[7] a) All complexes were characterized by IR as well as ^1H and ^{31}P NMR spectroscopy. All except **2** were oils, and correct microanalyses were not always obtained. The ^{13}C NMR spectra were complicated by extensive ^{19}F couplings; b) crystallographic data for **2** ($C_{49}H_{24}ClF_{78}IrOP_2$, $M_r = 2400.27$): triclinic, $P\bar{1}$, $T = -80\,^{\circ}C$, $a = 11.277(6)$, $b = 15.094(5)$, $c = 22.595(4)$ Å, $\alpha = 84.83(2)$, $\beta = 85.85(2)$, $\gamma = 80.15(3)^{\circ}$, $V = 3768(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 2.116\ g\,cm^{-3}$, ρ_{obs} (C_6H_5Br/CH_3I, 22 °C) $= 2.085\ g\,cm^{-3}$, crystal dimensions $0.34 \times 0.28 \times 0.22$ mm, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), scan mode $\theta/2\theta$, 12450 measured reflections, $0 \le h \le 12$, $-17 \le k \le 17$, $-25 \le l \le 25$, $2.00 \le \theta \le 24.03^{\circ}$, 11783 unique data, 9781 observed data ($> 2\sigma(I)$), absorption coefficient $2.082\ mm^{-1}$, min./max. transmission 83.6/99.9%, 1262 parameters, GOF = 1.050, $R1$ (2σ) = 0.046, $wR2 = 0.1195$, $R_{int} = 0.0324$, R indices (all data): $R1 = 0.0637$, $wR2 = 0.1442$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100131. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code +(1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).

[8] For example, *trans*-[IrCl(CO)($P(iPr)_3$)$_2$] exhibits Ir–P, Ir–Cl, and Ir–C bond lengths of 2.347(2), 2.421(5), and 1.80(2) Å, and L-Ir-L bond angles of $(90 \pm 1)^{\circ}$ and $(180 \pm 1)^{\circ}$ at room temperature: L. Dahlenburg, A. Yardimcioglu, *J. Organomet. Chem.* **1985**, *291*, 371.

[9] The Cambridge Structural Database contains many compounds with $(CF_2)_4$ segments, but only two with $(CF_2)_{\ge 6}$ segments: a) $CF_3(CF_2)_6$-*p*-$C_6H_4CO_2$-*p*-C_6H_4CN: P. Kromm, J.-P. Bideau, M. Cotrait, C. Destrade, H. Nguyen, *Acta Cryst.* **1994**, *C50*, 112; b) [(η^5-C_9H_7)CoI(CO){$(CF_2)_5CF_3$}]: C. R. Jablonski, Z. Zhou, *Can. J. Chem.* **1992**, *70*, 2544.

[10] B. Albinsson, J. Michl, *J. Phys. Chem.* **1996**, *100*, 3418.

[11] Reviews of several distinct mechanisms by which alkyl halides can undergo oxidative addition: a) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, California, **1987**, pp. 306–322; b) S. Henderson, R. A. Henderson, *Adv. Phys. Org. Chem.* **1987**, *23*, 1.

[12] a) PPh_3 is alkylated by CH_3I much faster than by $CF_3(CF_2)_7CH_2CH_2I$: P. Bernatis (University of Utah), unpublished results. b) A reviewer raised the question of the relative rates of radical reactions in fluorocarbons and organic solvents. One relevant observation is that **2** and $CH_3CH_2CHICH_3$ react more rapidly in $CF_3C_6F_{11}$ than THF.

[13] J. A. Labinger, J. A. Osborn, N. J. Coville, *Inorg. Chem.* **1980**, *19*, 3236.

[14] Additions of H_2 to **1**: P. P. Deutsch, R. Eisenberg, *Chem. Rev.* **1988**, *88*, 1147.

[15] Addition of $^3O_2$ and $^1O_2$ to **1**: M. Selke, W. L. Karney, S. I. Khan, C. S. Foote, *Inorg. Chem.* **1995**, *34*, 5715.

[16] Accordingly, *trans*-[IrCl(CO){$P(C_6F_5)_3$}$_2$] ($\tilde{\nu}_{CO} = 1994\ cm^{-1}$) is inert to O_2: L. Vaska, L. S. Chen, *J. Chem. Soc. Chem. Commun.* **1971**, 1080.

[17] P. M. Maitlis, A. Haynes, G. J. Sunley, M. J. Howard, *J. Chem. Soc. Dalton Trans.* **1996**, 2187.

