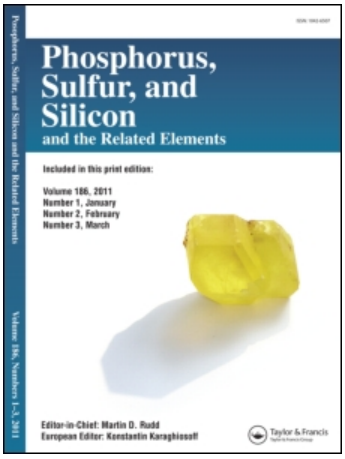


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

L-CYSTEINE COMPOUNDS WITH TWO ASYMMETRIC CENTRES AND THE RELATED CADMIUM COMPLEXES

Philippe Guerin[a]; Jean Paul Battioni[a]; Martine Leclerq[b]; Philippe Dumas[c]
[a] Laboratoire de Chimie de l'Ecole Normale Supérieure, associé au C.N.R.S. 24, Paris Cedex 05, France [b] Laboratoire de Chimie des Interactions Moléculaires, Collège de France, Paris, France [c] Laboratoire de Chimie macromoléculaire, associé au C.N.R.S. Université, Paris Cedex 05, France

To cite this Article Guerin, Philippe , Battioni, Jean Paul , Leclerq, Martine and Dumas, Philippe(1983) '*L*-CYSTEINE COMPOUNDS WITH TWO ASYMMETRIC CENTRES AND THE RELATED CADMIUM COMPLEXES', Phosphorus, Sulfur, and Silicon and the Related Elements, 15: 3, 351 — 357
To link to this Article: DOI: 10.1080/03086648308073314
URL: http://dx.doi.org/10.1080/03086648308073314

Phosphorus and Sulfur, 1983, Vol. 15, pp. 351–357
0308-664X/83/1503-0351/$18.50/0

L-CYSTEINE COMPOUNDS WITH TWO ASYMMETRIC CENTRES AND THE RELATED CADMIUM COMPLEXES

PHILIPPE GUERIN,* JEAN PAUL BATTIONI,*
MARTINE LECLERQ,** and PHILIPPE DUMAS***

**Laboratoire de Chimie de l'Ecole Normale Supérieure, associé au C.N.R.S. 24, rue Lhomond, 75 231 Paris Cedex 05 (France)*
***Laboratoire de Chimie des Interactions Moléculaires Collège de France, Place Marcellin Berthelot, 75005 Paris (France)*
****Laboratoire de Chimie macromoléculaire, associé au C.N.R.S. Université P. et M. Curie, 4, Place Jussieu, 75230 Paris Cedex 05 (France)*

(*Received December 13, 1982; in final form January 25, 1983*)

The cadmium complexes of *L*-cysteine alkyl esters have been shown to polymerize methylthiirane stereospecifically and stereoelectively. A series of *L*-cysteine esters with two asymmetric carbon atoms is prepared by reacting *L*-cysteine with the racemic mixture of various secondary alcohols: $CH_3CH(OH)R$ (with R = C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_{13}, $CH_2C_6H_5$) in the presence of dried HCl. It is shown that, under same experimental conditions, 1-phenyl ethanol (R = C_6H_5) gives rise to *S*-substitution instead of esterification. The structure of the resulting compound is confirmed, in particular, on the basis of ^{13}C and ^1H NMR spectra whose lines are assigned by comparison with spectra of model compound. The cadmium complexes of the various diastereoisomeric derivates of *L*-cysteine are prepared and characterized. Cadmium bis 2-octyl ester cysteinate is the first example of cadmium *L*-cysteinate derivate soluble in organic solvents. It is shown that all these complexes act as initiators for the polymerization of methylthiirane in homogeneous phase.

