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Poly(*O*-acyl-hydroxy-L-proline) I. Synthesis and Polymerization of *O*-Acetyl-, Butyryl-, Hexanoyl-, Dodecanoyl-, and Benzoyl-hydroxy-L-proline

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ABSTRACT: *O*-Acyl-hydroxy-L-prolines containing acetyl, butyryl, hexanoyl, dodecanoyl, and benzoyl groups were synthesized and polymerized. Acylations took place in methanesulfonic acid with anhydrides and/or acyl chlorides. It was possible to obtain *N*-carboxylic acid anhydrides (NCA's) by phosgene and subsequent silver oxide-charcoal treatment from these hydroxy-L-proline derivatives. These were polymerized in various solvent systems with triethylamine as the initiator. The intrinsic viscosity of these polymers in dichloroacetic acid was found to be 0.75 to 0.23. They were characterized by IR spectra, solubility in organic solvents and film forming ability. Introduction of various acyl groups to the poly(hydroxy-L-proline)s very strongly affected these physicochemical characteristics.

KEY WORDS *O*-Acyl-hydroxy-L-proline / Acylation / Methanesulfonic Acid / *N*-Carboxylic Acid Anhydride / Polymerization / Viscosity / IR / Solubility /

Hydroxy-L-proline (Hyp) and L-proline (Pro) are typical imino acids widely distributed in constructive proteins such as collagen and elastin. Collagen is well known as a supporting material in tendon, bone and blood vessels. One third of the constructive amino acids found in collagen is glycine and a fourth, Pro and Hyp. The secondary structure of collagen is a triple or super helix.

Many attempts have been made to prepare the analogues of collagen model peptides in order to find the relationship between the molecular conformation and the functional properties resulting from denaturation.

The triple helix of polyglycine and poly(Pro) can be found only under certain conditions. Hyp is well known a peptide residue which is connected to glycane or lipid in glycoprotein or lipoprotein, as in the case of arabinosyl-Hyp in lectin.[1] *O*-Acetyl-Hyp (*O*-Ac-Hyp) was first synthesized by Kolb *et al.*[2] and polymerized by Kurtz *et al.*[3] in 1958. In 1966, Fasman[4] determined the conformational aspects of poly(*O*-Ac-Hyp) by optical rotatory dispersion and ultraviolet spectrophotometry. They found two types of conformation in this polymer: form I corresponding to the *cis* conformation of the C–N bond in the peptide backbone and form II corresponding to the *trans* conformation. Thus the polymers of *O*-acyl-Hyp with aliphatic side chains of various lengths and aromatic groups should be prepared in order to study the effects of side group variations on the conformational stability of polymer backbones.

Recently, Nishi *et al.*[5] and Kaifu *et al.*[6] reported an easy and efficient procedure for preparing various types of acyl chitin using methanesulfonic acid (MSA) as the catalyst and solvent for the esterification of hydroxy groups in chitin with acyl chlorides or acid anhydrides. Applying this technique to the esterification of the hydroxy group in Hyp, it was possible to synthesize *O*-acetyl (Ac), butryl (But), hexanoyl (Cap), dodecanoyl (Lau), and benzoyl (Bz)-Hyp. Each acyl-Hyp was converted to an imino acid *N*-carboxylic acid anhydride (NCA) following treatment with phosgene and a

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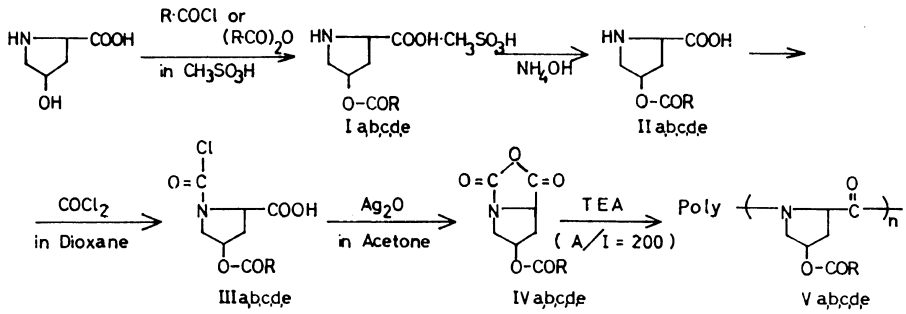

Figure 1. Synthesis of poly(*O*-Acyl-Hyp).

dehalogenation reagent. The polymerization conditions of the NCA were tested in various solvent systems. In this paper, we report on the synthesis and polymerization of *O*-Acyl-Hyp's and various characteristics of the polymers.

