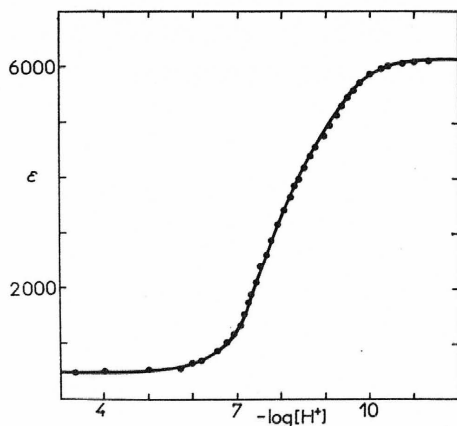


FIG. 1

Dependence of the Molar Absorption Coefficient of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid at 232 nm on the pH Value

Points — experimental values, solid line — theoretical curve.

approach each other closely. The K_{a2} values, pertaining to the dissociation of the proton from the carboxyhydroxamic and N-methylcarbohydroxamic groups, are virtually identical, which indicates the detachment of the proton from the same position in the molecule.

TABLE III

Positions of the Characteristic Infrared Absorption Bands of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (I) and N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (II)

Group vibration	Band position, cm^{-1}	
	I	II
O—H associated	3 400	3 400
N—H	3 050	3 050
O—H	2 800	2 800
C=O amide I	1 630	1 700
C=O asym (ionized carboxyl)	1 580	1 620
COO ⁻ sym	1 400	1 410
COO ⁻ asym	1 320	1 370

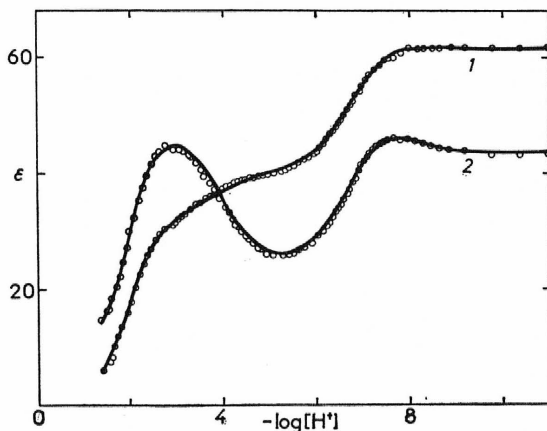


FIG. 2

Dependence of the Molar Absorption Coefficient of the System Cu(II)-N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid on the pH Value

$c_M = 3.0 \cdot 10^{-3} \text{ mol l}^{-1}$, $c_L = 1.5 \cdot 10^{-2} \text{ mol l}^{-1}$, $I 0.1 (\text{NaClO}_4)$; 1 650 nm, 2 760 nm; points — experimental values, solid lines — theoretical curves.

System Cu(II)-N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid

The formation of the copper(II) chelates was examined in the region of pH 1.38 to 11.0 in equimolar solutions and in solutions containing excess reagent ($c_M = 2.0$ to $3.0 \cdot 10^{-3} \text{ mol l}^{-1}$, $c_L = 0.2-1.5 \cdot 10^{-2} \text{ mol l}^{-1}$). In the region of pH < 3, the absorption curves exhibit a maximum at 740–750 nm; it shifted to approximately 650 nm on increasing the pH. The absorption curves of solutions of pH 3 to 5 intersect in an isosbestic point lying at 675 nm. In the range of pH 6 to 8 the absorbance of the solutions increases and the curves exhibit an absorption maximum near 670 nm. The curves of the dependence of absorbance on pH (A -pH curves) evaluated for 690 and 760 nm (Fig. 2) show the various ranges of formation and existence of the individual reaction products.

All the Job curves of isomolar solutions pH 3.0 as well as 5.5 exhibit in the region of 560 to 760 nm maxima evidencing the M : L ratio 1 : 1.

The ascending or descending branches of the A -pH curves were subjected to graphical and logarithmic analysis. In addition, the values of the molar absorption coefficients ϵ and of the equilibrium constants were obtained also by numerical calculations from the various pairs of points of the A -pH curves⁸. From these results and from the chelate compositions found it follows that under the conditions mentioned, the following equilibria of the copper(II) chelate formations establish:

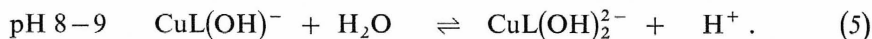
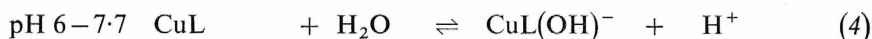
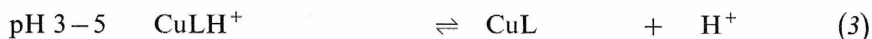
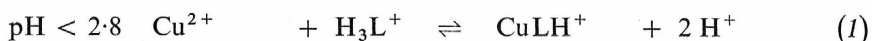
TABLE IV

Survey of the Constants of the Copper(II) Chelates of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (*I*) and N-Carboxymethylaminoaceto-hydroxamic Acid (*II*)

Temperature 20°C, ionic strength 0.1 (NaClO₄); the numerically obtained values are averages for 14–20 experimental points, always for three different wavelengths; concentrations: $c_M = 3.0 \cdot 10^{-3} \text{ mol l}^{-1}$, $c_L = 1.5 \cdot 10^{-2} \text{ mol l}^{-1}$ for *I*, and $c_M = 2.0 \cdot 10^{-3} \text{ mol l}^{-1}$, $c_L = 2.0 \cdot 10^{-2} \text{ mol l}^{-1}$ for *II*.

