Synthesis and Estimation of Poly[γ-(4-alkoxyphenyl)-benzyl-L-glutamate]s

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ABSTRACT: The synthesis and thermal properties of new thermotropic liquid crystalline (LC) poly[γ-4-(4'-alkoxyphenyl)benzyl-L-glutamate]s (**8**) are described. γ-4-(4'-Alkoxyphenyl)benzyl-L-glutamates (**6a—f**) are prepared by the addition of 4-alkoxy-4'-hydroxymethylbiphenyl (**3a—f**) to N-phthaloyl-L-glutamic anhydride (**4**), followed by removal of the N-protecting group. **8a—f** are synthesized by the polymerization of γ-4-(4'-alkoxyphenyl)benzyl-L-glutamate-N-carboxyanhydrides (**7a—f**), which are prepared by treatment of **6a—f** with phosgene. Although **8a—c** do not show transition peaks in DSC heating curves, **8d—f** show two endothermic transition peaks. Viewing on the hot stage with a polarizing microscope suggests that the first transition is due to the transition from the crystalline state to the 1st LC state and the second one is attributed to the transition from the 1st LC state to the 2nd LC state. Therefore, the long alkyl segment with more than a certain carbon number as the side chain of **8** is essential for the appearance of thermotropic LC state.
    KEY WORDS   Polypeptide / Poly(γ-benzyl-L-glutamate) / Thermotropic
Liquid Crystalline Polymer /

During the past years, numerous polymers have been reported to form thermotropic liquid crystalline (LC) states. These thermotropic LC polymers can be classified structurally into three types. Two of these types are well-known as main-chain and side-chain thermotropic LC polymers.[1] In the former, the mesogenic groups form the backbones of molecular chains; whereas in the latter, the mesogenic segments link to a polymer backbone as pendants in side chains. A third type[2] is relatively new and represented by polymers forming mesogenic rods surrounded by long hydrocarbon side chains. The transition from crystal to LC for the third type polymer seems to occur by melting of long hydrocarbon chains on heating and subsequently acting as solvents in the similar manner to the lyotropic LC state.[3] Therefore, the structures of polymers of the third type are closely relating to those of lyotropic LC polymers. For example, cellulose derivatives by Tseng et al.,[4,5] poly(γ-alkyl glutamate)s by Watanabe et al.[2,6] and poly(γ-alkoxybenzyl-L-glutamate)s by us[3,7] are thought to be thermotropic LC polymers of the third type.

In this paper, we report the sythesis and thermotropic LC behavior of new poly[γ-(4-

alkoxyphenyl)benzyl-L-glutamate]s, in which the backbone of poly(L-glutamate ester) is connected to a long alkyl chain through biphenyl segment.

EXPERIMENTAL

4-Alkoxy-4′-hydroxymethylbiphenyl (3)

3 was prepared by the reduction of methyl 4-(4′-alkoxyphenyl)-benzoate (2). The typical procedure is described for 3f. To 100 ml of methanol containing 3.43 g (0.0876 mol) of metal potassium and 20 g (0.0876 mol) of methyl 4-(4′-hydroxyphenyl)benzoate[8] (1), were added 34.1 g (0.0876 mol) of 1-bromodocosane at room temperature. After refluxing overnight, the precipitated KBr was filtered off while the solution was hot. The filtrate was cooled and the separated crystals were filtered off, followed by washing in cool methanol. 42.9 g of 2f were obtained in 91% yield as white leaf crystals pure enough for the next reaction.

40 g (0.0745 mol) of 2f were dissolved in 200 ml of dry THF and 2.5 g (0.0659 mol) of LiAlH$_4$ were added in small portions with stirring at 0°C. After standing overnight at room temperature, another 2.5 g of LiAlH$_4$ were added and the mixture was refluxed for 30 min. The decomposition of the resulting gray gel by pouring into crashed ice containing concd. HCl produced a precipitate. The precipitate was filtered off and dried. Recrystallization of precipitate from 1.2 l of hot ethyl acetate gave 35.6 g (94%) of pure 3f.

IR (KBr): 3280 (s; OH), 1260 (s; –O– aromatic ether), and 1060 cm^{-1} (m; –O– aromatic ether)

Analytical data of 3a—f were summarized in Table I.