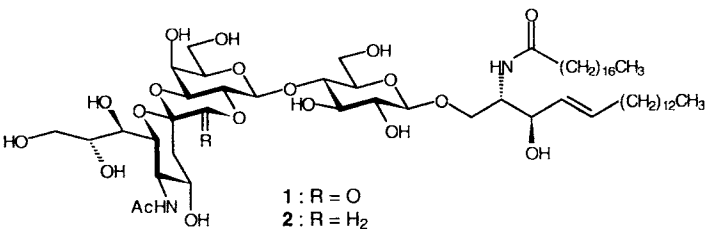
[18] a) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev.* **1994**, *94*, 373; b) M. J. Atherton, J. Fawcett, J. H. Holloway, E. G. Hope, A. Karaçar, D. R. Russell, G. C. Saunders, *J. Chem. Soc. Dalton Trans.* **1996**, 3215.

Synthesis of a Novel Stable GM_3-Lactone Analogue as Hapten for a Possible Immunization against Cancer**

Lutz F. Tietze* and Holger Keim

Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday

In addition to proteins and lipids, carbohydrates—of which gangliosides constitute a large part—are essential elements of the cell surface. They are anchored to the lipid bilayer of the membrane with their ceramide portion, and the carbohydrate moiety is exposed to the outside. Gangliosides play an important role in cell–cell and cell–matrix recognition and are relevant for cellular growth since they interact with many growth receptors, for example the epidermal growth factor receptor.[1] The GM_3 ganglioside is the smallest and most widespread ganglioside in human and animal tissue. It has been found in brain and nerve cells as well as in the membranes of melanoma and liver carcinoma cells in increased concentrations.[2] However, immunization experiments with monoclonal antibodies indicate that the actual tumor-associated antigen is not the GM_3 ganglioside itself but its lactone form **1**.[3] Consequently, a greatly increased density of the GM_3 lactone was discovered in melanoma cells. Furthermore, the existence of a threshold at which the antibody recognizes the cell has been shown.[4] The GM_3 ganglioside lactone[4] and lactam[5] hitherto used to obtain antibodies are unstable towards hydrolysis under physiological conditions. Therefore, there is much interest in developing hydrolysis-resistant analogues of **1** and, thus, making a defined immunogen available for immunization. Here we describe the synthesis of the hydrolysis-stable GM_3 ganglioside lactone analogue **2** containing an ether group.



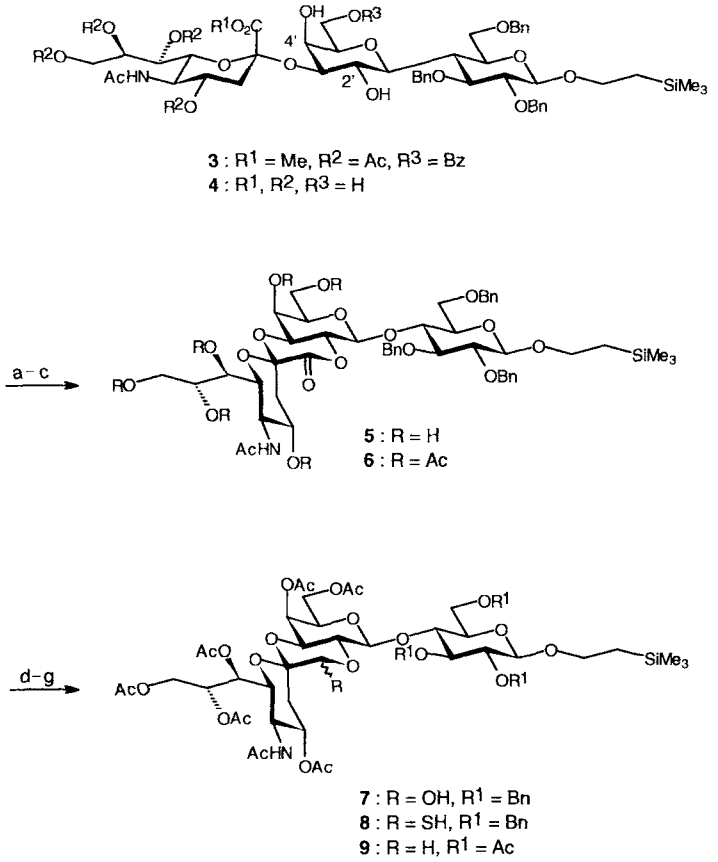
For the synthesis of **2** the cyclization of trisaccharide **3**[6]—with free hydroxy groups at C2′ and C4′ which is selectively built up from glucose, galactose and neuraminic acid by known procedures—with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to yield the C2′-Gal lactone **5** was initially attempted (Scheme 1). However, reaction of the free hydroxy groups led to both possible lactone isomers in 86% yield as a nonseparable mixture in a ratio of 1.7:1. Conversely, the acid-catalyzed reaction of the partially deprotected trisaccharide **4**, which was already described for the isolated GM_3 ganglioside,[7] provided the desired GM_3 ganglioside lactone **5** in 57% yield.