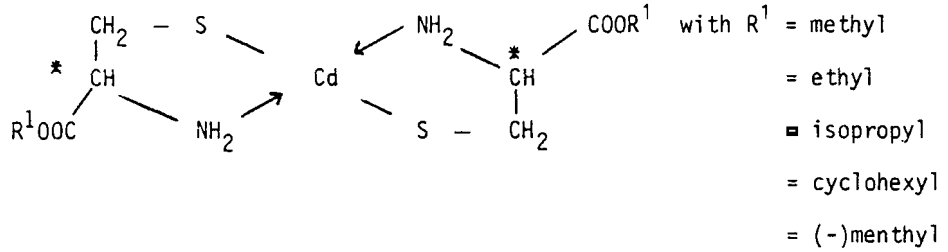
Une série d'esters de la *L*-cystéine, comprenant deux centres de chiralité sont préparés par réaction de la *L*-cystéine avec des alcools secondaires racémiques du type $CH_3CH(OH)R$ (avec R = C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_{13}, $CH_2C_6H_5$), en présence d'HCl gazeux sec. La réaction du phényl-1 éthanol (R = C_6H_5) avec la *L*-cystéine conduit dans les mêmes conditions d'expérience, uniquement au dérivé *S*-substitué; l'étude des spectres de RMN ^{13}C et ^1H a permis de confirmer la structure de ce produit. Les complexes correspondants du cadmium ont été préparés et caractérisés. Le composé bis octyl-2 cystéinate de cadmium est le premier exemple, dans cette série, de complexe soluble dans les solvants organiques. Tous ces sels de cadmium sont utilisés comme agent d'amorçage dans la polymérisation stéréospécifique du méthylthiiranne en phase homogène.

INTRODUCTION

The reaction between *L*-cysteine hydrochloride and primary or secondary alcohols is a classical method to prepare *L*-cysteine esters hydrochloride.[1-4] The reaction between cysteine alkyl esters and cadmium salts in aqueous solution leads to chiral cadmium complexes whose structure depends on the initial cadmium salt/cysteine derivative ratio.[5]

In previous papers[6,7] we have shown that the following cadmium chiral complexes of *L*-cysteine can polymerize methylthiirane stereospecifically, i.e. provide stereoreg-

ular polymer chains:



Furthermore, the polymerization is of the living type and is stereoelective (preferential choice of one of the enantiomers); macromolecular chains grow only on one cadmium valency.[6,7]

In this paper, we report the preparation of diastereoisomeric *L*-cysteine esters, i.e. esters with two asymmetric carbon atoms (one in the amino-acid moieties and one in the alcohol moieties) and their ^{13}C and ^{1}H NMR spectra. The following alcohols have been coupled to *L*-cysteine (Table I). Each of these racemic alcohols leads to a mixture of diastereoisomeric compounds.

However, with 1-phenylethanol, the single product of the reaction is the *S*-substituted derivative. A comparison of the ^{13}C and ^{1}H NMR spectra of the cysteine esters and *S*-substituted derivates allowed to correlate the different lines to the structure of the molecules. The ability of the cadmium complexes, thus prepared and characterized, to initiate the polymerization of methylthiirane has been considered as a preliminary approach to the understanding of the mechanism of polymerization of this monomer by cadmium complexes in homogeneous media.

RESULTS AND DISCUSSION

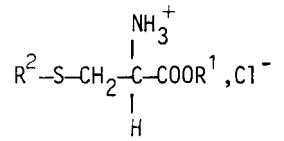
Though the synthesis of amino esters by coupling amino-acids with alcohols in the presence of dry gaseous HCl or HBr is a classical method, only a few cysteine esters have been prepared by this method:[1-4] esterification has been carried out with primary alcohols and the following secondary alcohols: cyclohexanol, isopropylalcohol and menthol.

Using the same method, the cysteinates listed in Table I have been prepared from the racemic chiral alcohols. *L*-cysteinates with $CH_3CH(OH)R$ [R = C_2H_5, $CH(CH_3)_2$ or $C(CH_3)_3$] were readily obtained; ^{13}C and ^{1}H NMR spectra are consistent with the ester structure (Table II) and presence of thiol group is confirmed from thiol characteristic reaction.[1]

In contrast, no correlation between the ester structure and NMR spectra was possible for the derivate of 1-phenyl-ethanol; this reaction between this alcohol and *L*-cysteine hydrochloride: chemical shift of cysteine methylene carbon (compound VI) is at 30.4, 30.7 ppm (two peaks) and secondary carbon $CH_3\underline{C}HC_6H_5$ at 44.5, 43.2 (two peaks) in place of around 24 and 75 ppm (compounds I–V).

