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Complexes of Polyethylene Oxide with Guanidine Hydrochloride and with Phenobarbital. Preliminary Structural Studies by Differential Scanning Calorimetry, Polarized Infrared Spectroscopy and X-Ray Fiber Photography[1,2]

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The complexes of polyethylene oxide (PEO) with guanidine hydrochloride and with phenobarbital were subjected to differential scanning calorimetry (DSC), polarized infrared (IR) spectroscopy and X-ray fiber photography, confirming the formations of the complexes and discussing the structures of PEO molecules in the complexes in comparison with PEO–urea complex or original samples of PEO.

The formations of the complexes of PEO with urea, with guanidine hydrochloride and with phenobarbital were confirmed by DSC curves of physical mixtures of the respective original components.

It may be concluded on the basis of the results by X-ray fiber photography that the three dimentional structure regarding the fiber identity period are different among ordinary PEO, PEO–guanidine hydrochloride complex and PEO–phenobarbital complex. The polarized IR spectroscopy informed that PEO molecule in PEO–guanidine hydrochloride complex may have a structure not so different from the 7_2 helix in the ordinary PEO. It was assumed that PEO molecule in PEO–phenobarbital complex is more distorted than that in PEO–guanidine hydrochloride complex in comparison with intact one, as the fiber identity period was considered to consist of one chemical unit.

Interactions of polyethylene oxide (PEO),[4] sometimes called polyethylene glycol (PEG), with various small molecules have been investigated in pharmaceutical field, regarding such as solubilization or incompatibility.[5–8] The elucidation of mechanisms of these kinds of pharmaceutical interactions may give useful informations not only for an improving of preparations but for an understanding of interactions between drugs and biological components.[1] From this point of view, structural studies of products in these interactions seem significant, while they have been scarcely attempted. In this connection, the crystalline structure of PEO-mercuric hydrochloride complex has been determined by X-ray diffraction study[9] and also it has been reported that a large single crystal of PEO–urea complex has a hexagonal cross section,[10] as may be applicable to structural studies of PEO–drug complexes.

1) This paper forms Part XXVI of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part XXV: K. Kono, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **21**, 366 (1973).
2) A part of this work is taken from the thesis of Kenji Kono for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo, 1971.
3) Location: *a) Ukima-1-3-32, Kita-ku, Tokyo, 115, Japan; b) Hongo-7-3-1, Bunkyo-ku, Tokyo, 113, Japan; c) Ebara-2-4-41, Shinagawa-ku, Tokyo, 142, Japan.*
4) This nomenclature conforms to that by M.J. Schick, "Nonionic Surfactants," Surfactant Science Series, Vol. 1, Marcel Dekker, Inc., New York, 1967.
5) B.N. Kabadi and E.R. Hammarlund, *J. Pharm. Sci.*, **55**, 1072 (1966).
6) P. Singh, J.K. Guillory, T.D. Sokoloski, L.Z. Benet, and V.N. Bhatia, *J. Pharm. Sci.*, **55**, 63 (1966).
7) T. Higuchi and J.L. Lach, *J. Am. Pharm. Assoc. Sci. Ed.*, **43**, 465 (1954).
8) D.E. Guttman and T. Higuchi, *J. Am. Pharm. Assoc. Sci. Ed.*, **44**, 668 (1955).
9) R. Iwamoto, Y. Saito, H. Ishihara, and H. Tadokoro, *J. Polymer Sci.*, **A, 6**, 1509 (1961).
10) *a)* F.E. Bailey, Jr. and H.G. France, *J. Polymer Sci.*, **49**, 397 (1961); *b)* H. Tadokoro, T. Yoshida, Y. Chatani, and S. Murahashi, *ibid.*, **B, 2**, 363 (1964).

The authors reported previously that guanidine hydrochloride forms a crystalline complex with PEO,[11] and Higuchi and Lach had already found PEO–phenobarbital complex[7] which was recognized in the present study to be obtained in crystalline state as will be described later. Thus, these two kinds of crystalline complexes seemed convenient for structural studies. Moreover, it was interesting why guanidine hydrochloride and phenobarbital form the crystalline complexes with PEO though they are different in physico-chemical properties, and why PEO–quanidine hydrochloride complex dissolves well in water while PEO–phenobarbital complex does not.