EXPERIMENTAL

Reagents and Materials

Pro and Hyp were obtained from Bryon Chemical Co., MSA, acetic anhydride, *n*-butyric anhydride, and benzoyl chloride were purchased from Wako Pure Chemical Ind., Ltd. Acetyl chloride, *n*-butyryl chloride, *n*-caproyl chloride, *n*-lauroyl chloride, and silver oxide came from Nakarai Chemicals, Ltd.

Measurement, Analysis, and Identification of the Products

IR absorption spectra were measured by the KBr method with a JASCO A-302 IR spectrophotometer.

Elemental analysis was carried out at the Analysis Center of Hokkaido University. Identification of the intermediate or the final products in each step of the synthesis was carried out by thin layer chromatography (TLC) using Yamato Replates with various solvent systems, such as a mixture of *n*-butanol–pyridine–acetic acid–water (15 : 10 : 3 : 12), an upper layer of the mixture of *n*-butanol–acetic acid–water (4 : 1 : 5) and a mixture of benzene–ethylacetate (5 : 3). The spots were developed with ninhydrine at 100°C or iodine vapour at room temperature.

Synthesis of O-Acyl-Hyp by the MSA Method

*O-Ac-Hyp (***IIa***) with Acetyl Chloride.* 13.1 g (0.1 mol) of Hyp was dissolved in 100 ml of MSA at room temperature and 11.0 g (0.14 mol) of acetyl chloride was added dropwise with cooling. The reaction mixture was stirred overnight at room temperature. To the reaction mixture, 1 liter of ether was added and the resulting syrupy *O*-Ac-Hyp methanesulfonate was then washed repeatedly with ether. The syrup was then dissolved in water (300 ml) and neutralized with ammonium hydroxide to eliminate the MSA. The mixture was concentrated to 50 ml and solidified by the addition of acetone (500 ml). This crude product was recrystallized from water–acetone–methyl cellosolve.

Yield: 12.5 g (72.2%), mp 179—182°C, $[\alpha]_D^{23}$ −30.0 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_7H_{11}O_4N$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.44; H, 6.39; N, 8.23.

*O-Ac-Hyp (***IIa***) with Acetic Anahydride.* 6.55 g (0.05 mol) of Hyp was treated with 7.65 g (0.075 mol) of acetic anhydride in MSA according to the method using acetyl chloride. The mixture was neutralized and crystallized by the addition of acetone. The product was recrystallized from water and acetone.

Yield: 2.0 g (23.1%), mp 177—179°C, $[\alpha]_D^{20}$ −34.5 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_7H_{11}O_4N$: C, 48.55; H, 6.40; N, 8.09. Found: C, 47.48; H, 6.52; N, 7.99.

*O-But-Hyp (***IIb***) with n-Butryl Chloride.* Hyp

(21.0 g (0.16 mol)), 25 g (0.235 mol) of *n*-butyryl chloride and MSA were used to give 22.0 g of the crude product, which was recrystallized from $CHCl_3$–acetone.

Yield: 10.9 g (33.9%), mp 204—205.5°C, $[\alpha]_D^{25}$ −22.4 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.63; H, 7.49; N, 6.97.

O-But-Hyp (**IIb**) *with n-Butyric Anhydride.* Hyp (13.1 g (0.1 mol)), 2.4 ml of *n*-butyric anhydride, and MSA were used. The reaction proceeded in a manner similar to that mentioned above, and 1 liter of ether was added to precipitate the methanesulfonate. The slightly yellowished syrup was repeatedly washed with ether, neutralized with ammonium hydroxide, and then concentrated to dryness. The residual solid was recrystallized from *n*-propanol.

