The Reaction of Copper(II) Complexes of Glycine Imines with Activated Olefins

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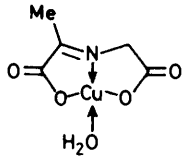
The reaction between *N*-pyruvoylideneglycinatocopper(II) and several activated olefins has been investigated. The products of the reaction are substituted proline derivatives which probably form by cyclization of the Michael adducts intermediates. The organic products have been isolated and characterized through their i.r., ^{1}H n.m.r., ^{13}C n.m.r. and mass spectra. The stereoisomeric composition of the products suggests that the cyclization occurs with a rather high degree of stereoselectivity. The possibility that the proline derivatives are formed *via* direct 1,3-anionic cycloaddition is presently discarded since this reaction is expected to occur with stereospecificity.

It has been known for some time that co-ordination of amino-acids and peptides to metal ions results in the activation of their methylene or methine protons in the α-position.[1] This reactivity is further enhanced in Schiff-base complexes of amino-acids and peptides which provide both versatile substrates for the homologation of amino-acids [2-7] and peptides,[8] and simple models of the biological transformations of amino-acids catalysed by vitamin B_6.[9,10] We recently reported that the imine moiety of *N*-salicylideneglycinatocopper(II) undergoes a cyclization reaction with acrylonitrile to give a substituted proline derivative.[11] The relevance of this result is related to the direct involvement in the reaction of the azomethine group, which is usually claimed to be protected by co-ordination to a metal ion. The reaction,



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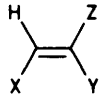
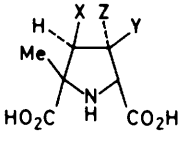


(2)

i NEt_3/pyridine
ii Dowex [H^+]

a: X = CN; Z = Y = H
b: X = CO_2Me; Z = Y = H
c: X = Ac; Z = Y = H
d: X = CHO; Z = Y = H
e: X = Y = CO_2Me; Z = H
f: X = Z = CO_2Me; Y = H
g: X, Y = CONHCO; Z = H



(3)

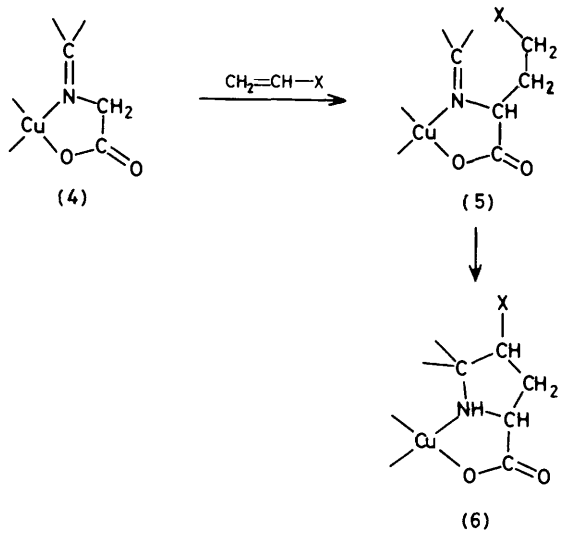
however, produces mixtures of mono- and di-alkylation products which are rather difficult to separate.[11,12] We report here that *N*-pyruvoylideneglycinatocopper(II) (1) † undergoes regiospecific alkylation reactions with a variety of activated olefins (2) to give the substituted prolines (3). Preliminary results concerning the preparation of (3a) and (3b) have been recently communicated.[13]

† Systematic name: *N*-(carboxyethylidene)glycinato(2−)-O^1,O^2,*N*-copper(II).

