Preparation and study of amino acid (DL-leucine, L-isoleucine, L-histidine) Schiff bases with ethyl-α-ketocyclopentylcarboxylate and the corresponding copper(II) complexes

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Abstract

Amino acid Schiff bases with ester function K(Rleu)·$2H_2O$ (**1**), K(Rile)·$2H_2O$ (**2**), K(Rhis)·H_2O (**3**) (Rleu, Rile and Rhis represent the Schiff base of DL-leucine, L-isoleucine and L-histidine, and ethyl-α-ketocyclopentylcarboxylate) were synthesized. Compounds **1, 2** and **3** were characterized by ^1H NMR spectroscopy. The copper(II) complexes, Cu(Rleu')·H_2O (**4**), Cu[Rile']·H_2O (**5**) and Cu(Rhis')·$2H_2O$ (**6**), were obtained with the N-deprotonated Schiff bases (Rleu', Rile' and Rhis'). The COO stretching bands in their IR spectra suggest that the carboxylate acts as a monodentate group when binding with copper. The temperature dependence of the susceptibility for **6** may be fit to the Curie–Weiss expression $\chi = 0.32/(T-26.2)$ emu mol^{-1} K^{-1}. The dehydration process of **6** leads to the anhydrous compound, enthalpy (53 ± 2kJ mol^{-1}) and activation energy (82 ± 5 kJ mol^{-1}).

Introduction

Several cations play an important part in many biochemical reactions such as transaminations or decarboxylations in which pyridoxal-dependent enzymes are involved. These reactions occur via the formation of a Schiff base between the pyridoxal and various amino acids [1]. Copper, zinc and other metal complexes with Schiff bases of amino acids and diverse carbonyl compounds such as pyridoxal, salicylaldehyde, camphor derivatives, pyruvic acid and acetylacetone are known [2, 3].

In the present work we have prepared and studied the Schiff bases obtained by the reaction between the β-ketoester, ethyl-α-ketocyclopentylcarboxylate and diverse amino acids. The ester function present in these compounds provides new possibilities for the coordination of copper. The study of the corresponding glycine Schiff base and its copper complex has been reported previously [3a].

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Results and discussion

Infrared spectra

Table 1 gives the assignments of the most important bands. The carboxylate group exhibits two frequencies corresponding to the asymmetric and symmetric stretching modes [4, 5]. In the copper complexes **4, 5** and **6** these frequencies are separated by 220–260 cm^{-1}, which suggests that the carboxylate acts as a monodentate group when binding with copper [6]. The broad bands of weak intensity located at 2137, 2128 and 2028 cm^{-1} in the spectra of 'DL-leu', 'L-ile' and 'L-his', respectively, correspond to the zwitterionic form of the free amino acids [4]. When the Schiff base potassium salts and the corresponding copper complexes are formed this band disappears since the zwitterionic form does not exist in these compounds. Compounds **1, 2** and **3** exhibit an intense band at 1651 cm^{-1} which can be attributed to vibrations of the ester group and which shifts towards lower frequencies when coordinated with copper to form the corresponding compounds **4, 5** and **6**.

Electronic spectra

Table 2 gives the maxima in the UV and visible spectra. The UV spectra of aqueous solutions of the Schiff base potassium salts exhibit two bands of strong

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TABLE 1. FT-IR important bands (cm^{-1})[a]

Compound	ν(OH)	ν(NH)	ν(COO)	ν(ester)	Other
K(Rile)·2H_2O	3428s	3329m	1623s 1365m	1651s	777m
Cu(Rile')·H_2O	3421b		1592s 1368m	1630s	1479s, 1312s 1044m, 752m
K(Rleu)·2H_2O	3421b	3338s	1578s 1386m	1651s	1402m, 777m
Cu(Rleu')·H_2O	3432s		1615s 1357s	1640s	1384m, 1366m
K(Rhis)·H_2O	3402s	3127b	1580s 1387s	1651s	1636s, 1272s, 1498s, 777s
Cu(Rhis')·2H_2O	3431s		1613s 1385s		1462m, 1292s, 890m

[a]s = strong, m = medium, b = broad.