γ-4-(4′-Alkoxyphenyl)benzyl N-phthaloyl-L-glutamate (5)

The typical procedure is described for 5f. A mixture containing 6.63 g (0.013 mol) of 3f and 3.38 g (0.013 mol) of N-phthaloyl-L-glutamic

Table I. Analytical data of 3a—f

	Formula (MW)	Yield[a] in %	mp °C	Elemental anal. Found (Calc) in % C	H
3a	C$_{14}$H$_{14}$O$_2$ (214.25)	68	159—160	78.51 (78.48)	6.60 (6.59)
3b	C$_{17}$H$_{20}$O$_2$ (256.33)	68	154—156	79.33 (79.65)	7.69 (7.86)
3c	C$_{21}$H$_{28}$O$_2$ (312.44)	66	140—141	80.95 (80.73)	8.91 (9.03)
3d	C$_{25}$H$_{36}$O$_2$ (368.54)	81	134—135	81.38 (81.47)	9.87 (9.85)
3e	C$_{29}$H$_{44}$O$_2$ (424.64)	85	132—133.5	82.01 (82.02)	10.73 (10.44)
3f	C$_{35}$H$_{56}$O$_2$ (508.80)	86	120—122	82.75 (82.62)	11.36 (11.09)

[a] Total yield from 1.

Table II. Analytical data of 5a—f

	Formula (MW)	Yield in %	mp °C	Elemental anal. Found (Calc) in % C	H	N
5a	C$_{27}$H$_{23}$NO$_7$ (473.46)	89	132—134	68.33 (68.49)	4.79 (4.90)	3.10 (2.96)
5b	C$_{30}$H$_{29}$NO$_7$ (515.54)	91	147—148	69.71 (69.89)	5.65 (5.67)	2.59 (2.72)
5c	C$_{34}$H$_{37}$NO$_7$ (571.64)	93	145—146	71.68 (71.43)	6.71 (6.52)	2.49 (2.45)
5d	C$_{38}$H$_{45}$NO$_7$ (627.75)	89	132—134	72.92 (72.70)	7.38 (7.23)	2.11 (2.23)
5e	C$_{42}$H$_{53}$NO$_7$ (683.85)	92	124—126	73.96 (73.76)	7.81 (7.81)	2.20 (2.05)
5f	C$_{48}$H$_{65}$NO$_7$ (768.05)	92	117—118	74.83 (75.06)	8.61 (8.53)	1.85 (1.82)

anhydride[9,10] (4) in 40 ml of dry benzene was refluxed for 24 h. After the reaction was finished, the crystalline product precipitated by cooling the solution was filtered off and dried. Recrystallization from benzene gave 9.2 g of a white crystalline 5f in 92%.

IR (KBr): 1690 (s; C=O), 1730 (s; C=O), 1750 (s; C=O), and 3230 cm^{-1} (m; OH)

Analytical data of 5a—f were summarized in Table II.

γ-4-(4'-Alkoxyphenyl)benzyl-L-glutamate (6)

A mixture containing 8.0 g (0.0104 mol) of 5f, 3.49 ml (0.0313 mol) of phenylhydrazine and 2.54 ml (0.0104 mol) of tri-n-butylamine in 20 ml of ethanol were stirred for 48 h at 40°C. After that, 20 ml of 2-butanone were added and the resulting mixture was refluxed for 30 min. After cooling to room temperature, 0.69 ml of acetic acid was added. The separated crystalline solid was filtered off and sufficiently washed with hot 2-butanone, followed with ethanol. 6a—f could not be recrystallized from any solvent because of poor solubility. However, they were pure enough for the next reaction.

IR (KBr): 1720 (s; C=O ester), 1640 (m; C=O acid), and 3320 cm^{-1} (w; OH)

Table III showed the analytical data of 6a—f.

γ-4-(4'-Alkoxyphenyl)benzyl-L-glutamate-N-carboxyanhydride (7)

Dry phosgene gas was introduced into 100 ml of dry dioxane dispersing 5.0 g of 6a—f at 40°C. After about 1 h, a clear colorless solution was obtained. Dry N$_2$ gas was then passed into the solution to remove the remaining phosgene. The solution was concentrated and the resulting solid was recrystallized from ethyl acetate-hexane several times. 4—4.5 g of 7a—f were obtained.