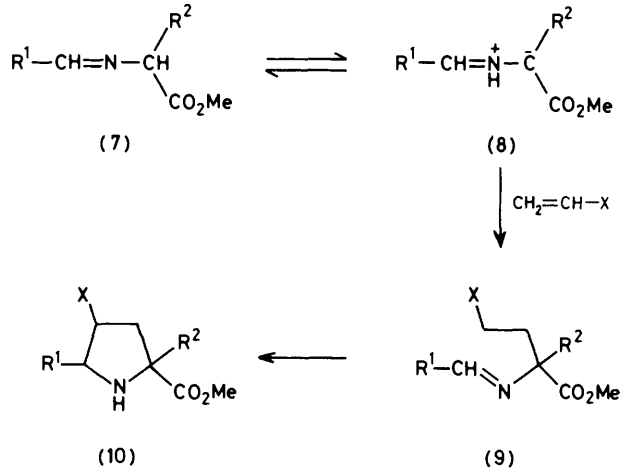
RESULTS AND DISCUSSION

Alkylation of the α-carbon atom of glycine residues co-ordinated to copper(II) by electrophiles such as aldehydes,[5] alkyl halides,[6] or acrylic compounds [7] has been found to occur only when the glycine fragment is bound to the metal ion in the form of a chelate Schiff base. Thus, while the reactions of simple glycinato-metal complexes with aldehydes can give the desired *C*-alkylation products because preliminary *N*-alkylation produces *in situ* the reactive Schiff base complexes, the corresponding reactions with alkyl halides or acrylic compounds invariably lead only to *N*-alkylation products. We have found that *N*-pyruvoylideneglycinatocopper(II) (1) and acrylic compounds (2) react under mild conditions to form the substituted proline derivatives (3). The reaction is easily carried out in pyridine, at room temperature, and in the presence of stoicheiometric amounts of triethylamine. The copper(II) ions are easily removed from the products by exchange with protons on a cation-exchange resin. This procedure has been found more advantageous than alternative methods (treatment with hydrogen sulphide or sodium borohydride) which can cause an alteration of the functional groups present in the products. An interesting feature of this reaction is its selectivity. The substituted prolines (3) are not contaminated by the Michael adducts (5) or by di-alkylation products, as it was found, for instance, in the reaction between *N*-salicylideneglycinatocopper(II) and acrylic compounds.[11,12] Therefore the reaction described here may prove of synthetic utility for the preparation of substituted proline derivatives of type (3). The products have been characterized on the basis of elemental analysis and i.r., ^{1}H n.m.r., ^{13}C n.m.r., and mass spectral evidence (Tables 1—4).

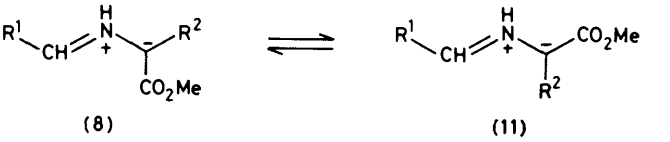
Much current interest in the reactions of imines of α-amino-acid esters (7) centres on their potential sources of 1,3-dipolar species (8).[14] These can undergo regiospecific Michael addition reactions to give compound (9),[15] and cycloaddition reactions to give (10) [16,19] with a variety of activated olefins. The cyclisation (9)→(10) is formally an example of a geometrically disfavoured 5-*endo-trig* process.[20,21] However, formation of pyrrolidines from imines of α-amino-acid esters and activated olefins has been reported to occur in either a single-step



or a two-step Michael addition-cyclization sequence.[18] The reactivity of the imine moiety in compound (4) is, therefore, formally similar to that of (7). This can be explained by considering that co-ordination of the imine



nitrogen to a metal ion in (4) is the potential source of a chelated carbanion with 1,3-dipolar character similar to (8). In addition, metal-chelate systems of type (4), cannot undergo dipole stereomutation [(8) ⇌ (11)],[17] which competes with the cycloaddition reaction when less reactive dipolarophiles are used, and should, in principle, provide better substrates than their organic counterparts.