TABLE 2. Electronic spectral and conductivity data of the compounds

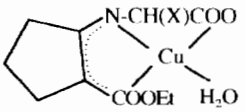
Compound	Solvent	λ_{max}(nm) (logϵ)	Λ^a (Ω^{-1} cm^2 mol^{-1})
K(Rhis)·H_2O	H_2O	300 (3.7), 202 (3.5)	53.7
	$CHCl_3$	300 (3.1), 203 (3.3)	0.06
K(Rile)·2H_2O	H_2O	301 (3.1), 189 (3.5)	54.3
	$CHCl_3$	294 (4.1), 242 (4.2)	0.04
	DMSO	303 (3.9), 255 (3.6)	12.5
K(Rleu)·2H_2O	H_2O	300 (3.2), 200 (3.2)	50.0
	$CHCl_3$	297 (3.5), 240 (3.3)	0.04
	DMSO	301 (3.6), 250 (3.4)	13.7
Cu(Rhis')·2H_2O	$CHCl_3$	610 (1.7), 445 (1.3), 330 (3.4), 241 (3.0)	0.05
	DMSO	610 (2.2), 590 sh[b], 450 (1.3)	0.49
	solid	630, [752, 640, 555][c], 461	
Cu(Rile')·H_2O	$CHCl_3$	727 (1.3), 300 sh, 240 (3.6)	1.7
	DMSO	675 (1.9), 322 (3.5), 259 (3.6)	1.5
	solid	680, [819, 756, 668][c]	
Cu(Rleu')·H_2O	$CHCl_3$	712 (1.6), 300 sh, 244 (3.5)	0.04
	DMSO	715 (1.7), 323 (3.4), 265 (3.4)	1.2
	solid	700, [832, 722, 625][c]	

[a]$c = 10^{-3}$ M. [b]sh = shoulder. [c]In brackets: Gaussian analysis.

intensity situated at 200 and 300 nm. These bands are associated with π–π^* transitions, the first with those of the imidazole, imine and carboxylate groups and the second with those of the ester group [7]. In the copper complex with L-histidine a band appears at 241 nm, indicating binding of imidazole to copper by pyridinic nitrogen (N3) [8, 9]. This band shifts towards higher wavelengths as a consequence of coordination when binding with copper in compound **6**.

In the solid state, complex **6** shows an asymmetric band that includes other transitions indicating a certain degree of distortion in the region with the lowest energy. Assuming a tetragonal distortion, three transitions could be expected which would correspond to the three Gaussian components (Table 2) [10, 11] into which the spectrum is split, and which could be attributed to transitions from (xz, yz), z^2 and xy to the x^2–y^2 orbital. The maximum of this band is located at 630 nm and is consistent with the value calculated (636 nm) by the equation proposed by Sigel and Martin [12] for copper complexes with amino acids. In chloroform and 'dmso' solutions this maximum does not shift noticeably and the curve remains asymmetric, which suggests that the solvent does not appreciably alter the environment of the ligand groups.

In the solid state, complexes **4** and **5** also show an asymmetric band in the visible spectrum; their maxima are 700 and 680 nm. The value calculated by the method of Sigel and Martin is 698 nm, assuming a distorted square-planar environment (see below), formed by the ester, carboxylate, imine and aqueous groups.



In this environment three transitions could be expected; this would be consistent with the assumption of three components into which the curve of the spectrum for the solid state is split and could also be attributed to the transitions for the previously indicated geometry [11] (Table 2). The spectra recorded in chloroform and in 'dmso' show a single symmetric d–d band whose maximum does not differ greatly from that of the maximum of the spectrum in the solid state, hence in these solvents the coordination environment is not appreciably modified.

Magnetic moments and ESR spectra

The magnetic moments of the compounds determined at room temperature have values of 1.9 and 2.0 μ_B for compounds **4** and **5**, which are similar to those shown by similar compounds [3a, 13]. The temperature dependent susceptibility for **6** may be fit to the Curie–Weiss expression $\chi = C/(T-\Theta)$. A least-squares fit of the data yields $C = 0.32$ emu mol^{-1} K^{-1} and $\Theta = 26.2$ K.

