Tetrahedron Vol. 40, No. 24, pp. 5207 to 5211, 1984
Printed in the U.S.A.

0040–4020/84 $3.00 + .00
Pergamon Press Ltd.

ASYMMETRIC EPOXIDATION OF ELECTRON-POOR OLEFINS—V[1]

INFLUENCE ON STEREOSELECTIVITY OF THE STRUCTURE OF POLY-α-AMINOACIDS USED AS CATALYSTS

STEFANO BANFI, STEFANO COLONNA* and HENRIETTE MOLINARI
Centro CNR and Istituto di Chimica Industriale dell'Università,
Via Golgi 19, 20133 Milano, Italy

and

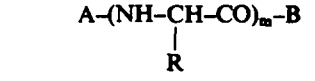
SEBASTIAN JULIA* and JOAN GUIXER
Departamento de Química Orgánica, Instituto Químico de Sarria,
Barcelona 17, Spain

(*Received in UK* 21 *November* 1983)

Abstract—New poly-α-aminoacids modified at the *C* or *N*-terminal groups are synthetised and employed in the asymmetric epoxidation of chalcone. Their influence on the stereoselectivity of the reaction is studied.

Few organic asymmetric reactions are truly catalytic in nature, the most relevant examples being enzymatic processes and homogeneous asymmetric hydrogenation. The two crucial drawbacks in asymmetric synthesis are the cost of many chiral reagents, which therefore must be quantitatively recovered, and the formation of optically active by-products. Both of these problems can be solved by employing an insoluble polymer as chiral catalyst. We have used this approach in the asymmetric epoxidation of *trans*-chalcone and other electron-poor olefins in the presence of poly-α-aminoacids; they offer, as catalysts, two other advantages: (i) a known configuration and conformation; (ii) the possibility of being prepared with predetermined stereochemical characteristics, which in turn can lead to a certain selectivity with respect to the substrate. Preliminary results[1] indicated that poly-α-aminoacids exhibited enzyme-like stereoselectivity leading to optically active oxiranes with enantiomeric excesses (e.e.) up to 96%. In this paper we focus attention on the role played by structural modification of the polypeptides in order to obtain further insights into the origin of the asymmetric induction.

The poly-α-aminoacids used have the general structure **1**,



1

where m is the average degree of polymerisation and A and B are the *N*-terminal and *C*-terminal unit, respectively. They are prepared by the corresponding *N*-carboxyanhydrides (NCA) using different initiators (I) of polymerisation, namely water for the homopolymers **1a–c**, **2a** and **3a**, and n-hexadecylamine, n-butanol, sodium methoxide, and Ⓟ–CH_2OH (Ⓟ– = cross-linked polystyrene), respectively, for the catalysts **1d–g**, in acetonitrile or dioxane as solvents (Scheme 1).

1a;	A = H;	R = CH_3;	m = 6;	B = OH
1b;	A = H;	R = CH_3;	m = 19;	B = OH
1c;	A = H;	R = CH_3;	m > 50;	B = OH
1d;	A = H;	R = CH_3;	m = 10;	B = $NH(CH_2)_{15}CH_3$
1e;	A = H;	R = CH_3;	m > 50;	B = $O(CH_2)_3CH_3$
1f;	A = H;	R = CH_3;	m > 50;	B = OCH_3
1g;	A = H;	R = CH_3;		B = OCH_2Ⓟ
2a;	A = H;	R = $(CH_3)_2CHCH_2$-	m = 10;	B = OH
3a;	A = H;	R = $CH_3CH_2CH(CH_3)$-;	m = 10;	B = OH

Scheme 1.

The polymerisation proceeds through two different pathways: by normal amine initiation (path a), or *via* activated monomer (path b).[2] In the former case the reaction is a multistep nucleophilic attack by the terminal amino group on the 5-carbonyl of the NCA, followed by ring-opening and evolution of carbon dioxide with formation of the poly-α-aminoacid, whose average degree of polymerisation (m) is given by the molar ratio NCA:I. This pathway operates with primary amines in polar solvents.

Alternatively (path b), abstraction of a proton from the monomer leads to the *N*-carboxyanhydride anion, the "active monomer", which gives rise to a rapid chain growth. This route is favoured with tertiary amines and other bases such as methoxide, and leads to a polyaminoacid with a degree of polymerisation higher than that expected on the basis of the NCA:I ratio.