The substituted prolines (3) are obtained as diastereoisomeric mixtures, although in each case except for (3a),[13] the number and relative intensity of the C(2)-methyl signals in the proton and carbon-13 n.m.r. spectra indicate that one isomer is formed with a rather high degree of stereoselectivity. The gas-chromatographic/mass-spectrometric analysis of the *N*-trifluoroacetyl dimethyl esters of (3a—g) confirms in several cases the diastereoisomeric composition of the products inferred from n.m.r. spectra, while in other cases [*e.g.* (3d) and (3e)] the number of isomers seems to be higher. These possibly arise from epimerisation processes during derivatization and we are currently investigating this point in more detail. Detection of the Michael adduct (5),[11,12] though in small amounts,[22] indicates that at least in the case of *N*-salicylideneglycinatocopper(II) formation of prolines (6) can occur in the two-step path. We could find Michael adducts in no more than trace amounts on reaction of compound (1) with acrylic compounds,[22] although the isolation of prolines (3) as mixtures of diastereoisomers, unless these arise by epimers equilibration, suggests that in this case also the reaction proceeds in a two-step Michael addition-cyclisation sequence. Easy 5-*endo-trig* cyclisations of the Michael adducts (9) actually occur with a comparable degree of stereoselectivity,[19] while cycloadditions to imines of α-amino-acid esters are known to be stereospecific.[17] Inspection of molecular models indicates that cyclization of the Michael adducts (12) is almost impossible from a side of the molecular plane opposite to that from where alkylation of the α-carbon atom has occurred. This is particularly evident if the α-carbon substituent of the amino-acid residue occupies an axial position. The marked preference for this axial disposition of the amino-acid side-chain in Schiff's base chelates derived from a

TABLE 1

Elemental analyses, selected i.r. data, and yields of substituted 5-carboxy-2-methylprolines (3c—g)

Compd.		Found (Calc.) % C	H	N	Yield (%, isolated)	Selected i.r. data (cm^{-1}) [a]
(3c)	$C_9H_{13}NO_5 \cdot H_2O$	46.15 (46.35)	6.25 (6.48)	6.08 (6.01)	80	1 760 (CO_2H), 1 720 (COMe), 1 630 (NH_2^+, CO_2^-).
(3d)	$C_8H_{11}NO_5 \cdot H_2O$	43.95 (43.83)	6.1 (5.98)	6.4 (6.39)	75	1 740 (CO_2H, CHO), 1 640 (NH_2^+, CO_2^-).
(3e)	$C_{11}H_{15}NO_8 \cdot H_2O$	43.1 (42.98)	5.5 (5.58)	4.65 (4.56)	65	1 750 (CO_2Me, CO_2H), 1 640 (NH_2^+, CO_2^-).
(3f)	$C_{11}H_{15}NO_8 \cdot H_2O$	43.0 (42.98)	5.35 (5.58)	4.55 (4.56)	67	1 750 (CO_2Me, CO_2H), 1 630 (NH_2^+, CO_2^-).
(3g)	$C_9H_{10}N_2O_6$	44.55 (44.63)	4.2 (4.16)	11.45 (11.57)	70	3 250 (NH), 1 740 (CO, CO_2H), 1 640 (NH_2^+, CO_2^-).

[a] Recorded as KBr pellets.

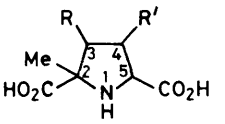


TABLE 2

^{1}H N.m.r. data of prolines (3c—g) in D_2O [a]

Compd.[b]	2'-Me	3-H	4-H	5-H	R,R'	Isomers ratio
(3c)	1.68 (s) [1.64] [1.55]	3.50 (dd) ($J_{3,4}$ + $J_{3,4'}$ 12.9 Hz)	2.3—3.1 (m)	4.40 (dd) ($J_{5,4}$ + $J_{5,4'}$ 16.1 Hz)	2.28 [(s) (R = COMe)] [2.35] [2.38]	0.70 : 0.25 : 0.05
(3d)	1.70 (s) [1.82] [1.60]	2.0—3.1 (m)		4.3 (m)	5.26 [R = $CH(OH)_2$] [c] (J 3.4 Hz)	0.85 : 0.10 : 0.05
(3e)	1.59 (s) [1.76] [1.72] [1.68]	3.6—4.1 (m) [d]		4.77 (d) [e] ($J_{5,4}$ 10.0 Hz)	3.78 (s), 3.82 (s) (R,R' = CO_2Me)	0.60 : 0.15 : 0.15 : 0.10
(3f)	1.83 (s) [1.80] [1.73] [1.66]	3.6—4.1 (m) [d]		4.83 (d) [e] ($J_{5,4}$ 8.0 Hz)	3.81 (s), 3.84 (s) (R,R' = CO_2Me)	0.60 : 0.30 : 0.05 : 0.05
(3g)	1.70 (s) [1.84] [1.59]	3.66 (d) ($J_{3,4}$ 8.3 Hz)	4.14 (~t)	4.60 (d) ($J_{5,4}$ 9.3 Hz)		0.85 : 0.10 : 0.05