The ESR spectra of microcrystalline samples of **6** are isotropic with g_{iso} values of 2.107 and 2.113 at 77 K and room temperature, respectively. The spectra in chloroform solution are also isotropic, with values of 2.100 and 2.108 at 77 K and room temperature, respectively. These spectra are compatible with the assumption of a tetragonal environment [14], which would not appreciably change with the temperature. This behaviour is consistent with the slight variation of the spectra in solid state and in solution.

Thermal analysis

The data referring to the thermogravimetric analysis (TG) and the differential thermal analysis (DTA) are shown in Table 3. The thermograms of the Schiff base potassium salts, recorded in air or in argon, reveal an initial weight loss corresponding to the loss of hydration water molecules. In the corresponding DTA diagrams this loss of water molecules causes the appearance of an endothermic peak.

Dehydration of the copper complexes **4** and **5** in air or argon occurs simultaneously with decomposition of the complexes, so that there is a short plateau in the corresponding TG diagrams for this process. In the DTA diagrams obtained under the same circumstances, an exothermic peak is observed which could include both processes, dehydration and decomposition. This decomposition of the copper complexes probably consists of the loss of the ethylcarboxylate group, as has been observed in the pyrolysis of ethyl-α-ketocyclopentylcarboxylate [15].

The dehydration of **6** gives rise to a well-defined plateau for the anhydrous complex and an endothermic peak in the DTA diagrams in air or argon. The exothermic peak at 193 °C observed in the DTA diagram in air corresponds to a sharp weight loss in the TG obtained under the same conditions. This weight loss (18%) could be due to the loss of the ethylcarboxylate group (20.6%).

The end thermogravimetric residues of the potassium salts are composed of potassium carbonate which was identified by IR spectroscopy. These residues contain a certain proportion of carbon, especially if the atmosphere used is argon. The copper complexes always lead to the formation of CuO as the final residue in air.

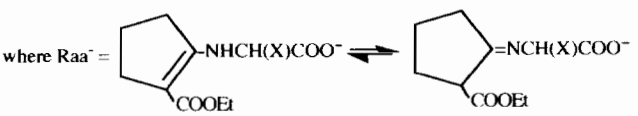
The activation energy for **6** was calculated by the method proposed by Horowitz and Metzger [16] and by the weight loss data provided by the thermograms recorded under an argon atmosphere [17]. The values obtained, assuming first order kinetics for the dehydration, are 87 and 77 kJ mol^{-1}. The dehydration enthalpy for this process is 53 kJ mol^{-1} and was determined from the corresponding DSC curve.

Experimental

Preparation of amino acid Schiff base potassium salts

The compounds were prepared by mixing the corresponding amino acid (0.02 mol of DL-leucine, L-isoleucine or L-histidine) with ethyl-α-ketocyclopentylcarboxylate (10 ml, 0.08 mol) and KOH (0.02 mol). The suspension obtained was stirred until a yellowish solution resulted. A microcrystalline precipitate was obtained when this solution was placed in a vacuum dessicator. The precipitate was isolated by filtration and washed with ether. The proposed formulae for the compounds are as follows

$K(Raa)\cdot nH_2O$



1: $K(Rleu)\cdot 2H_2O$, X = $-CH_2CH(CH_3)_2$, $n = 2$
2: $K(Rile)\cdot 2H_2O$, X = $-CH(CH_3)CH_2CH_3$, $n = 2$
3: $K(Rhis)\cdot H_2O$, X = $-CH_2Im$, $n = 1$

$K(Rleu)\cdot 2H_2O$ (**1**), DL-leucine Schiff base. Found: C, 50.8; H, 7.7; N, 3.9%; yield 30–40%. $\delta_H(CDCl_3, SiMe_4)$: 0.85 (6H, d, $-CHMe_2$), 1.21 (3H, t, $-CH_2Me$), 1.69 (6H, br m, $-CH_2CH_2CH_2-$), 2.43 (2H, m, $-CH_2CHMe_2$), 3.71 (2H, q, $-CH_2Me$), 4.02 (1H, m, $-CHCO_2-$) and 7.96 (1H, d, NH).