Yield: 8.60 g (42.8%), mp 203—205°C, $[\alpha]_D^{22.5}$ −25 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.75; H, 7.50; N, 6.94.

O-Cap-Hyp (**IIc**). Hyp (17.0 g (0.13 mol)), caproyl chloride (25 g (0.186 mol)), and MSA were used. After neutralization with ammonium hydroxide, the crude product was recrystallized from water.

Yield: 13.8 g (78.9%), mp 202.5°C, $[\alpha]_D^{22.5}$ −27 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_{11}H_{19}O_4N$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.54; H, 8.43; N, 6.08.

O-Lau-Hyp (**IId**). Hyp (13.1 g (0.1 mol)), lauroyl chloride (30.6 g (0.14 mol), and MSA were used. The crystallized *O*-Lau-Hyp MSA salt (**Id**) was neutralized with ammonium hydroxide. The crude product was recrystallized from methanol.

Yield: 19.5 g (90.7%), mp 189—190°C, $[\alpha]_D^{24}$ −13 ($c=1$, AcOH).

Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.14; H, 10.12; N, 4.49.

O-Bz-Hyp (**IIe**). Hyp (13.1 g (0.1 mol)) and benzoyl chloride (19.6 g (0.14 mol)) were allowed to react in MSA. The crystalline *O*-Bz-Hyp MSA salt (**Ie**) was neutrallized. The crude product, 18.8 g, was recrystallized from water.

Yield: 16.6 g (86.2%), mp 218—219°C, $[\alpha]_D^{22}$ −5 ($c=1$, 0.1 *N* HCl).

Anal. Calcd for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.49; H, 5.48; N, 6.09.

Preparation of N-Carboxylic Acid Anhydrides (NCA's)

L-*Proline NCA (Pro NCA)*

Pro (2.0 g (0.017 mol)) was suspended in 40 ml of absolute dioxane and dry phosgene was bubbled through the mixture for 30 min at 40°C, to dissolve all the material. Dry nitrogen was blown through the solution at 40°C to remove any excess phosgene. After the dioxane was evaporated under reduced pressure, oily proline *N*-carbonyl chloride was dissolved in 40 ml of absolute acetone and stirred with 2.3 g (0.01 mol) of silver oxide and 0.5 g of dry charcoal until the reaction mixture showed only one spot in TLC (benzene–ethyl acetate, 5:3). The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure below 40°C. The crystalline residue was washed several times with dry *n*-hexane, collected and dried under reduced pressure. Yield: 1.5 g (73%), mp 49.5°C (lit. 45°C).[7]

O-Acetyl-Hyp NCA (O-Ac-Hyp NCA) (**IVa**)

The procedure for this was similar to that used for Pro NCA. Through treatment with silver oxide (5.0 g), *O*-Ac-Hyp NCA was obtained from the *N*-carbonyl chloride which had come from the reaction of *O*-Ac-Hyp with phosgene in dioxane. Yield: 4.5 g (78%), mp 122°C (lit. 120°C).[3]

O-Butyryl-Hyp NCA (O-But-Hyp NCA) (**IVb**)

5.0 g of *O*-But-Hyp was converted to 5.3 g (93%) of NCA which was then recrystallized from ethyl acetate–*n*-hexane. Yield: 4.0 g (76%), mp 64—67°C.

O-Hexanoyl-Hyp NCA (O-Cap-Hyp NCA) (**IVc**)

A procedure essentially the same as that for Pro NCA was used. 2.0 g of *O*-Cap-Hyp was converted to NCA. Yield 0.95 g (35.9%), mp 39.5°C (dec.).

O-Dodecanoyl-Hyp NCA (O-Lau-Hyp NCA) (**IVd**)

A procedure essentially the same as the above was used. 6.3 g of *O*-Lau-Hyp were converted to 5.8 g of the NCA which was then recrystallized. Yield: 5.2 g (77%), mp 61—62°C.