In the present study, the two crystalline complexes of PEO with guanidine hydrochloride and with phenobarbital mentioned above were subjected to differential scanning calorimetry (DSC), polarized infrared (IR) spectroscopy and X-ray fiber photography, confirming the formations of the complexes and discussing the structures of PEO molecules in the complexes in comparison with PEO–urea complex or original samples of PEO.

Experimental

Materials——As the samples of PEO of relatively low molecular weight, PEG 1000, PEG 4000 and PEG 6000, the numbers of which mean the respective approximate molecular weights, were kindly supplied by Nippon Soda Company. As the samples of PEO of high molecular weight, PEO WSR N·10, PEO WSR N·3000 and PEO Coagulant of Union Carbide Chemicals Company were used, which have the approximate molecular weights of 10^5, 6×10^5 and 5×10^6, respectively. All the above samples of PEO were purified by repeating reprecipitation from benzene and ethyl ether, and dried in vacuum desiccator throughly, being identified by their X-ray diffraction patterns and IR absorption spectra. Phenobarbital was used after recrystallization from water. The water used as solvent was prepared by distillation after treated with ion-exchange column. The rest of the materials were of the reagent grade.

Preparation of Complexes——*a*) PEO (or PEG)–Urea Complex and PEO (or PEG)–Guanidine Hydrochloride Complex: Ten ml of 6.0% (w/v) methanolic solution of urea (or 9.6% (w/v) methanolic solution of guanidine hydrochloride) was mixed with 10 ml of 4.4% (w/v) benzene solution of PEO (or PEG), kept standing for 24 hr at 25°, and the crystalline complex was obtained as the coprecipitate which was separated by filtration. It was ascertained that there was given no precipitate when any of the two components of the complex was excluded in the above mixture system.

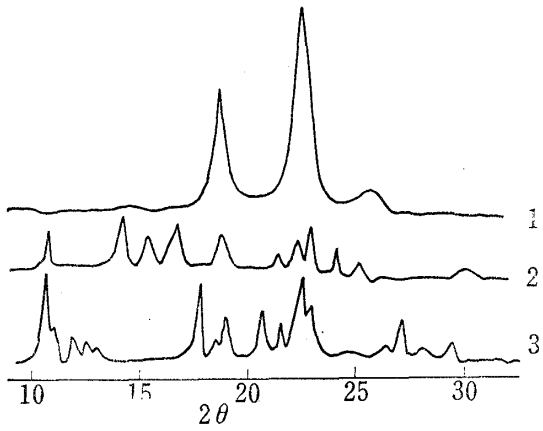

Fig. 1. Powder X-Ray Diffraction Patterns of PEG 4000, Phenobarbital and PEG-Phenobarbital Complex by Cu-$K\alpha$ Radiation

1: PEG 4000
2: phenobarbita
3: PEG 4000–phenobarbital complex

b) PEO(or PEG)–Phenobarbital Complex: On referring to the report by Singh, *et al.*,[6] 2 g of PEO (or PEG) was added in 500 ml of 0.1% aqueous solution of phenobarbital, shaken for 24 hr at 25°, and the coprecipitate was separated by filtration. Although there has been no discussion of the crystallinity of PEO–phenobarbital complex,[6,7] the coprecipitate obtained here was recognized to be a crystalline complex, as shown in Fig. 1, for example.

Differential Scanning Calorimetry (DSC)——This was done using a Perkin–Elmer Model DSC 1B differential scanning calorimeter.

X-Ray Diffraction Studies——a) Powder X-ray diffractometry was carried out using a Toshiba Model ADX-102 diffractometer by Ni-filtered Cu-$K\alpha$ radiation.

b) X-Ray fiber photography of uniaxially oriented specimen was carried out using a flat camera and cylindrical camera. The camera distance was calibrated by means of the silicone powder pattern obtained from the silicone powder on the specimen. The thin uniaxially oriented film specimen of PEO–guanidine hydrochloride complex for the measurement[12] was obtained by dipping a pair of forceps into the concentrated

11) K. Kono, T. Nagai, and H. Nogami, presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1970, No. 0B11-2.

12) The samples of PEO in the systems were of high molecular weight because of the easiness of making the film specimens.

aqueous solution and withdrawing them, while that of PEO–phenobarbital complex[12] was obtained by withdrawing the forceps from the viscous sample swelled with addition of ethyl acetate. The respective thin film specimens were fixed on a metal holder by epoxy resin as a binding agent.