$K(Rile)\cdot 2H_2O$ (**2**), L-isoleucine Schiff base. Found: C, 50.9; H, 7.4; N%, 4.1%; yield 35%). For both compounds **1** and **2**; Calc. for $C_{14}H_{26}KNO_6$: C, 49.0;

TABLE 3. Thermal analysis of the compounds

Compound	Atmosphere	DTA peaks (°C)[a]	TG (°C) (%weight loss, obs./calc.; compound)
K[Rhis]·H_2O ($KC_{14}H_{18}O_4N_3 \cdot H_2O$)	air	98en, 400ex	120, [4.3/5.1; K(Rhis)] 500, (80.3/79.2; K_2CO_3)
	Ar	90en, 450 ex	110, [4.8/5.1; K(Rhis)]
Cu[Rhis']·$2H_2O$ ($CuC_{14}H_{17}O_4N_3 \cdot 2H_2O$)	air	96en, 193ex, 250ex, 360ex	100, [8.0/9.2; Cu(Rhis')] 350, (21/20.3; CuO)
	Ar	88en, 208ex	100, [8.2/9.2; Cu(Rhis')]
K[Rile]·$2H_2O$ ($KC_{14}H_{22}O_4N \cdot H_2O$)	air	80en, 260ex, 330ex, 360ex	100, [9.4/11.0; K(Rile)] 600, (78.6/79.8; K_2CO_3+C)
	Ar	85en, 215en, 285en, 414ex	100, [9.3/11.0; K(Rile)]
Cu[Rile']·H_2O ($CuC_{14}H_{21}O_4N \cdot H_2O$)	air	132ex, 169ex, 243ex, 375ex 402ex	140, [4.9/5.1; Cu(Rile')] 460, (77.1/77.2; CuO)
	Ar	131ex, 172ex, 460ex	140, [5.0/5.1; Cu(Rile')]
K[Rleu]·$2H_2O$ ($KC_{14}H_{22}O_4N \cdot H_2O$)	air	117en, 177ex, 197en, 277ex 300ex	130, [9.0/10.5; K(Rleu)] 600, (81.8/80.0; K_2CO_3)
	Ar	105en, 203en, 290en	130, [9.5/10.5; K(Rleu)]
Cu[Rleu']·H_2O ($CuC_{14}H_{21}O_4N \cdot H_2O$)	air	171ex, 212ex, 265ex, 469ex	140, (5.0/5.1; Cu(Rleu')] 600, (75.5/77.2; CuO)
	Ar	99en, 174ex	140, [5.1/5.1; Cu(Rleu')]

[a]en = endothermic, ex = exothermic.

H, 7.6; N, 4.1%. δ_H($CDCl_3$, $SiMe_4$): 0.81 (6H, br m, –CH*Me*CH_2*Me*), 1.18 (3H, t, –CH_2*Me*), 1.73 (6H, br m, –*C*H_2*C*H_2*C*H_2–), 2.42 (2H, br t, –CHMe*C*H_2Me), 3.59 (2H, q, –*C*H_2Me), 4.00 (1H, br m, –*CH*CO_2–), 8.07 (1H, q, NH).

K(Rhis)·H_2O (**3**), L-histidine Schiff base. Found: C, 47.9; H, 5.9; N, 12.0%; yield 40%. Calc. for $C_{14}H_{20}KN_3O_5$: C, 48.1; H, 5.7; N, 12.0%. δ_H(D_2O, $SiMe_4$): 1.04 (3H, t, –CH*Me*), 1.49 (2H, m, –CH_2*C*$H_2$$CH_2$–), 2.18 (4H, m, –*C*$H_2$$CH_2$*C*$H_2$–), 2.88 (2H, m, –*C*$H_2$Im), 3.93 (2H, 9, –*C*$H_2$Me), 6.74 (1H, br s, *C4*Im) and 7.51 (1H, br s, *C2*Im). Conductivity measurements for 10^{-3} M solutions of **1, 2** and **3** (see Table 2) indicate non-electrolytic behaviour in non-polar solvents.