O-Benzoyl-Hyp NCA (O-Ba-Hyp NCA) (**IVe**)

4.0 g of *O*-Bz-Hyp was converted to 3.8 g of the crude crystalline NCA, which was then recrystallized. Yield: 2.8 g (63%), mp 166—167°C.

Table I. Characteristics and analysis of *O*-acyl-hydroxy-L-prolines and NCA

Hyp derivative	Found/%			Calcd/%			mp	$[\alpha]_D^T$	Yield	NCA	NCA Yield
	C	H	N	C	H	N	°C		%	mp/°C	%
O-Ac Hyp[a]	47.48	6.52	7.99	48.55	6.40	8.09	177—179[c]	-34.5^{20}	23.1	122.0[d]	73.0
[b]	48.44	6.39	8.23				179—182	-30.0^{23}	72.2		
O-But Hyp[a]	53.75	7.50	6.94	53.72	7.51	6.96	203—205	$-25.0^{22.5}$	42.8	88—91	60.0
[b]	53.63	7.49	6.97				205—205.5	-22.4^{25}	33.9		
O-Cap Hyp[b]	57.54	8.43	6.08	57.62	8.35	6.11	202.5	$-27.0^{22.5}$	78.9	30.5	35.9
O-Lau Hyp[b]	65.14	10.12	4.49	65.14	9.97	4.47	189—190	-13.0^{24}	90.7	61—62	76.5
O-Bz Hyp[b]	61.49	5.48	6.09	61.27	5.57	5.96	218—219	-5.0^{22}	86.2	166—167	63.1

[a] Prepared with acid anhydride. [b] Prepared with acid chloride.
[c] Lit. mp 179—181°C. [d] Lit. mp 120°C.[3]

Polymerization

The NCA of Pro and *O*-Ac, But, Cap, Lau, and Bz-Hyp's thus obtained were polymerized in a 5% solution in dioxane ($\mu = 0.42$ D), methylene dichloride ($\mu = 1.14$ D), acetonitrile ($\mu = 3.44$ D), or a mixed solvent of methylene dichloride and acetonitrile (1 : 1, v/v) ($\mu = 2.29$ D), using triethylamine as the initiator at a monomer to initiator molar ratio (A/I) of 200. The polymerization mixture was stirred for four days at room temperature and the polymer was then precipitated by the addition of a poor solvent such as methanol, ether or water. The polymer was collected centrifugally, washed with methanol and ether repeatedly and then dried *in vacuo*.

RESULTS AND DISCUSSION

Preparation of O-Acyl-Hyp

Methanesulfonic acid was found quite useful as a reagent for the esterification of Hyp. Using this reagent, a series of *O*-acyl-Hyp derivatives having aliphatic side chains of different lengths and an aromatic group were successfully prepared. *O*-Ac- and But-Hyp were prepared from acid anhydrides or acyl chlorides in MSA.

O-Cap, Lau, and Bz-Hyp's were prepared from the corresponding acyl chlorides in MSA. The characteristics and analysis of *O*-acyl-Hyp thus obtained are shown in Table I.

All the acylation reactions were carried out at the lowest possible temperatures so as to prevent the decomposition of the starting materials and formation of by-products with MSA, taking into consideration the melting point of MSA, 20°C. Since Hyp was not easily soluble in MSA at *ca.* 20°C, slight heating and stirring of the reaction mixture were necessary. However, excess heating sometimes caused formation of complex products from Hyp, an acylating reagent, and MSA.

A neutralization reaction was necessary to prepare *O*-acyl-Hyp, since at times the *O*-acyl-Hyp MSA salts could not be obtained in the crystalline state. All the *O*-acyl-Hyp MSA salts mentioned above were neutralized by aqueous ammonium hydroxide solution without alkaline hydrolysis of the ester bonds. After neutralization, the final products were obtained by crystallization and recrystallization from suitable solvent system, such as acetone/methyl cellosolve, methanol, propanol, butanol, and water.