[a] Chemical shifts in δ(p.p.m.); signal multiplicity is given in parentheses. [b] Data refer to the most abundant isomer in the mixture. Methyl signals belonging to the minor isomers are reported in square brackets. [c] The carbonyl group seems completely hydrated in solution, the proton signal refers to R = $CH(OH)_2$. [d] Obscured by methyl esters signals. [e] This signal is partly obscured by HDO, the J value was determined from spectra recorded in D_2O–CF_3CO_2D.

TABLE 3

Carbon-13 n.m.r. spectra of prolines (3c—g) in D_2O [a]

Compound [b]	2'-Me	2-C	3-C	4-C	5-C	C=O	Others
(3c)	22.2 (q)	73.9 (s)	52.4 (d)	38.8 (t)	57.8 (d)	173.1 (s) 174.9 (s)	31.0 (q) } 212.1 (s) } (3'-COMe)
	[21.8 (q)] [23.8 (q)]	[69.9 (s)] [71.8 (s)]	[54.0 (d) 58.3 (d)]	32.3 40.5 (t)	61.4 (d)] 62.4 (d)]	[171.6 (s)] [175.8 (s)] [176.2 (s)]	[29.5 (q), 30.4 (q)] [211.5 (s), 213 (s)]
(3d)	22.3 (q)	71.3 [d]	48.1 (d)	38.1 (t)	61.7 [d]	172.5 (s) 175.7 (s)	89.7 (d) [3'-$CH(OH)_2$] [e]
	[18.0 (q)] [24.3 (q)]		[29.4 (t), 46.7 (d),	36.0, 52.9 (d)]		[173.1 (s)] [173.3 (s)] [174.6 (s)] [174.9 (s)]	[89.1 89.4 (d)]
(3e) [c]	19.1 (q)	72.9 (s)	48.8 (d)	55.4 (d)	62.9 (d)	171.1 (s) 172.4 (s) 174.1 (s)	54.0 (q) } 54.3 (q) } (OMe)
	[19.3 (q)] [22.4 (q)] [24.4 (q)]	[72.1 (s)] [72.3 (s)] [72.6 (s)]	[48.1 (d) 49.3 (d) 49.6 (d)]	53.8—57.5 [f]	62.5 (d)] 63.7 (d)]	[170—175 [f]]	[53.8—57.5 [f]]
(3f) [c]	21.8 (q)	72.7 (s)	48.7 (d)	56.2 (d)	60.9 (d)	170.6 (s) [g] 171.1 (s) 172.2 (s) 172.6 (s) 173.4 (s)	54.3 (q) } 54.6 (q) } (OMe)
	[14.2 (q)] [17.9 (q)] [21.9]	[72.2 (s)] [72.4 (s)]	[48.9 (d) 49.1]	54.0—58.3 [f]	60.4 (d)] 64.1 64.3 (d)]	[170—176 [f]]	[54.0—58.3 [f]]
(3g) [c]	23.0 (q)	72.4 (s)	48.3 (d)	56.1 (d)	62.0 (d)	169.6(s) 172.2 (s) 176.9 (s)	
	[19.8 (q)] [24.9 (q)]	[71.8 (s)] [75.0 (s)]	[47.5 (d), 55.3 (d),	50.4 (d), 56.9 (d),	53.0 (d)] 62.6 (d)]	[170.6 (s), 174.3 (s), 176.6 (s)] [171.2 (s), 176.3 (s), 178.8 (s)]	

[a] Chemical shifts in δ(p.p.m.) relative to TMS, with dioxan as internal reference [δ(TMS) = δ(dioxan) +67.5]. Signal multiplicity is given in parentheses. [b] Data refer to the most abundant isomer in the mixture. Signals belonging to the minor isomers and clearly resolved from noise are reported in square brackets. For several signals of low intensity lying close to intense signals it is impossible to ascertain the multiplicity. [c] The assignments of 3-C and 4-C signals for these compounds might be inverted. [d] These signals are broad; the unresolved splittings probably arise from coupling with the adjacent nitrogen nucleus. [e] The carbonyl group seems completely hydrated in solution, the signal refers to $CH(OH)_2$. [f] Several signals. [g] One of these C=O signals belongs to a minor isomer.