The average degree of polymerisation of catalysts **1a–g**, **2a**, **3a** was evaluated by ^{1}H-NMR spectroscopy and by titration of the terminal amino and carboxylic group, respectively, according to the literature.[3]

In the case of poly-L-leucine **2b** the *N*-terminal amino-group was modified *via* methylation with formaldehyde and formic acid to give **4** (Scheme 2).

Poly-L-proline **5** having a *cis* conformation was prepared according to the literature[4] from the corresponding NCA, with n-butylamine as initiator, in acetonitrile as solvent (see Experimental).

RESULTS AND DISCUSSION

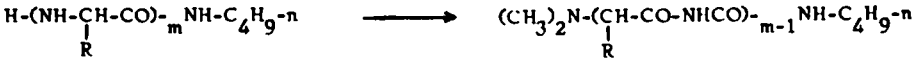
Catalysts **1–5** were tested in the epoxidation of *trans*-chalcone **6a** with H_2O_2 in NaOH at room temperature in toluene (Scheme 3). They always afford (−)-**7a**, having the (2*R*, 3*S*) absolute configuration.[5]

The results are reported in Table 1, and in Table 2 are collected the data already published[1] for the same reaction performed with the poly-α-aminoacids **1h**, **i**, **2b**, **3b** (Scheme 4) having n-butylamine at a terminal *C* group.

They clearly indicate that in all cases examined similar asymmetric inductions are obtained with the homopolymers having either an amidic or a carboxylic terminal group. Only with poly-L-isoleucine does the optical yield depend on the nature of the *C*-terminal group; *trans*-epoxy-chalcone **7a** is obtained with 85% and 54% e.e., with catalysts **3b** and **3a**, respectively.

Dimethylation of the NH_2 group afforded polyaminoacid **4** capable of giving high chemical yield and e.e. The substitution of n-butyl by the n-hexadecyl group has no effect on the stereoselectivity of the epoxidation reaction. Even when the polyaminoacid is anchored on a polymeric matrix **1g** the obtained oxirane **7a** has a high optical purity, the e.e. being 84%. These results, as a whole, lead to the conclusion that the nature of the terminal group of the homopolypeptide does not affect the degree of asymmetric synthesis.

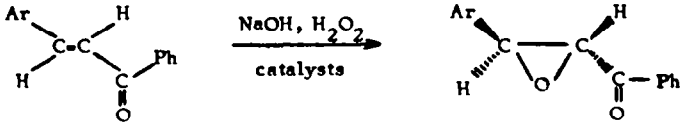
The origin of asymmetric induction in this epoxidation reaction remains an unsolved problem; we had previously proposed[1] a tentative explanation in terms of hydrogen bonding between the carbonyl function of the substrate and the peptide group of the catalyst. A new piece of evidence in favour of this hypothesis is the fact that the poly-L-proline *cis*



2b

R = $(CH_3)_2CH-CH_2-$; m = 30

Scheme 2.



6

6a; Ar = Ph
6b; Ar = $pNO_2-C_6H_4$

7

7a; Ar = Ph
7b; Ar = $pNO_2-C_6H_4$

Scheme 3.

1h; A = H; R = CH_3; m = 10; B = $NH(CH_2)_3CH_3$
1i; A = H; R = CH_3; m = 30; B = $NH(CH_2)_3CH_3$
2b; A = H; R = $(CH_3)_2CH-CH_2$; m = 10; B = $NH(CH_2)_3CH_3$
3b; A = H; R = $CH_3CH_2CH(CH_3)$; m = 10; B = $NH(CH_2)_3CH_3$

Scheme 4.

Table 1. Epoxidation of chalcone **6a** in toluene at room temperature in the presence of catalysts **1a–g**, **2a**, **3a**, **4** and **5**

Catalyst	Time (hr)	Yield (%)	$[\alpha]_{578}^{20}$ (CH_2Cl_2)	e.e. (%)
1a	126	30	- 23	12
1b	26	76	-171	80
1c	48	92	-205	96
1d	48	95	-191	89
1e	48	84	-201	94
1f	48	26	-166	78
1g	48	82	-181	84
2a	29	80	-208	97
3a	144	8	-116	54
4	120	73	-197	92
5	194	0	-	-

Table 2. Epoxidation of chalcone **6a** in toluene at room temperature in the presence of catalysts **1h**, **i**, **2b**, **3b**

Catalyst	Time (hr)	Yield (%)	$[\alpha]_{578}^{20}$ (CH_2Cl_2)	e.e. (%)
1h	24	78	-180	84
1i	24	57	- 200	93
2b[a]	28	60	-181	84
3b[a]	72	76	-204	95

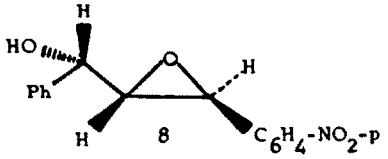
a) Reaction performed in CCl_4.