Preparation of copper complexes Cu(Rleu')·H_2O (4) and Cu(Rile')·H_2O (5)

The potassium Schiff base solution (0.01 mol and 20 cm^3 of H_2O) was added dropwise to the solution of copper acetate monohydrate (0.01 mol and 100 cm^3 of H_2O). The compounds precipitated as green micro-crystalline powders. The precipitate was isolated by filtration, washed with water and placed with calcium chloride in a dessicator under light vacuum conditions. The blue filtrate was treated with an equal volume of methanol, and blue crystals, characterized by elemental analysis, of $Cu(aa)_2$ were obtained (aa = leucine or isoleucine). The conductivity values show the non-electrolytic behaviour of **4** and **5** (Table 2).

Cu(Rleu')·H_2O (**4**). Found: C, 48.4; H, 6.4; N, 3.9; Cu, 18.3%; yield 35%.

Cu(Rile')·H_2O (**5**). Found: C, 48.5; H, 6.3; N, 4.0; Cu, 18.6%; yield 40%.

Calc. for both compounds **4** and **5**, $CuC_{14}H_{21}NO_5$: C, 48.2; H, 6.6; N, 4.0; Cu, 18.3%.

Preparation of Cu(Rhis')·$2H_2O$ (6)

The potassium Schiff base of the histidine was prepared *in situ* by mixing ethyl-α-ketocyclopentylcarboxylate (0.01 mol), L-histidine (0.01 mol) with a solution of KOH (0.01 mol and 30 cm^3 of H_2O). The reaction was completed when the oily drops of the β-ketoester were no longer observed. A solution of copper acetate (0.01 mol and 100 cm^3 of H_2O) was added dropwise to this solution and a green precipitate was obtained. The solid was isolated by filtration, washed several times with water and placed in a dessicator with calcium chloride. The same compound **6** was obtained by mixing equimolar amounts of **3** and copper acetate in water. Conductivity measurements show the non-electrolytic behaviour of **4, 5** and **6**. (Table 2).

Cu(Rhis')·$2H_2O$ (**6**). Found: C, 43.7; H, 5.4; N, 10.3; Cu, 15.9%; yield 40%. Calc. for $CuC_{14}H_{21}N_3O_6$: C, 42.9; H, 5.6; N, 10.7; Cu, 16.2%.

Instrumental techniques and reagents

The amino acids, ethyl-α-ketocyclopentylcarboxylate and copper acetate monohydrate were obtained from Lancaster Products. C, H and N analyses were performed with a Perkin-Elmer 2400 elemental analyzer. Copper content was determined complexometrically with 'edta' using murexide as the indicator.

Thermogravimetric (TG) curves were obtained in flowing air and argon (45 cm^3 min^{-1}) using a Perkin-Elmer model 3600 instrument coupled to a data station; the heating rates were 5, 10 and 20 °C min^{-1}. Differential thermal analysis (DTA) was performed using a Perkin-Elmer model 3600 instrument and the same conditions as for the TG curve, using alumina as the reference. The sample weights for DTA and TG analysis were 7–10 mg. The DSC curves were registered on a Perkin-Elmer DSC-4 apparatus, at a scanning rate of 5 °C min^{-1}, under an argon atmosphere. The sample weights employed were 4–6 mg and the apparatus was previously calibrated with a sample of purum indium.

Fourier transform infrared (FT-IR) spectra of the compounds were recorded using KBr pellets on a Perkin-Elmer M1700 apparatus. The electronic spectra were recorded with a Varian-Techtron spectrophotometer, model 635, using the diffuse reflectance technique for the solid samples. NMR measurements were performed on a Bruker WP 200SY instrument.

Magnetic moments were determined by the Gouy method using a Stanton MC-5 balance and $HgCo(SCN)_4$ as calibrant. The susceptibility data were corrected for diamagnetism by using Pascal constants. Magnetic susceptibility measurements of **6** in the temperature range 60–300 K were made using a fully automatic DSM 5 pendule susceptometer. The maximum field was 15 kG with $H\delta H/\delta z = 30$ kG^2 cm^{-1}. The ESR spectrum of **6** was recorded in the solid state and chloroform solution at room temperature and 77 K on a Bruker (model ER 200D, X band) spectrometer using 'dpph' as the calibrating field marker.

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