In order to identify the chemical nature of compound VI which was assumed at first to be a *S*-substituted derivative, this product was reacted with thionyl chloride in methanol and a *S*-substituted cysteine methyl ester was obtained. This result is

TABLE I

L-cysteinate derivates: 

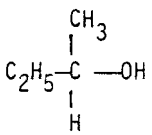
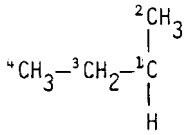
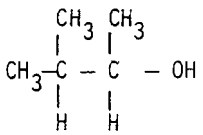
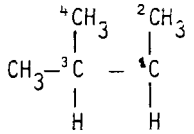
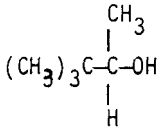
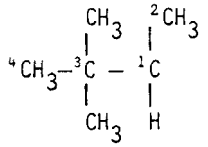
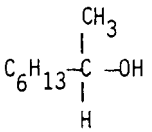
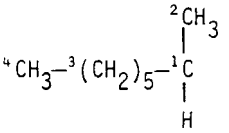
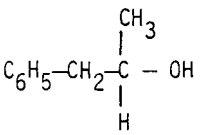
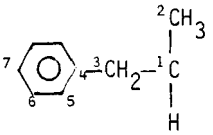
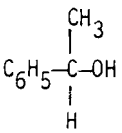
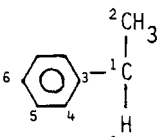
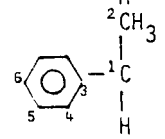
Alcohol	Compound	R^1	R^2	Yield %	Mp °C	$[\alpha]_D^{25}$ (g/100 ml in EtOH)
	I		H	53	124	−22.8(1.8)
	II		H	49	132	−53.3(2.0)
	III		H	55	168	−17.2(2.2)
	IV		H	50	45	−39.2(1.5)
	V		H	23	75	−43.2(1.1)
	VI	H		83	153	+18.1(1.3)
CH_3OH	VII	CH_3		85	176	−23.5(2.1)

TABLE II

^{13}C NMR chemical shifts of *L*-cysteine derivates: $R^2—S—CH_2—\underset{\underset{H}{|}}{\overset{\overset{NH_3^+}{|}}{C}}—COOR^1—Cl^-$

Compound	I	II	III	IV	V	VI	VII
R^1	C_1 77.1	C_1 80.0	C_1 82.5	C_1 73.1 / 73.3	C_1 75.1 / 74.8		
	C_2 18.6	C_2 17.7	C_2 14.3	C_2 18.2 / 18.3	C_2 19.2 / 18.7	—	53.8
	C_3 28.0	C_4 17.9	C_3 33.7	C_3 21.4 / 28.6 / 30.6 / 34.5	C_3 41.1 / 41.3		
	C_4 9.0	C_3 19.3	C_4 24.9 / 24.6	C_4 12.6	C_4 136.6 / 136.9		
					C_5 128.9 / C_7 129.0		
					C_6 127.8 / 128.0		
						C_1 43.2 / 44.5	C_1 43.7 / 44.7
R^2	—	—	—	—	—	C_2 21.1 / 21.5	C_2 21.3 / 21.6
						C_3 142.7 / 142.9	C_3 142.3 / 142.7
						C_4 127.1	C_4 127.1
						C_5 128.6	C_5 128.7
						C_6 127.5	C_6 127.6
$—CH_2—$	23.9	23.9	23.7 / 23.9	24.5	24.0	30.4 / 30.7	30.4 / 30.7
$—\overset{\overset{NH_3}{|}}{\underset{|}{C}}—$	54.5	54.5	54.7 / 54.5	61.6	54.3 / 54.2	52.1	52.2
$—C\overset{=O}{\underset{—O}{}}$	167.5	167.4	167.6	165.7	166.7 / 166.9	169.8	168.6