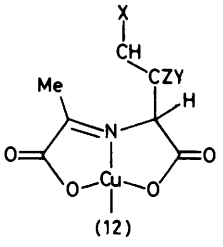
TABLE 4

Mass spectral data of prolines (3a—g)

Compound	*m/e* (%)
(3a)	82 (54), 99 (5), 107 (66), 108 (13), 127 (6), 153 (100), 154 (9), 167 (3), 198 (M^+, 0.8), and 199 ($M + 1^+$, 0.4).
(3b)	82 (80), 99 (86), 108 (46), 126 (22), 140 (77), 154 (9), 172 (15), 186 (100), 200 (1), and 232 ($M + 1^+$, 0.5).
(3c)	44 (100), 82 (73), 99 (5), 108 (8), 126 (5), 128 (18), 152 (2), 170 (43), 171 (4), 197 (1), 215 (M^+, 0.2), and 216 ($M + 1^+$, 0.3).
(3d) [a]	44, 80, 94, 95, 108, 109, 122, 139, 144, and 158.
(3e)	82 (47), 108 (69), 126 (26), 140 (88), 166 (81), 184 (19), 198 (15), 200 (13), 212 (29), 230 (7), 244 (100), 258 (7), 289 (M^+, 1.0), and 290 ($M + 1^+$, 0.8).
(3f)	82 (37), 108 (26), 126 (37), 140 (46), 184 (24), 198 (15), 212 (100), 226 (5), 228 (4), 244 (11), 271 (2), and 289 (M^+, 1.0).
(3g)	81 (33), 82 (21), 99 (46), 108 (35), 126 (21), 137 (17), 151 (62), 153 (40), 179 (19), 197 (100), 242 (M^+, 1.5), and 243 ($M + 1^+$, 1.2).

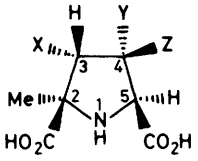
[a] This compound apparently decomposes on being heated in the ionization chamber.

variety of carbonyl compounds, including pyruvic acid, has been clearly demonstrated.[10,23] It originates from a significant steric interaction between the azomethine carbon substituent and the α-carbon side-chain in equatorial position, and qualitatively explains the low reactivity attainable by model systems related to



(12)

pyridoxal catalysis when cleavage of the C_α–H bond is required, since this C_α–H bond is confined to an unfavourable equatorial position for an easy breaking process.[10,24,25] The conformational restriction undergone by the Michael adducts (12), therefore, produces the observed stereoselectivity in the subsequent cyclization reaction: the major diastereoisomers of (3a—g) should contain in each case *cis*-carboxy-groups in the 2 and 5



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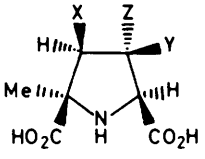

(14)

positions of the pyrrolidine ring, (13) and (14). To decide whether the more abundant isomer in (3a—g) is (13) or (14) we note that the most significant steric interaction occurring on cyclization of the adducts (12) is that between the 2-methyl group and the *cis*-3-X-substituent in the copper complex of (13). In fact, the lowest degree of stereoselectivity is observed in the products (3a) obtained from acrylonitrile,[13] where the size of the X group is the smallest within the series of olefins studied. On steric grounds, therefore, we expect that compound (14) represents the major isomer of the prolines (3). This interpretation is partly confirmed by the ^{1}H n.m.r. data in Table 2, which show that the vicinal coupling constant $J_{5,4}$ is larger in (3e) and (3g) than it is in (3f), in accord with the larger values usually found for *cis*-couplings than for *trans*-couplings of protons in these pyrrolidine ring positions.[26] The difference between $J(cis)_{5,4}$ and $J(trans)_{5,4}$ may seem rather small, but it is confirmed by the $J_{5,4} + J_{5,4'}$ values found for (3a—c). We are currently trying to achieve the complete separation of a set of isomeric prolines (3) for a more detailed analysis of the n.m.r. data.