IR (KBr): 1720 (s; C=O ester), 1780 (s; C=O NCA), and 1860 cm^{-1} (m; C=O NCA)

Table III. Analytical data of 6a—f

	Formula (MW)	Yield in %	mp °C	Elemental anal. Found (Calc) in %		
				C	H	N
6a	C$_{19}$H$_{21}$NO$_5$ (343.37)	81	191—192	66.31 (66.46)	6.19 (6.16)	3.93 (4.08)
6b	C$_{22}$H$_{27}$NO$_5$ (385.44)	88	201—202	68.47 (68.55)	6.88 (7.06)	3.53 (3.63)
6c	C$_{26}$H$_{35}$NO$_5$ (441.55)	87	198—199	69.98 (70.71)	8.14 (7.99)	3.07 (3.17)
6d	C$_{30}$H$_{43}$NO$_5$ (497.65)	85	194—195	72.22 (72.40)	8.45 (8.71)	2.63 (2.81)
6e	C$_{34}$H$_{51}$NO$_5$ (553.76)	91	189—190	73.91 (73.74)	9.39 (9.28)	2.10 (2.53)
6f	C$_{40}$H$_{63}$NO$_5$ (637.91)	84	183—184	75.57 (75.31)	9.62 (9.96)	1.85 (2.20)

Table IV. Analytical data of 8a—f

	Formula (MW)	Yield in %	$\bar{M}_n$[a]	Elemental anal. Found (Calc) in %		
				C	H	N
8a	(C$_{19}$H$_{19}$NO$_4$)$_n$ (325.35)$_n$	73	25400	69.59 (70.14)	5.66 (5.89)	4.30 (4.31)
8b	(C$_{22}$H$_{25}$NO$_4$)$_n$ (367.43)$_n$	70	34200	71.73 (71.91)	6.91 (6.86)	3.05 (3.81)
8c	(C$_{26}$H$_{33}$NO$_4$)$_n$ (423.53)$_n$	72	20800	72.99 (73.73)	7.63 (7.85)	3.09 (3.31)
8d	(C$_{30}$H$_{41}$NO$_4$)$_n$ (479.64)$_n$	80	30700	73.88 (75.12)	8.06 (8.62)	2.24 (2.92)
8e	(C$_{34}$H$_{49}$NO$_4$)$_n$ (535.74)$_n$	95	13400	75.51 (76.22)	8.83 (9.22)	2.00 (2.61)
8f	(C$_{40}$H$_{61}$NO$_4$)$_n$ (619.90)$_n$	96	14300	76.49 (77.50)	9.17 (9.92)	2.22 (2.26)

[a] By titration of amino endo groups with 1/200 N perchloric acid.

Poly[γ-4-(4'-alkoxyphenyl)benzyl-L-glutamate]
(**8**)

4.0 g of **7a—f** (NCA) were dissolved in 100 ml of dry dioxane at room temperature with exclusion of moisture. Triethylamine as initiator was added to the solution at an initiator/NCA ratio of 1/100. The mixture was polymerized in a sealed tube at 40°C for 4 days and at 80°C for 3 days according to Blout's method.[11] Then the sealed tube was opened and the viscous solution was concentrated to 20 ml, followed by being poured into 400 ml of ethanol. Reprecipitation was repeated using dioxane and ethanol as the solvent and precipitant.

IR (KBr): 3300 (s; amide), 3040 (w; amide), 1720 (s; C=O ester), 1650 (s; amide I), 1550 (m; amide II) and 1520 cm^{-1} (m; amide III)

Analytical data of prepared polymers (**8a—f**) were summarized in Table IV.

Determination of Number-Average Molecular Weight of **8**

8a—f were exactly weighed in the range of 0.045—0.055 g and dissolved in 20 ml of dry benzene. Then, two drops of crystal violet in benzene prepared by dissolving 20 mg of crystal violet in 10 ml of dry benzene, were added to the above solution as an indicator. The resulting violet solution was titrated till it became colorless by 1/200 N perchloric acid prepared by mixing 2.0 ml of 1/10 N perchloric acid–acetic acid solution (factor = 1.004), 18.0 ml of acetic acid and 20.0 ml of dry benzene.