Products in solution in D_2O except IV in CD_3OD (δ ppm/TMS).

confirmed by comparison with ^{13}C NMR spectrum of the *S*-benzyl cysteine methyl ester: the methyl carbon line is at 53.8 ppm, the methylene carbon of benzyl group is at 35.5 ppm and the chemical shift of cysteine methylene group at 30.6 ppm; the chemical shift of the carbon bound to sulphur differs much from those bound to oxygen of the ester groups. In the presence of anhydrous HCl, a highly stable phenylmethylcarbonium is formed from 1-phenyl ethanol and reacts with the thiol group of *L*-cysteine in a nucleophilic substitution to give compound VI. This finding shows that the ester formation is not a competitive reaction as the carboxylic group remains free; also with 1-phenyl 2-propanol, chemical shifts in ^{13}C NMR of reaction product V are again coherent with the ester structure; a stable carbonium ion is not formed.

The use of racemic alcohols gives rise to diastereoisomeric mixtures; some carbons and protons are stereosensitive: peaks in NMR spectra are split (table II and experimental part).

Preliminary attempts to separate diastereoisomers have been made by successive recrystallizations in isopropylalcohol–diethylether mixtures, but only partial separation has been obtained so far for compounds III and VI (^{13}C and ^{1}H NMR analysis): the highest melting point obtained for IV was 202°C $[[\alpha]_D^{25} = -26.5$ (C = 1.8 in ethanol)] instead of Mp = 168°C $[[\alpha]_D^{25} = -17.5$ (C = 1.7 in ethanol)] in the initial mixture; NMR analysis shows a 80/20 diastereoisomers ratio. With VI, we obtain a 70/30 ratio Mp = 178°C and $[\alpha]_D^{25} = -6.70$ (initially 50/50: 152°C and 18.1).

Reaction between *L*-cysteine derivates and cadmium salts leads to cadmium bis-cysteinates. Formula agree with butterfly compounds;[9] products I′, II′, III′, V′, VI′ are not directly soluble in organic solvents as benzene, tetrahydrofuran or methylthiirane (monomer); solubility occurs during first stages of polymerization after insertion of one or more monomer units between cadmium and ligand. Complex IV′, on the contrary, is soluble in organic solvents and in methylthiirane. We have used these complexes as initiators to polymerize methylthiirane; corresponding polymers are highly isotactic. Preliminary results, using compound III, show that the presence of an asymmetric carbon in the ester group far from the cadmium atom can modify strongly the stereoelective polymerization:[10] preferential polymerization of one of the two enantiomers depends also on the diastereoisomeric composition of the initiator.

In conclusion, direct esterification of *L*-cysteine can be extended to a series of secondary alcohols with an asymmetric centre. These *L*-cysteine derivatives may be used in coordination chemical studies on metalloenzymes, for example, models to probe the nature of metallothioneins sites, these proteins being involved in metal detoxification and/or metabolism.[11,12] Moreover it will be of great interest to prepare pure diastereoisomers of *L*-cysteine esters; the best way will be to obtain optically pure enantiomers of the secondary alcohols before esterification; their cadmium derivatives can be used as chiral precursors in order to elucidate nature and structure of chiral active centres in the stereoelective polymerization of methylthiirane in homogeneous phase. The cadmium complex directly soluble in organic solvents is especially interesting: ^{113}Cd NMR will be available on the initiator and it will be possible to observe the first steps of the polymerization as well as the association state of the complex and the coordination of nitrogen and sulphur on the cadmium atom.

EXPERIMENTAL PART

Preparation of the L-cysteine derivatives. Alcohols were commercial products (Aldrich). 1-phenyl 2-propanol was prepared by reduction of 1-phenyl 2-propanone with lithium aluminium hydride in anhydrous tetrahydrofuran.[8] Compounds I–VI were prepared according to the following method: 0,05 mole of anhydrous cysteine hydrochloride (SIGMA) is reacted with 0,75 mole of secondary alcohol under a dry HCl stream; time and temperature of reaction varies with the alcohol: I (2 h, 95°C), II (2 h, 110°C), III (15 h, 115°C), IV (2 h, 105°C), V (2 h, 130°C), VI (0.5 h, 130°C).