5, a poly-L-aminoacid lacking amidic hydrogens, is a quite inefficient catalyst both from the chemical and stereoselective point of view.

The optical yield drops dramatically when the length of the polymer chain is less than 10 units, as in catalyst **1a**. This behaviour is related to the fact that polyaminoacids with DP > 10 have a higher content of α-helix conformation,[6] the secondary structure usually favouring asymmetric induction in the epoxidation reaction.[1]

The work-up of the reaction is simpler with the polymer-supported catalyst **1g** and with poly-α-aminoacids with DP > 50, since they are more easily filtered off. Another favourable feature of insoluble polymers as catalysts is that they can be reused several times,[7] the drawback being a loss of stereoselectivity; indeed, catalyst **1g**, recycled twice, gave the epoxy-chalcone **7a** with 75% and 52% e.e., successively.

An important application of poly-α-aminoacids as chiral catalysts is in the preparation of optically active a,β-epoxy-alcohols.[8] These compounds are useful intermediates for the synthesis of methymicycin, erythromycin and leucotrienes C-1.[9] They can be obtained according to the literature[10] by reduction of the corresponding ketones with zinc borohydride. We have shown[8] that, starting from the *p*-nitro-substituted epoxy-chalcone **7b** (95% e.e.), the borohydride reduction leads to the "erythro" alcohol **8** having the same optical purity of the starting material.



EXPERIMENTAL

M.ps are uncorrected. The optical rotations were determined with a Perkin–Elmer P-141 and P-241 polarimeters. IR spectra were recorded on a Perkin–Elmer 157 and 377 spectrophotometer. ^{1}H–NMR spectra were recorded on a Varian 90 and a Bruker WP 80 instrument, using TMS as internal standard. Enantiomeric excess was determined by ^{1}H NMR with the use of europium Eu(hfc)$_3$ using a Bruker WP 80 instrument. All products showed elemental analyses in agreement with the proposed structure.

Starting materials. Compound **6a** was a commercial product. Compound **6b** was prepared according to the literature.[11]

Synthesis of catalysts

N-*Benzyloxycarbonyl-L-alanine* (L-Alanine NCbzo) was prepared according to the lit.[12] The compound (60% yield) had m.p. 82° (lit.[12] m.p. 84°).

N-*Carboxy-L-alanine anhydride* (L-alanine NCA) was prepared according to the lit.[13] in 75% yield, m.p. 89° (lit.[14] m.p. 92°).

Poly-L-alanine **1a.** Acetonitrile (20 ml) containing 7.2 mmoles water was added to a solution of *N*-carboxy-L-alanine anhydride (2.5 g, 21.7 mmol) in anhydrous acetonitrile (50 ml). The reaction was stirred for 4 days at room temp. The solvent was then removed under reduced pressure, the solid residue was stirred overnight in Et_2O (100 ml), filtered and dried *in vacuo*. The degree of polymerisation (m) was determined by NMR and titration of terminal acid and basic groups (see below).

Compound **1a** (70% yield) had m = 6, $[\alpha]_D^{20} = -76.7°$ (c, 0.3 in CF_3COOH); IR (KBr) 3299, 2937, 2870, 1635, 1542, 1469, 1367.

Poly-L-alanine **1b** was prepared following the procedure as for compound **1a**, using 1.45 mmol of water.

Compound **1b** (78% yield) had m = 19, $[\alpha]_D^{20} = -144.8$ (c, 0.5 in CF_3COOH); IR (KBr) 3508, 3291, 1658, 1543.

Poly-L-alanine **1c** was prepared similarly, but using 0.43 mmole of water.

Compound **1a** (75% yield) had m > 50; $[\alpha]_D^{20} = -154°$ (c, 1 in CF_3COOH); IR (KBr) 3300, 3060, 1660, 1630, 1540, 1305.

Poly-L-alanine **1d.** n-Hexadecylamine (0.52 g, 2.17 mmol) in anhydrous acetonitrile (20 ml) was added to *N*-carboxy-L-alanine anhydride (2.5 g, 21.7 mmol) in 50 ml of the same solvent. The reaction was stirred for 4 days at room temp. The solvent was then removed under reduced pressure, the solid residue was stirred overnight in Et_2O (100 ml), filtered off, and dried *in vacuo*.