Infrared (IR) Absorption Spectroscopy——The absorption spectra in the region from 4000 to 600 cm^{-1} were obtained using a Perkin–Elmer Type 621 double beam IR spectrophotometer. The polarized ones were obtained with a polarizer and a AgCl sheet. The uniaxially oriented film specimens of PEO and of PEO–guanidine hydrochloride complex for the measurement[12] were prepared by dissolving the respective samples in water on a AgCl sheet and then rolling with a spatula, while that of PEO–phenobarbital complex[12] was obtained by dissolving in pyridine and then rolling.

Result and Discussion

Confirmation of Complex Formation of PEO with Guanidine Hydrochloride

The complexes of PEO with urea and with phenobarbital subjected to the present study were identified with those in the existing reports[7,10] according to powder X-ray diffraction patterns and IR absorption spectra. The formation of PEO–guanidine hydrochloride complex was confirmed as will be described below.

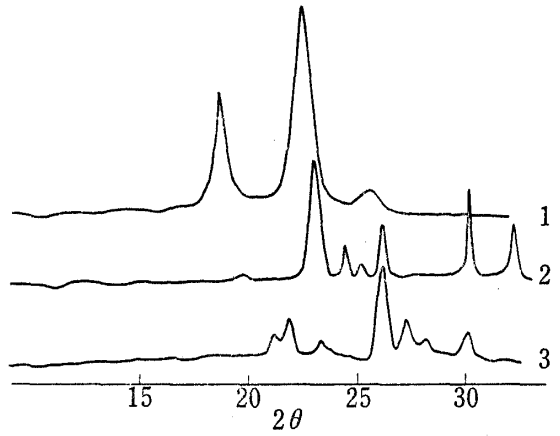

Fig. 2. Powder X-Ray Diffraction Patterns of PEG 4000, Guanidine Hydrochloride and PEG 4000–Guanidine Hydrochloride Complex by Cu-$K\alpha$ Radiation

1: PEG 4000
2: guanidine hydrochloride
3: PEG 4000–guanidine hydrochloride complex

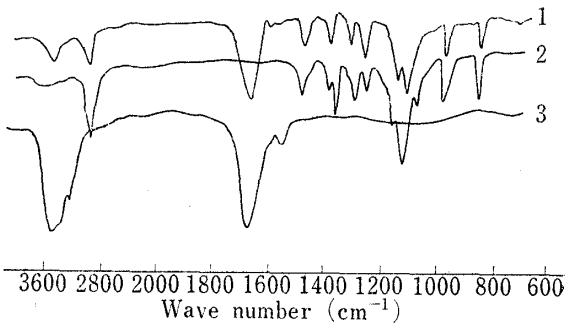

Fig. 3. IR Absorption Spectra of PEG 4000, Guanidine Hydrochloride and PEO 4000–Guanidine Hydorchloride Complex, according to KBr Disk Method

1: PEG 4000-guanidine hydrochloride complex
2: PEG 4000
3: guanidine hydrochloride

As an example, Fig. 2 shows the powder X-ray diffraction patterns of PEG 4000, guanidine hydrochloride and PEG–guanidine hydrochloride complex, the last one being different from each of the former two original components. IR absorption spectra also are different among these three, as shown in Fig. 3.

PEG 4000 and guanidine hydrochloride melted near 66° and 172°, respectively, while the complex did near 142°. Moreover, the complex was less hygroscopic than guanidine hydrochloride. Regarding the complexes of the other kinds of PEO with guanidine hydrochloride, the formations were confirmed in the same way.

Differential Scanning Calorimetry (DSC)

The DSC curves of PEG 4000–urea system as an example are shown in Fig. 4, where the weight ratio of urea to the ethylene oxide monomer unit of PEG 4000 was 2: 1 on referring to the report of Bailey, *et al.*[10a] Four peaks were observed on the DSC curve in the case of the physical mixture, while only one in the case of the complex prepared. The endothermic peak near 413°K common to both cases was identical with the melting point of the complex