RESULTS AND DISCUSSION

A general procedure for the synthesis of substituted γ-benzyl-L-glutamates and β-benzyl-L-asparates has been reported by Ledger *et al.*[12] They reacted alkalimetal salts of L-glutamic acid and L-aspartic acid copper complexes with substituted benzyl halide to obtain the esters in 8—45%. However, we could not prepare our desired esters by this procedure because of impure products and poor yields.

Another procedure to obtain γ-esters L-glutamate has been reported by Yamamoto *et al.*[13] and Feijen *et al.*,[14] who synthesized the esters by the addition of alcohol to *N*-phthaloyl-L-glutamic anhydride.

We also tried their procedure and succeeded in preparing the γ-esters (**6a—f**) of L-glutamic acid by the reaction of *N*-phthaloyl-L-glutamic anhydride (**4**) with the corresponding *p*-substituted benzyl alcohol (**3a—f**) as described in the reaction scheme.

The substituted benzyl alcohols (**3a—f**) were prepared in moderate yield from methyl 4-(4'-hydroxyphenyl)-benzoate[8] (**1**) and alkyl-bromide by Williamson's ether synthesis, followed by the reduction. Analytical data of new compounds (**3a—f**), which will have high potentials as precursors for liquid crystalline compounds, are summarized in Table I.

The anhydride (**4**) was prepared from *N*-phthaloyl-L-glutamic acid[9] by the method of King *et al.*[10] Compound **4** was supplied for the next reaction after drying at 140°C to remove a
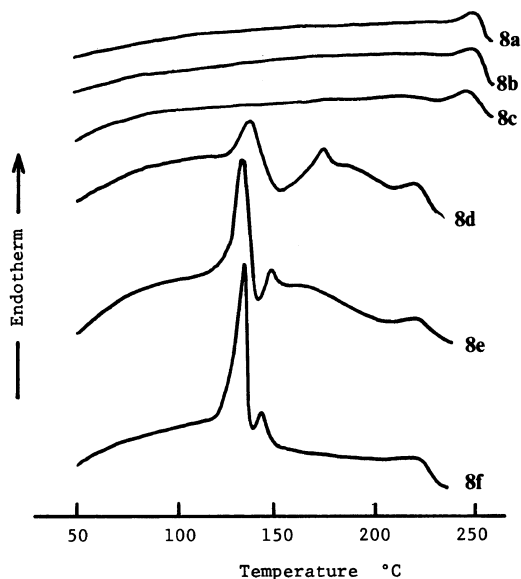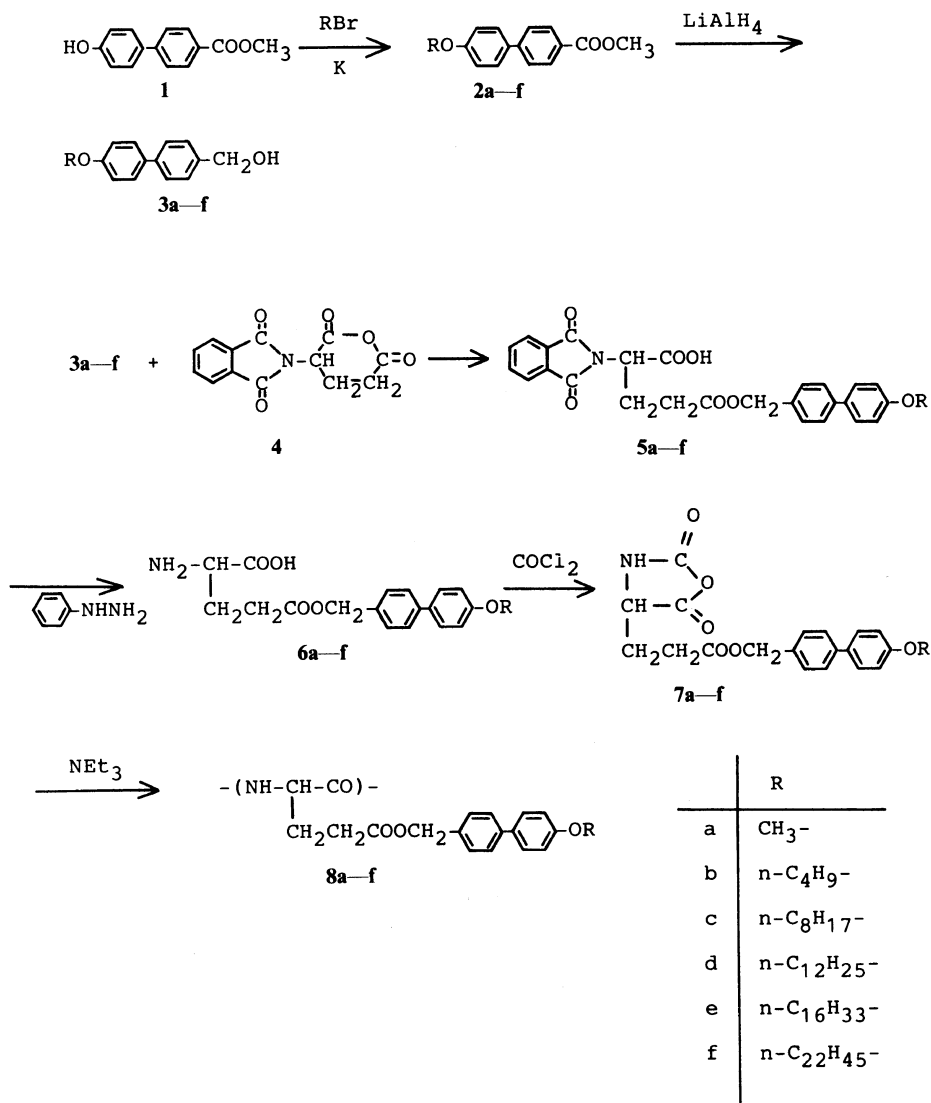