Solutions are cooled and in the case of compounds I, II, III, V, 200 ml of diethylether are added; precipitation occurs overnight and the solution is filtered. Excess of 2-octanol (compound IV) or 1-phenyl 2-propyl alcohol (compound VI) is eliminated by distillation under reduced pressure and it remains a viscous product; diethylether (200 ml) is added with methanol (5 ml) to compound VI (8 g) and the solution is stirred for one day at room temperature to induce crystallization. Compound IV crystallizes slowly at 0°C (1 week). Crude products (I, II, III, V) are washed with diethylether and finally crystallized from isopropylalcohol. Products I, II, III, V, VI are soluble in water and alcohols, insoluble in acetone, diethylether and benzene. Compound IV is soluble in organic solvents as benzene, diethylether, tetrahydrofuran.

Elemental analysis

I = calc.: C, 39.34; H, 7.49; S, 14.99; Cl, 16.62; N, 6.56. Found: C, 39.48; H, 7.67; S, 14.65; Cl, 16.33; N, 6.74.

II = calc.: C, 42.20; H, 7.91; S, 14.06; Cl, 15.06; N, 6.15. Found: C, 41.95; H, 8.12; S, 13.89; Cl, 15.23; N, 6.23.

III = calc.: C, 44.72; H, 8.28; S, 13.25; Cl, 14.70; N, 5.70. Found: C, 44.37; H, 8.33; S, 13.39; Cl, 14.63; N, 6.23.

IV = calc.: C, 48.98; H, 8.90; S, 11.87; Cl, 13.17; N, 5.19. Found: C, 48.32; H, 9.03; S, 11.52; Cl, 12.85; N, 5.23.

V = calc.: C, 52.27; H, 6.53; S, 11.61; Cl, 12.88; N, 5.08. Found: C, 52.53; H, 6.31; S, 11.22; Cl, 13.06; N, 5.14.

VI = calc.: C, 50.48; H, 6.12; S, 12.33; Cl, 13.57; N, 5.35. Found: C, 50.75; H, 6.95; S, 12.13; Cl, 13.83; N, 5.27.

Compound VII is prepared from VI (3 g), methanol (10 ml) and thionyl chloride (2,5 ml). The mixture is heated 4 h at 45°C and stirred overnight at room temperature. Adduct of diethylether allows precipitation and after filtration crude product is crystallized in methanol.

Partial separations of diastereoisomers in the case of compounds IV and VII are made by dissolution of cysteinate hydrochloride in isopropylalcohol (80°C) and addition of diethylether (1/3), till liquid appears turbid; precipitation occurs overnight at 4°C.

Chemical shifts in ^1H NMR (products dissolved in D_2O, IV excepted in solution in CD_3OD, 25°C, δ ppm/TMS):

I: 0.87 (t, J = 6 Hz, 3 H), 1.26 (d, J = 6 Hz, 3 H), 1.66 (m, 2 H), 3.31 (d, J = 6 Hz, 2 H), 4.33 (t, J = 5 Hz, 1 H), 4.90 (m, 1 H).

II: 0.92 (d, J = 6 Hz, 6 H), 1.26 (d, J = 6 Hz, 3 H), 1.86 (m, 1 H), 3.10 (d, J = 5 Hz, 2 H), 4.10 (t, J = 5 Hz, 1 H), 4.80 (m, 1 H).

III: 0.93 (s, 9 H), 1.25 (d, J = 6 Hz, 3 H), 3.16 and 3.21 (d, J = 5 Hz, 2 H), 4.43 and 4.51 (t, J = 5 Hz, 1 H), 4.83 (m, 1 H).

IV: 0.89 (t, J = 6 Hz, 3 H), 1.23 (d, J = 6 Hz, 3 H), 1.82 (m, 10 H), 3.12 (d, J = 5 Hz, 2 H), 4.15 (t, J = 5 Hz, 1 H), 4.80 (m, 1 H).