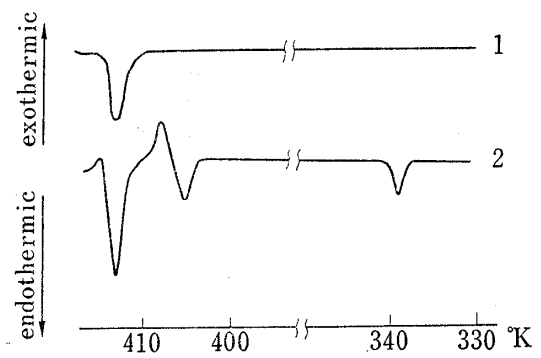

Fig. 4. DSC Curves of PEG 4000–Urea System at scanning Speed of 2°/min

1: PEG 4000–urea complex
2: physical mixture of PEG 4000 and urea

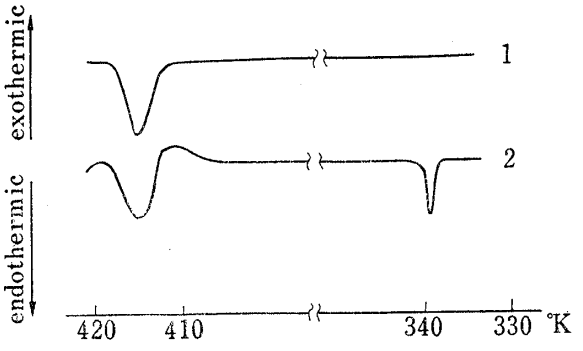

Fig. 5. DSC Curves of PEG 4000–Guanidine Hydrochloride System at scanning Speed of 4°/min

1: PEG 4000–guanidine hydrochloride complex
2: physical mixture of PEG 4000 and guanidine hydrochloride

reported by Bailey, *et al.*[10a] Therefore, the four peaks in the case of the physical mixture were considered as follows: the endothermic one near 339°K due to the melting of PEG 4000, the endothermic one near 405°K due to the melting of urea, the exothermic one near 408°K due to the complex formation involving subsequent solidification, and the endothermic one near 413°K due to the melting of the complex.

Fig. 5 shows the DSC curves of the PEG 4000–guanidine hydrochloride system as an example. The physical mixture of both components also gave the two characteristic peaks on the curve, *i.e.*, the exothermic one due to the complex formation and the endothermic one due to the melting of the complex, though the former was not so distinct as in the case of PEO–urea system. Here, the mixing ratio in weight of PEO to guanidine hydrochloride was 1: 1, as the result in the mixing ratio 1: 2 was similar to that in 1: 1. The melting (or transition) point of guanidine hydrochloride was not observed in case of PEO–guanidine hydrochloride system, as it is higher than the melting point of PEO–quanidine hydrochloride complex.

The physical mixture of PEO and phenobarbital did not give the exothermic peak due to the complex formation upon examining at several heating speeds, while did the endothermic one near the same temperature as the melting point of the sample of the complex prepared.

It is difficult to discuss the complex forming process on the basis of the above thermograms only. However, it is assumed that some change in crystalline state, such as a formation of spherulite,[10b] may take place through a complex forming process, having influence on the exothermic peak of the DSC curve. The fact that the exothermic peak due to the complex formation was observed in the cases of PEO–urea and PEO–guanidine hydrochloride systems while not in the case of PEO–phenobarbital system may suggest that PEO–urea and PEO–guanidine hydrochloride complexes have a similarity in the complex forming process.

Polarized Infrared (IR) Spectroscopy and X-Ray Fiber Photography

As an example, the polarized IR spectra of PEO Coagulant and PEO Coagulant–guanidine hydrochloride complex are shown in Fig. 6 and 7, respectively. The spectra of PEO and of guanidine hydrochloride did not overlap each other, as shown in Fig. 3, and thus the spectrum of the complex of these two components may be interpreted in terms of the bands due to PEO and guanidine hydrochloride, respectively. The spectral bands due to PEO in PEO–guanidine hydrochloride complex were not remarkably different from those of the original sample of PEO except for the following points: (a) the parallel band at 959 cm^{-1} and the perpendicular one at 947 cm^{-1} were doublet in PEO, while nearly singlet in PEO–guanidine hydrochloride complex; (b) the parallel band at 1103 cm^{-1} in PEO shifted to 1093^{-1} in PEO–guanidine