To transform **5** into analogue **9** it was first peracetylated to give **6**; subsequent reduction of the lactone functionality led to lactol **7**, which was converted into thiohemiacetal **8**. Hydrogenolytic cleavage of the thiol moiety completed the sequence. The Red-Al derivative Na[$AlH(OCH_2CH_2OCH_3)_2$-OEt][8] proved to be the best reagent for reducing the carboxy functionality to afford **7** in 80% yield with conservation of the acetyl groups. Reaction with diisobutylaluminium hydride (DIBAL) mostly led to deacylated products; $LiBH_4$ and $NaBH_4$ yielded the corresponding, undesired diols as main products, as expected.

Conversion of the hemiacetal of **7** into the ether functionality of **9** proved extremely difficult, mainly due to the low reactivity of the hydroxy group, and almost led to failure of the entire project. The glycosidic bond at C1 was cleaved in all attempts to reductively remove the hydroxy group directly, for example with triethylsilane and boron trifluoride etherate. The obvious transformation into an *O,S*-acetal also failed initially. Activation of the hydroxy group by conversion into the acetate or trichloroacetimidate by standard procedures was achieved in very high yields. However, during the subsequent reaction with

[*] Prof. Dr. L. F. Tietze, Dr. H. Keim
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: Int. code +(551)39-9476
e-mail: ltietze@gwdg.de

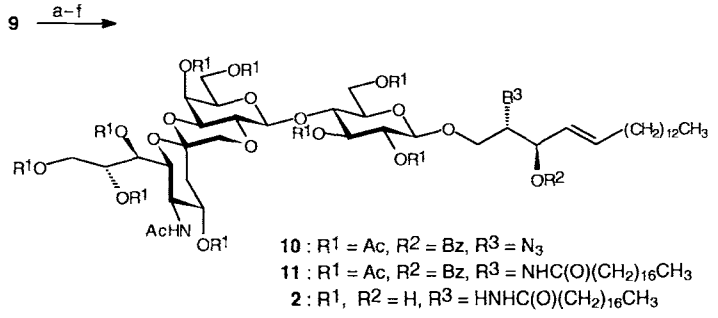
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 500) and the Fonds der Chemischen Industrie. H. K. thanks the latter for a doctoral scholarship.



Scheme 1. a) NaOMe, MeOH, 30 h, room temperature (RT); b) HOAc, 3 d, RT, 57% (two steps); c) Ac_2O, pyridine, 4-(dimethylamino)pyridine (DMAP), 14 h, RT, 94%; d) Na[AlH($CH_2OEt)_2OEt$], toluene, −55 °C, 1 h, 80%; e) $(PyS)_2$ (5 equiv), nBu_3P (5 equiv), CH_2Cl_2, 3 d, RT, 6 h reflux, 71%; f) Raney nickel, EtOH, H_2 (1 atm), 30 h, RT; g) Ac_2O, pyridine, DMAP, CH_2Cl_2, 14 h, RT, 85% (two steps).

thiophenol in the presence of boron trifluoride etherate or trimethylsilyl triflate (TMSOTf), a competitive reaction took place at C1 of the glucose unit leading to the dithiophenyl glycosides. Only reaction with five equivalents each of bis(pyridinium) disulfide and *n*-tributylphosphane[9] resulted in the desired transformation of the lactol. Remarkably, the free thiohemiacetal **8** was obtained in 71% yield as a result of overreduction instead of the expected *S*-pyridyl derivative.

Subsequent conversion into the acetyl-protected GM_3-lactone analogue **9** was achieved by hydrogenation with H_2 and Raney nickel and concomitant cleavage of the benzyl groups in an excellent yield of 85%. The presence of the ether **9** was proven with NMR spectroscopy by $^1H-^1H$ correlation experiments. Two doublets at $\delta = 3.44$ and 3.89 ($^2J(H,H) = 11.5$ Hz) can be assigned to the two geminal protons at C1″.