EXPERIMENTAL

All chemicals were reagent grade and used as received. Elemental analyses were from the microanalytical laboratory of the University of Milano. ^{1}H N.m.r. spectra at 80 MHz were obtained on a Bruker WP–80 spectrometer; sodium 3-(trimethylsilyl)[$^2H_4$]propionate was used as an internal reference for D_2O solutions. Natural abundance ^{13}C n.m.r. spectra were recorded on a Varian XL–100A spectrometer operating at 25.2 MHz, in pulsed Fourier-transform, proton-noise decoupled, and single-frequency off-resonance decoupled mode. The field frequency was locked to internal D_2O. Peak positions were measured relative to TMS ($SiMe_4$) with dioxan as internal reference; δ(TMS) = δ(dioxan) +67.5.[27] I.r. spectra were recorded as KBr pellets on a Beckman Acculab 1 instrument. Mass spectra and combined g.l.c.–m.s. experiments were carried out on a Varian MAT 112 spectrometer equipped with a Varian Aerograph 144010 gas chromatograph. A glass column (1 m × 3 mm) packed with 1.35% neopentylglycol succinate on Chromosorb G, 80—100 mesh, was used at 190 °C (He, flow rate 20 cm^3 min^{-1}).

Dimethyl maleate and dimethyl fumarate were prepared according to literature methods.[28] *N*-Pyruvoylideneglycinatocopper(II) was prepared by adding an equimolar amount of freshly prepared cupric hydroxide to a solution of 10.6 g of glycine and 12.5 g of pyruvic acid in 50 cm^3 of 3 : 1 water–ethanol. After being stirred at room temperature for several hours, the product was filtered off, washed with water–ethanol, and dried by azeotropic distillation with benzene in a Dean-Stark apparatus (Found: C, 28.15; H, 2.6; N, 6.35. Calc. for $C_5H_5CuNO_4 \cdot 0.3H_2O$: C, 28.32; H, 2.66; N, 6.60%).

The reactions between *N*-pyruvoylideneglycinatocopper-(II) and the acrylic compounds were carried out according to the following procedure. *N*-Pyruvoylideneglicinatocopper-(II) (10 mmol) was dissolved in degassed pyridine (100 cm^3) and then triethylamine (1.4 cm^3) and the acrylic compound (10 mmol) were added with stirring to the solution. The mixture was allowed to react for 40 h and then evaporated to dryness under reduced pressure at room temperature. The residue was treated several times with water–ethanol and re-evaporated to dryness under reduced pressure in order to remove any traces of pyridine. The residue was then dissolved in water (300 cm^3) and passed through a column (18 × 3.2 cm) of Dowex 50W × 8 (H^+ form) resin. The column was eluted with water (3 l) and the eluant evaporated almost to dryness under reduced pressure. The product, (3), was recovered by adding a small amount of

ethanol to the residue, filtering it, and drying it *in vacuo*. The yields and analytical and spectral data of the products are collected in Tables 1—4.

The *N*-trifluoroacetyl dimethyl esters of (3) were prepared following usual procedures.[29] The amino-acid (10 mg) was treated with a freshly prepared solution of dry hydrogen chloride (4 mol dm^{-3}; 10 cm^3) in anhydrous methanol, and heated in a sealed tube at 85 °C for 1 h. The solution was evaporated to dryness under reduced pressure and the residue was treated with 10 cm^3 of a 20% solution of trifluoroacetic anhydride in methylene chloride for 1 h at 60 °C. After evaporation to dryness under reduced pressure, the residue was dissolved in methylene chloride (1 cm^3) and an aliquot (1 μl) of this solution was injected into the gas chromatograph. The g.l.c.–m.s. experiments are currently under investigation, detailed results will be reported separately.

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