O-Ac- and But-Hyp were also prepared using perchloric acid as the catalyst in a yield of 63.5% in acetic acid and 60.6% in butyric acid, respectively. When synthesizing Hyp having longer or aromatic acyl groups, it seems that preparation of anhydrous carboxylic acids containing acyl chlorides or acyl anhydrides of the same acyl groups would be very complicated. The MSA method may be suitable in this point.

Preparation of O-Acyl-Hyp NCA

It is well known that the NCA of Pro cannot be obtained by a reaction with dichloroformate where an additional reaction of dehalogenation is necessary. Katchalsky[3,7] and Randall[8] used silver oxide and an equivalent mole of triethylamine for this purpose. In the case of *O*-Acyl-Hyp, we found silver oxide treatment to be most suitable. As indicated in

Table II. Analysis and intrinsic viscosity of poly(*O*-acyl-Hyp)s

Polymer	Found/%			Calcd/%			$[\eta]^{25}_{DCA}$	Yield
	C	H	N	C	H	N		%
Pro	59.75	7.27	14.17	61.84	7.27	14.42	1.110[a]	50.5[a]
O-Ac Hyp	54.16	5.99	9.19	54.19	5.85	9.03	0.704[b]	100[b]
O-But Hyp	57.78	7.27	7.32	59.00	7.15	7.65	0.130[b]	61.0[b]
O-Cap Hyp	62.28	8.16	6.58	62.54	8.11	6.63	0.305[b]	74.0[b]
O-Lau Hyp	68.67	10.04	4.71	69.11	9.90	4.74	0.243[b]	89.6[b]
O-Bz Hyp	65.63	5.14	6.44	66.35	5.10	6.45	0.327[c]	86.6[a]
Hyp[d]	50.02	6.54	11.66	53.09	6.24	12.38	—	—

[a] Polymerized in acetonitrile.
[b] In dichloromethane.
[c] In mixed solvent of dichloromethane and acetonitrile.
[d] Prepared from poly(*O*-Bz Hyp) by saponification.

Table III. Polymerization behavior in different solvents

	Solvent			
	Dioxane	CH_2Cl_2	CH_2Cl+ CH_3CN (1:1)	CH_3CN
Polarity (D) of solvent	0.42	1.14	2.29	3.44
Pro	ppt	ppt	ppt	ppt
O-Ac Hyp	ppt	+	+	ppt
O-But Hyp	turbid	+	+	ppt
O-Cap Hyp	+	+	+	+
O-Lau Hyp	+	+	+	turbid
O-Bz Hyp	ppt	+	ppt	ppt

+, clear viscous solution; turbid, turbid solution; ppt, polymer precipitated.

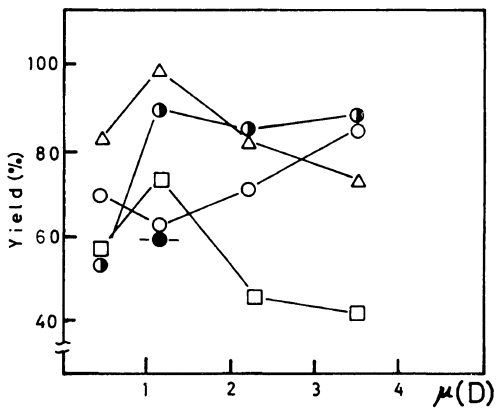

Figure 2. Effect of solvent polarity (μ) on polymer yield: a (△), poly(*O*-Ac-Hyp); b (●), poly(*O*-But-Hyp); c (□), poly(*O*-Cap-Hyp); d (◑), poly(*O*-Lau-Hyp); e (○), poly(*O*-Bz-Hyp).

Table I, the NCA of all *O*-Acyl-Hyp were obtained in a crystalline state in relatively good yields. In the case of *O*-Cap-Hyp NCA, the yield of NCA was relatively low because of its high solubility in ordinary organic solvents and the difficulty in finding a solvent system that would ensure crystallization in good yield. Thus, polymerization was carried out without any crystallization procedures.