Figure 1. DSC heating curves of **8a—f**. Heating rate, 5°C min^{-1}.

Scheme

|	R
a	CH_3-
b	$n-C_4H_9-$
c	$n-C_8H_{17}-$
d	$n-C_{12}H_{25}-$
e	$n-C_{16}H_{33}-$
f	$n-C_{22}H_{45}-$

trace amount of acetic acid.

γ-4-(4'-Alkoxyphenyl)benzyl N-phthaloyl-L-glutamate (5a—f) were prepared by the addition of 3a—f to 4 in 89—93% yields. Principally, the addition of alcohol to 4 can give α- and γ-esters *via* two different reaction mechanisms. Actually, if N-carbobenzoxy-L-glutamic anhydride instead of 4 is employed, the corresponding mixture of α-ester as the

main-product and γ-ester as the by-product is obtained.[15,16] However, with respect to 4, the reference data reported previously suggest that the fusion reaction[10,17,18] as well as reaction in nonpolar solvents[14,18] produced exclusively γ-esters.
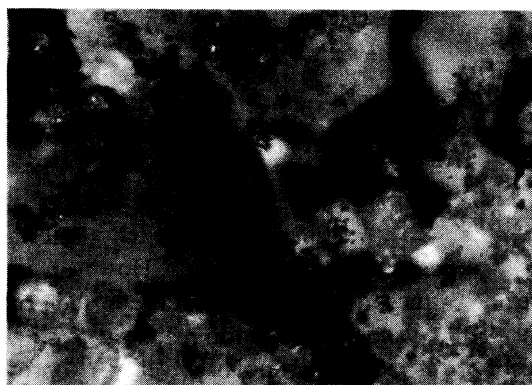
Removal of the phthaloyl group by hydrazinolysis was well known even before this protecting group found its way into peptide
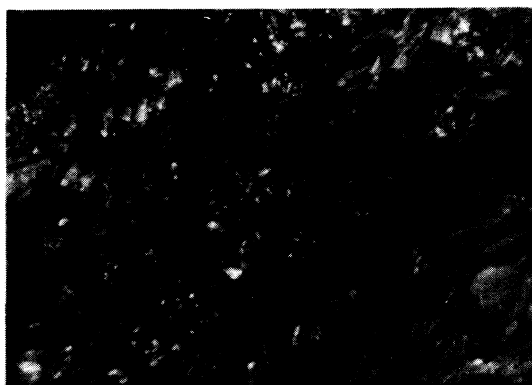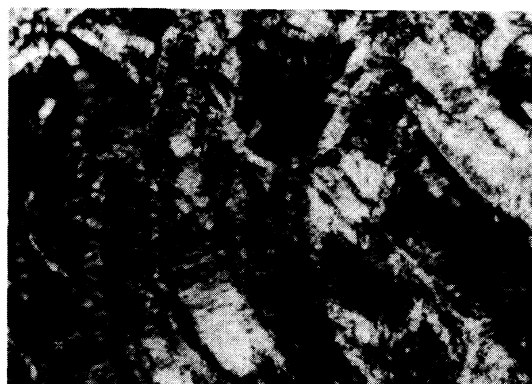
Figure 2. Polarizing micrographs of **8f**.