Equilibrium	Const.	Logarithm of the constant		
		<i>I</i>		<i>II</i>
		graphically		
		numerically		
$[\text{CuLH}][\text{H}]^2/[\text{Cu}][\text{H}_3\text{L}]$	$K_{2\text{H}}$	—1.74	—1.75	—
$[\text{CuLH}][\text{H}]/[\text{Cu}][\text{H}_2\text{L}]$	$K_{1\text{H}}$	0.16 0.15 ^a	0.15	— 0.86
$[\text{CuLH}]/[\text{Cu}][\text{HL}]$	$\beta_{1\text{H}}$	7.74	7.73	6.13
$[\text{CuL}][\text{H}]/[\text{CuLH}]$	K'	—3.85	—3.88	— 3.90
$[\text{CuL}]/[\text{Cu}][\text{L}]$	β_1	13.10	13.08	11.32
$[\text{CuL}(\text{OH})][\text{H}]/[\text{CuL}]$	k_1	—6.65	—6.65	— 5.92
$[\text{CuL}(\text{OH})_2][\text{H}]/[\text{CuL}(\text{OH})]$	k_2	—7.90	—7.88	—10.26

^a $c_M = c_L = 2.0 \cdot 10^{-3} \text{ mol l}^{-1}$.



The values of the equilibrium constants of these reactions as well as the stability constants of the various chelates are given in Table IV, the spectral characteristics are given in Table V. In order to verify the correctness of the considered copper(II) chelate formation equilibria and of the equilibrium constants and molar absorptivities found, the theoretical curve of the dependence of the absorbance on pH was calculated and plotted for the wavelengths of 760 and 650 nm (Fig. 2).

From a comparison of the studied reagent as an N-methylhydroxylamine derivative with the acid *II* as a hydroxylamine derivative it follows clearly that the CuLH^+ , CuL , as well as $\text{CuL}(\text{OH})^-$ species are very similar for the two compounds from the point of view of their optical properties, regions of existence, and stability (Tables IV and V). Marked differences in these properties appear in the case of the chelates formed from the two reagents at $\text{pH} > 8$, where the reagent *I* cannot react in the tautomeric enol form, in contrast to the reagent *II*. It is thus obvious that in the chelates CuLH^+ , CuL , and $\text{CuL}(\text{OH})^-$ of both reagents, in addition to the amine nitrogen and the carboxylic group also the hydroxamic group in the keto form

TABLE V
Spectrophotometric Characteristics of the Copper(II) Chelates of N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (*I*) and N-Carboxymethylaminoaceto-N'-methylhydroxamic Acid (*II*)

Chelate	<i>I</i>			<i>II</i>			
	pH	λ_{max} nm	ϵ graph. numer.	pH	λ_{max} nm	ϵ	
CuLH^+	2.8	750	49.3	49.7	2.8	760	40.4
CuL	3—5	650	40.2	40.3	3—5.3	650	72.0
$\text{CuL}(\text{OH})^-$	6—7.7	670	62.5	62.6	6.5—9	600	79.0
$\text{CuL}(\text{OH})_2^{2-}$	8—9	670	62.5	62.6	9—11	560	112.5

(acting as a single-donor group and coordinating *via* the oxygen atom with the formation of a six-membered chelate ring) takes part in the coordination. The great difference in the properties of the chelates $\text{CuL}(\text{OH})_2^{2-}$ is likely to be due to the capability of the reagent *II* to react at $\text{pH} > 8$ also in the tautomeric enol form.

REFERENCES

1. Karlíček R., Jokl V.: This Journal 42, 637 (1977).
2. Karlíček R.: This Journal 40, 3825 (1975).
3. Karlíček R., Majer J.: This Journal 37, 151 (1972).
4. Havel J., Pajrtová O.: Scr. Fac. Sci. Univ. Brno, in press.
5. Albert A., Serjeant E. P.: *The Determination of Ionization Constants*. Chapman and Hall, London 1971.
6. Plapinger R. E.: J. Org. Chem. 24, 802 (1959).
7. Manole S. F., Filippov M. P., Barba N. A.: Zh. Org. Khim. 7, 2452 (1971).
8. Sommer L., Jin Tsin-Jao: Chem. Listy 55, 576 (1961).
9. McBryde W. A. E.: Analyst (London) 94, 337 (1969).

Translated by P. Adámek.