Polymerization

O-Acyl-Hyp NCA were polymerized in solvents of different polarities (dioxane: $\mu=0.45$ D to acetonitrile: $\mu=3.34$ D) using triethylamine as the initiator. The effect of th solvent on polymerization is summarized in Tables II and III, and Figures 2 and 3.

Elemental analysis, intrinsic viscosity, and polymer yield are shown in Table II. Good agreement of the calculated values with those found by elemental analysis indicates that no degradation of the side chains took place.

The intrinsic viscosity of 0.13—0.70 suggests that the MW of these polymers are likely to be 2×10^3—22×10^3, according to the intrinsic viscosity–MW relationship proposed for poly(L-Pro) by Fasman and Blout.[9,10] The MW of poly(*O*-But-Hyp), calcu-

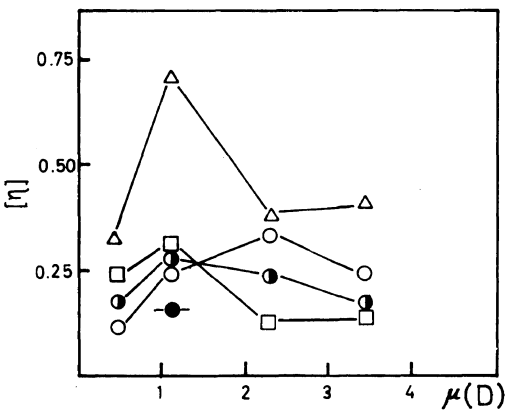

Figure 3. Effect of polymerization solvent polarity (μ) on intrinsic viscosity of polymers: a (△), poly(*O*-Ac-Hyp); b (●), poly(*O*-But-Hyp); c (□), poly(*O*-Cap-Hyp); d (◑), poly(*O*-Lau-Hyp); e (○), poly(*O*-Bz-Hyp).

lated by the method mentioned above, was remarkably small. Using the intrinsic viscosity–MW relationship proposed for poly(γ-benzyl L-glutamate),[11] the MW of this polymer was estimated as 15×10^3.

In Table III, the polymerization behavior in different solvent systems is summarized. Polymerization of all *O*-Acyl-Hyp NCA in dichloromethane gave clear and viscous solutions. But a polymerization system in acetonitrile became a turbid or precipitated mixture.

Figure 2 shows the relationship between polymer yield and the polarity of the polymerization solvent.

It was found that when polymerizing the *O*-Acyl-Hyp with aliphatic side chains such as Ac, Cap, and Lau, the polymer yield decreased with an increase in the polarity of the solvent. But in the case of *O*-Acyl-Hyp with an aromatic side group, the polymer yield was higher in a solvent with higher polarity.

The relationship between polymer viscosity in dichloroacetic acid and the polarity of the polymerization solvent is shown in Figure 3.

Apparently, there are different solvent effects exerted on MW depending on the structure of side groups; the MW of the polymers from Hyp with Ac, But, Cap, and Lau groups, showed a maximum at a dipole moment around 1 D, while that from the Hyp with a Bz group at a dipole moment around 2—3.5 D.

Infrared Absorption Spectra

The IR spectra of poly(*O*-acyl-hydroxy-L-proline)s are shown in Figure 4. The strong absorption of amide I (1650—1680 cm^{-1}), characteristic of polypeptides, appeared in all acylated poly(Hyp), but no trace of the absorption band of amide II, due to vibration of N–H bonds, appeared in any of the samples, since the main chains of the samples consisted of imide bonds. Absorptions due to aliphatic methylene chains also appeared around 2900 and 700—800 cm^{-1} and increased in proportion to the lengths of the methylene chains attached to the poly(Hyp). On acylation, new absorptions around 1735 cm^{-1}, due to the ester bonds, appeared in all the poly(*O*-Acyl-Hyp).