Compound **1d** (92% yield) had $[\alpha]_D^{20} = -106°$ (c, 1 in CF_3COOH); IR (KBr) 3290, 3060, 1660, 1630, 1540, 1305.

Poly-L-alanine **1e.** n-Butanol (0.16 g, 2.17 mmol) in anhydrous dioxane (20 ml) was added to a solution of *N*-carboxy-L-alanine anhydride (2.5 g, 21.7 mmol) in 50 ml of the same solvent. The reaction was stirred for 15 days at room temp. The solvent was then removed under reduced pressure, the solid residue was stirred overnight in diethyl ether (100 ml), filtered off and dried *in vacuo*. The compound **1e** (90% yield) had $[\alpha]_D^{20} = -134°$ (c, 1 in CF_3COOH); IR (KBr) 3300, 3060, 1660, 1630, 1540, 1305.

Poly-L-alanine **1f.** Sodium methoxide (0.11 g, 2.17 mmol) in anhydrous dioxane (50 ml) was added to a solution of *N*-carboxy-L-alanine anhydride (2.5 g, 21.7 mmol) in 50 ml of the same solvent. The reaction was stirred for 7 days at room temp. After the same work-up as for **1d** and **1e** the product (89% yield) had $[\alpha]_D^{20} = -123°$ (c, 1 in CF_3COOH); IR (KBr) 3300, 3060, 1660, 1630, 1540, 1305.

Poly-L-alanine **1g.** A solution of hydroxymethylated crosslinked polystyrene (0.39 g, 2.17 mmol of hydroxyl group) in anhydrous dioxane (50 ml) was added to *N*-carboxy-L-alanine anhydride (2.5 g, 21.7 mmol) in 50 ml of the same solvent. The reaction was stirred at room temperature for 15 days, and treated as for **1d** and **1e**. Compound **1g** (91% yield) had IR (KBr) 3290, 3060, 1660, 1630, 1540, 1305. It was insoluble in CF_3COOH.

N-*Benzyloxycarbonyl-L-leucine* (L-leucine NCbzo) was prepared following the procedure described for *N*-benzyloxycarbonyl-L-alanine. The product (76.5% yield) is an oil.[15]

N-*Carboxy-L-leucine anhydride* (L-leucine NCA) was prepared as described.[13] The anhydride obtained (58% yield) had m.p. 71° (lit.[16] 65–70°).

Poly-L-leucine **2a.** Acetonitrile (20 ml) containing 1.8 mmol of water was added to a solution of *N*-carboxy-L-leucine anhydride (2.8 g, 18 mmol) in 50 ml of anhydrous acetonitrile. The reaction was carried out as described for poly-L-alanine **1a.** Compound **2a** (80% yield) had m = 10, $[\alpha]_D^{20} = -103.4°$ (c, 0.32 in CF_3COOH); IR (KBr) 3302, 2936, 2869, 1654, 1593, 1468, 1367.

N-*Benzyloxycarbonyl-L-isoleucine* (L-isoleucine NCbzo) was prepared following the procedure described for *N*-benzyloxycarbonyl-L-alanine. The product (76% yield) is an oil.[17]

N-*carboxy-L-isoleucine anhydride* (L-isoleucine NCA) was prepared according to the lit.[16] The product (60% yield) had m.p. 66–68° (lit.[16] 70–72°).

Poly-L-isoleucine **3a.** Acetonitrile (20 ml) containing 1.8 mmol of water was added to *N*-carboxy-L-isoleucine anhydride (2.8 g, 18 mmol) in 50 ml anhydrous acetonitrile. The reaction was carried out as described for poly-L-alanine **1a.** Compound **3a** (85% yield) had m = 10, $[\alpha]_D^{20} = -94.6°$ (c, 0.28 in CF_3COOH); IR (KBr) 3270, 3082, 2964, 1712, 1630, 1543, 1462, 1384.

Poly-L-leucine **4.** Poly-L-leucine **2b** (1g, 0.29 mmol) formaldehyde (8.5 ml) and formic acid (15 ml) were stirred at 60° for 5 h, then the crude product was acidified with 4N HCl and evaporated. The residue was stirred 5 min with 32% NH_3, filtered and washed with ether. The compound obtained (40% yield) had $[\alpha]_D^{20} = -108.5°$ (c, 0.4 in CF_3COOH). The ninhydrin test for primary amino groups was negative.

N-*Benzyloxycarbonyl-L-proline* (*L-proline NCbzo*), prepared according to lit.[4] (60% yield), had m.p. 76° (lit.[4] m.p. 77°).

L-proline NCA, prepared according to lit.,[4] had m.p. 48° (lit.[4] m.p. 45°).