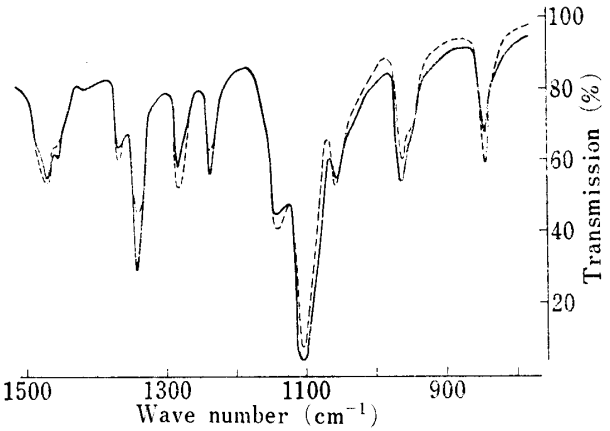

Fig. 6. Polarized IR Spectra of the Oriented Film of PEO Coagulant

----- by perpendicularly polarized radiation
—— by parallel polarized radiation

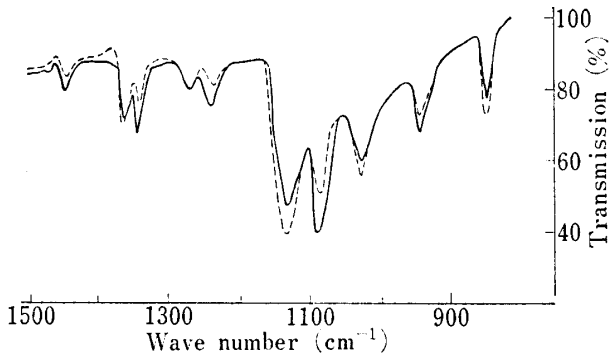

Fig. 7. Polarized IR Spectra of the Oriented Film of PEO Coagulant–Guanidine Hydrochloride Complex

----- by perpendicularly polarized radiation
—— by parallel polarized radiation

hydrochloride complex. The skelton of PEO molecule is considered to take a succession of nearly trans, trans and gauche conformation having relation to the absorption bands between 1500 and 800 cm^{-1}, and the doublet bands around 950 cm^{-1} and around 1350 cm^{-1} are attributed to the crystal splitting.[13] Upon the formation of PEO–guanidine hydrochloride complex, the doublet band around 950 cm^{-1} in PEO changed to nearly singlet. This result could not be explained in terms of a change in the crystal splitting because the band around 1350 cm^{-1} remained doublet. Therefore, it was considered that PEO molecule in the complex does not have a planar zigzag conformation, but has a structure not so different from the 7_2 helix in the ordinary PEO, as had been discussed in the case of PEO–urea complex.[10b]

The X-ray fiber photograph of the uniaxially oriented film specimen of PEO Coagulant–guanidine hydrochloride complex as an example is shown in Fig. 8, giving the fiber identity period as 9.2Å calculated from the meridional reflection which appeared at the second layer line. The fact that the first meridional reflection appeared at the second layer line may

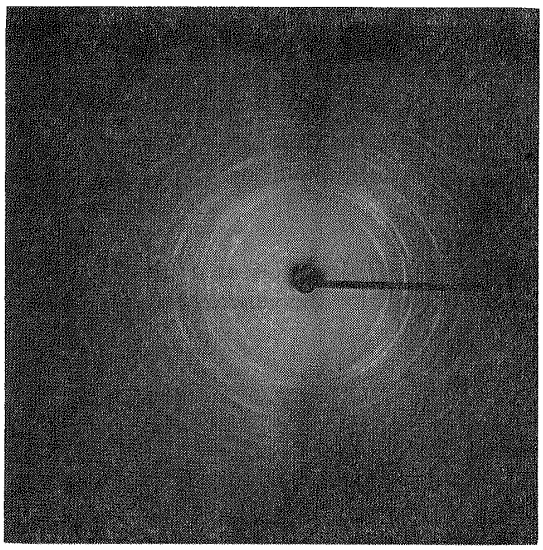

Fig. 8. X-Ray Fiber Photograph of the Oriented Film of PEO Coagulant–Guanidine Hydrochloride Complex