V: 1.31 and 1.36 (d, J = 6 Hz, 3 H), 2.93 (d, J = 5 Hz, 2 H), 3.33 (m, 2 H), 4.33 (t, J = 5 Hz, 2 H), 5.21 (m, 1 H), 7.16 (s, 5 H).

VI: 1.67 and 1.69 (d, J = 6 Hz, 3 H), 3.10 (m, 2 H), 4.21 (m, 2 H), 7.43 (s, 5 H).

VII: 1.68 and 1.70 (d, J = 6 Hz, 3 H), 3.11 (m, 2 H), 3.86 (s, 3 H), 4.22 (m, 2 H), 7.43 (s, 5 H).

Preparation of cadmium complexes. Cadmium complexes are obtained by reaction between *L*-cysteine derivative hydrochloride (I, II, III, V, VI, VII) and cadmium nitrate; 5 mmol of *L*-cysteinate, HCl is dissolved in water (5 ml) and the solution cooled to 0°C. To this solution is added an ice cold solution of sodium hydroxide (0,4 g) in water (5 ml). A solution of cadmium nitrate tetrahydrate (1,7 mmol) in water (7 ml) is added dropwise with stirring. On standing, colourless crystals of the product separated and within half an hour precipitation is complete. The crystals are collected and washed successively with water, alcohol and diethylether. Products are dehydrated by drying in vacuum at 70°C during one day.

2-octyl *L*-cysteinate (HCl 5 mmol) is dissolved in water and two equivalents of base are needed at 0°C. 0.5 equivalent of cadmium chloride is added dropwise with stirring. Next day a waxy product is separated and is crystallized in methanol or benzene. Elemental analysis are in agreement with the expected composition: one cadmium atom for two corresponding cysteinate groups

I′ (Mp 158°C) calc.: Cd, 24.20; C, 36.17. Found: Cd, 23.71; C, 35.96.

II′ (Mp 158°C) calc.: Cd, 22.83; C, 38.98. Found: Cd, 23.22; C, 37.93.

III′ (Mp 168°C) calc.: Cd, 21.60; C, 41.51. Found: Cd, 21.63; C, 40.35.

IV′ (Mp 176°C) calc.: Cd, 19.50; C, 45.80. Found: Cd, 19.70; C, 43.72.

V′ (Mp 102°C) calc.: Cd, 19.10; C, 48.94. Found: Cd, 18.31; C, 46.83.

VI′ (Mp 183°C) calc.: Cd, 20.06; C, 46.39. Found: Cd, 18.47; C, 44.32.

ACKNOWLEDGMENTS

The authors are indebted to Miss Christiane Derouet (Laboratoire de Chimie-Ecole Normale Supérieure) for the recording of ^{13}C NMR spectra.

REFERENCES

1. M. Joullie, M. Laurre, G. Maillard, P. Muller and R. Zaovi, French Patent 676251 (1960).
2. M. Joullie, French Patent 55792 (1966).
3. P. Chauvin, French Patent 7412290 (1975).
4. P. Wirth, French Patent (drug special patent) 3974 (1965).
5. L. J. Porter, D. D. Perrin and R. W. Hay, *J. Chem. Soc. part A*, 118 (1969).
6. Ph. Dumas, Ph. Guerin and P. Sigwalt, *Nouv. J. Chimie*, **4**, 95 (1980).
7. Ph. Dumas, Ph. Guerin and P. Sigwalt, *Makromol. Chem.*, **182**, 2225 (1981).
8. H. O. House, *Modern synthetic reactions*, W. A. Benjamin, Inc. (1972) pp. 47.
9. W. Cooper, D. R. Morgan and R. T. Wragg, *Europ. Pol. J.*, **5**, 71 (1969).
10. Ph. Dumas, Ph. Guerin and P. Sigwalt, to be published.
11. J. H. R. Kägi, S. R. Himmelhoch, P. D. Whanger, J. L. Bethune and B. L. Vallee, *J. Biol. Chem.*, **249**, 3537 (1974).
12. Y. Kojima and J. H. R. Kägi, *Trends Biochem. Sci.*, 90 (1978).