Poly-L-proline **5.** A solution of n-butylamine (0.124 mmol) in 45 ml of anhydrous acetonitrile was added to a solution of L-proline NCA (0.7 g, 4.96 mmol) in 15 ml of the same solvent. The reaction was stirred for 5 days at room temp. The solvent was then eliminated *in vacuo*, and the solid residue was washed with Et_2O and dried *in vacuo* for 5 h at 40°.

Compound **5** (60% yield) had m = 35; IR[4] (KBr) 3400, 2975, 2900, 1650, 1450, 1355, 960.

Titration of acid and basic groups

The titrations were performed as earlier described.[3] For acid terminal groups the polyaminoacid (0.020 g) was suspended in benzene (5 ml) and dimethylformamide (1 ml) was added. Using thymol blue as indicator, the solution was titrated to a deep blue end-point with 0.1 N sodium methoxide. For basic groups the polyaminoacid (0.040 g) suspended in glacial acetic acid (20 ml) was titrated to a blue end-point with 0.1 N perchloric acid in acetic acid, using crystal violet as indicator.

Epoxidation of chalcone in the presence of catalysts **1a–1g, 2a, 3a, 4, 5**

General procedure[1] The catalyst **1–5** (400 mg), 0.1–0.9 mmol was added to a solution of chalcone **6a** (2.4 mmol) in toluene (6 g) and the mixture was stirred at room temp for 30 minutes. Then 4.4 ml of a solution of NaOH in H_2O_2 (0.08 g ml^{-1}) was added and the mixture was stirred at room temp for the appropriate time (Table 1). The reaction was monitored by TLC and silica using petroleum ether-diethyl ether 9:1 as eluant and with starch iodide paper, adding alkaline H_2O_2 solution (2.2 ml) when the oxidant was exhausted. The catalyst was filtered off and washed with CH_2Cl_2 (50 ml). The organic phase was washed with water (3 × 25 ml), dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on SiO_2 using petroleum ether-diethyl ether 9:1 as eluant. Optical rotations, chemical yields and e.e. are listed in Table 1.

REFERENCES

[1]Part 4. S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana and A. Alvarez, *Tetrahedron* **39**, 1635 (1983) and references therein.

[2]B. M. Abo-El Khair, T. Komoto and T. Kawai, *Makromol. Chem.* **176**, 2505 (1976); M. Goodman and E. Peggion, *Pure Appl. Chem.* **53**, 699 (1981).
[3]M. Sela and A. Berger, *J. Am. Chem. Soc.* **75**, 6350 (1953); M. Sela and A. Berger, *Ibid.* **77**, 1893 (1955); M. Sela, A. Berger and E. Katchalski, *Anal. Chem.* **25**, 1554 (1953).
[4]A. Berger, J. Kurtz and E. Katchalski, *J. Am. Chem. Soc.* **76**, 5552 (1954); T. Kawai, K. Kim and T. Komoto, *Makromol. Chem.* **180**, 465 (1979).
[5]B. Marsman and H. Wynberg, *J. Org. Chem.* **44**, 2312 (1979).
[6]H. R. Kricheldorf and D. Muller, *Macromolecules* **16**, 615 (1983).
[7]S. Julia, J. Guixer, J. Masana, J. Rocas, S. Colonna and H. Molinari, *J. Chem. Soc. Perkin I* 1317 (1982).
[8]S. Banfi, S. Colonna, H. Molinari and S. Julia, *Synth. Commun.* 901 (1983).
[9]B. E. Rossiter, T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **103**, 464 (1981).
[10]T. Nakata, T. Kanaka and T. Oishi, *Tetrahedron Letters* 4723 (1981).
[11]L. Bonsignore, S. Cabiddu, A. Maccioni and E. Marongiu, *Gazz. Chim. Ital.* **106**, 617 (1976).
[12]M. Bergmann and L. Zervas, *Ber.* **65**, 1192 (1932).
[13]D. Konopinska and J. Z. Sunion, *Angew. Chem. Int. Ed. Engl.* **6**, 248 (1967).
[14]K. Veyanagi and S. Inoue, *Makromol. Chem.* **177**, 2807 (1976).
[15]D. Ben Ishai and E. Katchalski, *J. Am. Chem. Soc.* **72**, 1862 (1950).
[16]A. Farthing, *J. Chem. Soc.* 3213 (1950).
[17]M. Winitz, L. Bloch-Frantrenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker and J. P. Greenstein, *J. Am. Chem. Soc.* **78**, 2423 (1956).