Comparatively strong absorptions appeared at 1425 cm^{-1} and 1651 cm^{-1}, due to frequency of C=O and C–N bonds, respectively, suggesting that the main chain configuration was a poly(L-Pro) I type. Other absorptions appeared at 1448 and 1643 cm^{-1}, corresponding to the poly(L-Pro) II type. Since these absorptions were seen for all samples, it is considered that both types of conformations exist in each sample.

Solubility Properties

As can be seen in Table IV, a marked improvement in the solubility properties of the polymers in the organic solvents was attained.

Poly(L-Pro) was soluble only in acidic solvents such as formic, acetic, propionic, and dichloroacetic acids. Poly(*O*-Ac-Hyp) and poly(*O*-But-Hyp) were soluble in organic solvents such as dichloromethane, chloroform, and ethylene dichloride in addition to the acidic solvents used for poly(L-Pro). Poly(*O*-Cap- and *O*-Lau-Hyp) were also soluble in ordinary organic solvents such as benzene, toluene, and ethyl acetate in addition to the acidic and haloalkyl solvents.

Introduction of long alkyl side chains into poly(Hyp) resulted in remarkably enhancing its solubility in organic solvents. Poly(*O*-Bz-Hyp) was soluble only in haloalkyl solvents and DCA.

Film Forming Capacity

Films of the polymers synthesized in this study were made by the following procedures. The polymers were dissolved in each solvent mentioned above, cast on glass surfaces, and then blow-dried in IR irradiation with clean air. The glass surfaces