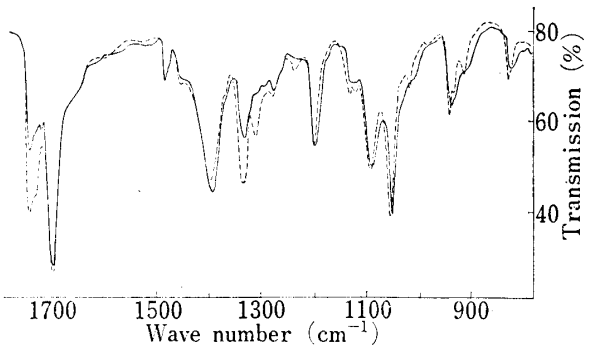

Fig. 9. Polarized IR Spectra of the Oriented Film of PEO WSR N·3000–Phenobarbital Complex

----- by perpendicularly polarized radiation
—— by parallel polarized radiation

13) W.H.T. Davison, *J. Chem. Soc.*, **1955**, 3270.

suggest that the fiber identity period consists of two chemical units and is longer than the ethylene oxide monomer unit.[14]

The polarized IR spectra of PEO WSR N·3000–phenobarbital complex as an example are shown in Fig. 9. The spectra of the two original components overlapped partly, and thus it was a little difficult to find the change in PEO chain upon the complex formation compared with the case of PEO–guanidine hydrochloride complex described already. There was found no singlet band around 950 cm^{-1} in the complex, though it was observed in the case of PEO–guanidine hydrochloride complex.

The X-ray fiber photograph of the uniaxially oriented film specimen of PEO WSR N·3000–phenobarbital complex as an example is shown in Fig. 10. In addition to Fig. 1, Fig. 10 indicates that PEO–phenobarbital complex is obtained in crystalline state. In. Fig. 10, the first meridional reflection appeared at the first layer line. The fiber identity period was given as 10.3Å and was considered to consist of one chemical unit.[14]

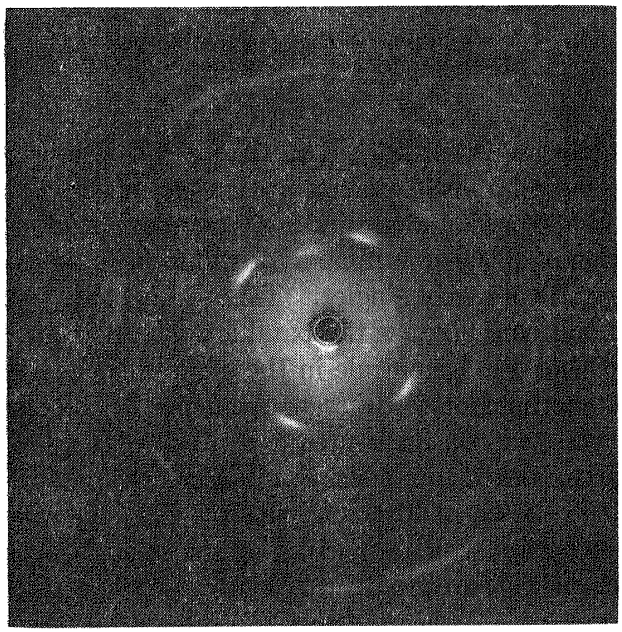

Fig. 10. X-Ray Fiber Photograph of the Oriented Film of PEO WSR N·3000–Phenobarbital Complex

Conclusively, the three dimentional structure regarding the fiber identity period are different among ordinary PEO,[15] PEO–guanidine hydrochloride complex and PEO–phenobarbital complex. In the case of PEO–guanidine hydrochloride complex, the polarized IR spectroscopy informed that PEO molecule in the complex may have a structure not so different from the 7_2 helix in the ordinary PEO. In the case of PEO–phenobarbital complex, though there was given little information by the polarized IR spectroscopy because the spectra of the two original component overlapped partly, it was assumed that PEO molecule in the complex is more distorted than that in PEO-guanidine hydrochloride complex in comparison with intact one, as the fiber identity period was considered to consist of one chemical unit. Further investigations should be made in order to get a complete understanding of the structures of these complexes, for example, by Raman spectroscopy or by fiber X-ray photography of a doubly oriented specimen.

Acknowledgement The authors gratefully acknowledge the award of Research Grant from Naito Foundation (to T.N.). Thanks are also given to Nippon Soda Co. Ltd. for the generous supply of samples of PEO.

14) B.K. Vainshtein, "Diffraction of X-Rays by Chain Molecules," Elsevier Publishing Co., Amsterdam, 1966.

15) H. Tadokoro, Y. Chatani, T. Yoshimura, S. Tahara, and S. Murahashi, *Makromol. Chem.*, 73, 109 (1964).