143°C

132°C

50°C

synthesis. In addition to hydrazine,[10,19,20] phenylhydrazine,[14,21] and hydroxylamine[22] have been applied for the same purpose. First, treatment of **5a—f** with hydrazine hydrate gave a mixture of the desired ester (**6a—f**) and its phthaloylhydrazinium salts. Although this salt formed from **6a—f** and phthaloyl-hydrazide (tetrahydrophthalazine-1,4-dione) could be decomposed by acidification, the resulting **6a—f** and insoluble phthaloylhydra-zide could not be separated because of poor solubility. Second, attempts to remove the phthaloyl group by hydroxylamine were also unsuccessful, since the reaction resulted in a mixture of unreacted material and the product. Finally, removal of the phthaloyl group of **5a—f** was performed using phenylhydrazine. After the reaction finished, washing of filtrated product by hot 2-butanone and ethanol gave **6a—f** in 81—91% yield. The esters (**6a—f**) obtained in this way could not be recrystallized from any solvent becasue of poor solubility, but elemental analysis indicated that they were pure enough for the next reaction. Furthermore, specific rotatory powers of **6a—f** showed that these esters were not racemized, e.g., $[\alpha]_D^{20} = +7.8$ (c 1.00, 99% dichloroacetic acid) for **6a** and $[\alpha]_D^{20} = +10.4$ (c 1.00, water) for glutamic acid obtained from **6a** by hydrolysis.

N-Carboxyanhydrides (**7a—f**) were pre-pared in 60—70% yields by treatment of **6a—f** with phosgene in dioxane. The polymerization of **7a—f** was carried out in dry dioxane using triethylamine as an initiator. After reprecipi-tation using dioxane and ethanol, polymers **8a—f** were obtained in 70—96% yields.

The number-average molecular weights ($\bar{M}_n$) of **8a—f** were determined by titration of amino endgroups with $1/200\,N$ perchloric acid

$$\bar{M}_n = \frac{2 \times 10^5 \times M}{1.004 \times X} \quad (1)$$

($F = 1.004$) according to eq 1:
where $\bar{M}_n$ is the number-average molecular weight, M is the weight (g) of polymer to be titrated and X is the volume (ml) of $1/200\,N$ perchloric acid to titrate the polymer. The values of $\bar{M}_n$ are summarized in Table IV.

Mesurements of differential scanning calo-rimetry (DSC) gives information on the ther-mal transitions of thermotropic LC polymers. Figure 1 shows DSC heating curves of **8a—f**. No transition peak without decomposition over 200°C was observed in the case of **8a—c**. Meanwhile, two endotherm transition peaks and a decomposition peak were observed in **8d—f**. On heating **8f** on the hot stage with a polarizing microscope, at about 130°C it melt-ed, but not clear. Birefringence changed at about 140°C, but it could be observed up to the decomposition at 230°C (Figure 2). From these results it seems that the first large en-dotherm transition at 132°C of **8f** in DSC curve is the transition from the crystalline state to the 1st LC state and the second small endotherm transition at 142°C is the 1st LC to the 2nd LC state, which is stable up to the decomposition temperature of 230°C. The same behavior was observed in **8d** and **8e**, but not **8a—c**. It may be concluded that long al-kyl segment as the side chain of poly[γ-(4-alkoxyphenyl)benzyl-L-glutamate) is essen-tial for formation of the LC state.

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