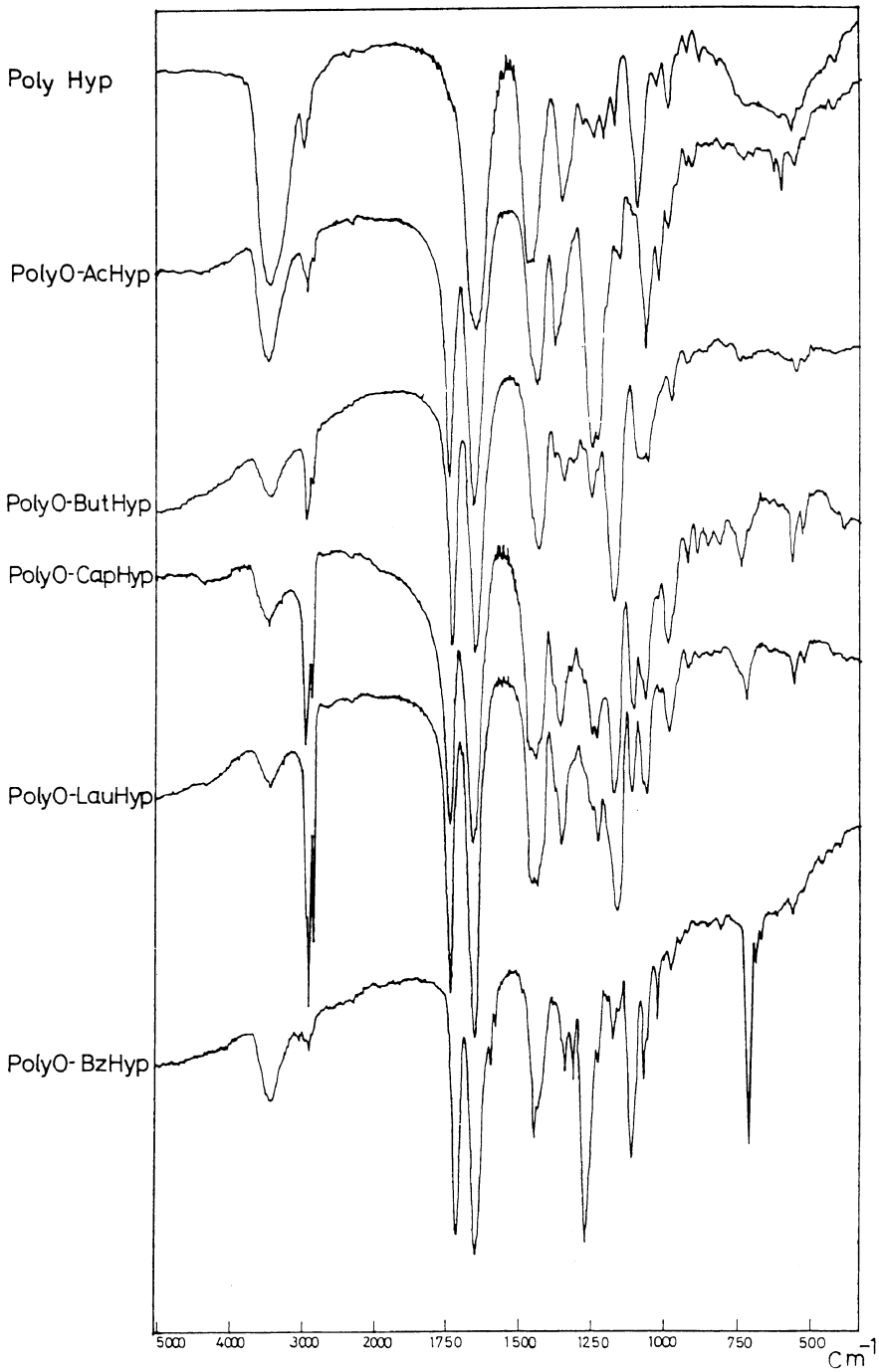

Figure 4. IR spectra.

Table IV. Solubility of poly(*O*-acyl-Hyp)s

Solvents	Polymers					
	Pro	*O*-Ac Hyp	*O*-But Hyp	*O*-Cap Hyp	*O*-Lau Hyp	*O*-Bz Hyp
Dichloromethane	(+)	+++	+++	+++	+++	+++
Chloroform	(+)	+++	+++	+++	+++	+++
Carbon tetrachloride	(+)	−	(+)	++	+++	−
Dichloroethane	(+)	++	+++	+++	++	++
Tetrachloroethane	−	+	++	++	+++	++
DMF	−	(+)	(+)	++	−	(+)
DMA	(+)	−	−	−	−	(+)
DMSO	−	(+)	+	−	−	(+)
Dioxane	−	−	+	+++	++	−
THF	−	−	(+)	+++	+	+
Formic acid	+++	+++	+++	(+)	−	−
Acetic acid	+++	++	++	++	(+)	−
Propionic acid	++	+	++	+	+++	−
DCA	+++	+++	+++	+++	+++	+++
Benzene	−	−	+++	+++	+++	(+)
Toluene	−	−	(+)	++	+++	(+)
Cyclohexane	−	−	−	−	+	−
Diethylether	−	−	−	+	++	−
Acetone	−	−	−	+++	−	−
Methanol	−	−	(+)	−	−	−
Ethanol	−	−	−	−	−	−
Propanol	−	−	(+)	−	−	−
Acetonitrile	−	−	+	+	(+)	−
Ethyl acetate	−	−	−	+	+	−
Water	+++	+	−	−	−	−

Abbreviations: DMF, dimethylformamide; DMSO, dimethyl sulfoxide; DMA, dimethylacetamide; THF, tetrahydrofuran; DCA, dichloroacetic acid.

Normalization of solubility: +++, 10 mg/0.1 ml at room temp within 10 min; ++, 10 mg/0.1 ml at 50—60°C within 10 min; +, 10 mg/0.1 ml at 50—60°C over 10 min; (+), 10 mg/0.1 ml swell; −, 10 mg/0.1 ml insoluble.

were well coated by the thin films of the polymers. Films of poly(*O*-Lau- and *O*-Cap-Hyp) were obtained by peeling them off the glass surfaces.

Poly(*O*-Acyl-Hyp), containing *O*-acetyl, butyryl, hexanoyl, dodecanoyl, and benzoyl groups also gave the films.

It should be worth while to investigate the relationship between the physicochemical properties and biomedical compatibility. A study of the wetting characteristics, conformational studies by NMR and molecular motion studies with spin-probed ESR and of the blood compatibility of these polymers are now in progress at our laboratory[12-15] and will be published in subsequent papers.

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