Scheme 2. a) CF_3COOH/CH_2Cl_2 (2/1), 30 min, RT; b) CCl_3CN (30 equiv), DBU, CH_2Cl_2, 1 h, 0 °C, 93% (two steps); c) CH_2Cl_2, azido sphingosine (3 equiv), $BF_3 \cdot Et_2O$ (3 equiv), 4-Å molecular sieves, 1 h, −40 °C, 66%; d) NEt_3 (5 equiv), PhSH (5 equiv), $(PhS)_2Sn$, CH_2Cl_2 (5 equiv), 4 h, RT; e) stearic acid (5 equiv), EDC (5 equiv), CH_2Cl_2, 2 h, RT, 73% (two steps); f) NaOMe, MeOH, 20 h, RT, 77%.

To convert **9** into the complete GM_3 ganglioside lactone analogue **2**, the protecting group at C1 was removed by reaction with trifluoroacetic acid in dichloromethane (Scheme 2). Unfortunately, epimerization took place at C2 of the neuraminic acid to an extent of 17% and led to the thermodynamically more stable β anomer, which fortunately was easily removed by chromatography (silica gel) at the stage of **10**. The two anomers could be distinguished by their ^1H NMR signals for 3″-H_{eq} at $\delta = 2.50$ for the α anomer and 1.96 for the β anomer. Lewis acids such as boron trifluoride etherate or zinc chloride employed to cleave the C1 protecting group effected almost complete epimerization; no reaction took place with tetrabutyl ammonium fluoride.

For the further transformation into the ganglioside **10**, reaction of the hydroxy group at C1 was carried out to lead to the trichloroacetimidate. Subsequent glycosylation with azido sphingosine at −40 °C in dichloromethane, catalyzed with boron trifluoride etherate, afforded the sphingosine derivative **10** in two hours. No further epimerization was observed under these reaction conditions. Reduction of the azido group in **10** to the corresponding amine was effected in good yields with $NHEt_3^+[(PhS)_3Sn]^-$.[12] Once again many reagents were tested—such as triphenylphosphane, 1,3-propanedithiol, and H_2S—but all led to poorer results. In the final steps of the synthesis of the free GM_3-lactone analogue **2**, the amine reacted with stearic acid upon addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to provide ceramide **11**, which was deprotected by solvolysis with sodium methanolate in methanol.

In cooperation with the Abteilung für Hämotologie und Onkologie as well as the Abteilung für Immunologie at the Universität Göttingen we are currently testing the biological activity of **2**. We are also forming conjugates with bovine serum albumin (BSA) and the keyhole-limpet hemocyanin (KLH), which are used for immunization.

Received: December 19, 1996 [Z9907IE]
German version: *Angew. Chem.* **1997**, *109*, 1704–1706

Keywords: acetals · gangliosides · glycosylations · neuraminic acids · tumor therapy

[1] Q. Zhou, S. Hakomori, K. Kitamura, Y. Igarashi, *J. Biol. Chem.* **1994**, *269*, 1959.
[2] a) W. B. Hamilton, F. Helling, K. O. Lloyd, P. O. Livingston, *Int. J. Cancer* **1993**, *53*, 566; b) C.-C. Sung, D. K. Pearl, S. W. Coons, B. W. Scheithauer, P. C. Johnson, A. J. Yates, *Cancer* **1994**, *74*, 3010.
[3] G. Magnusson, K. Ding, U. Nilsson, A. K. Ray, A. Rosén, H.-O. Sjögren in *Complex Carbohydrates in Drug Research* (Eds.: K. Bock, H. Clausen), Copenhagen, **1994** (*Alfred Benzon Symp.* **1994**, *36*, 89).
[4] G. A. Nores, T. Dohi, M. Taniguchi, S. I. Hakomori, *J. Immunol.* **1987**, *139*, 3171.
[5] M. Wilstermann, L. O. Kononov, O. Nilson, A. K. Ray, G. Magnusson, *J. Am. Chem. Soc.* **1995**, *117*, 4742.
[6] A. Hasegawa, K. Adachi, M. Yoshida, M. Kiso, *J. Carbohydr. Chem.* **1992**, *11*, 95.
[7] R. K. Yu, T. A. W. Koerner, S. Ando, H. C. Yohe, J. H. Prestegard, *J. Biochem.* **1985**, *98*, 1367.
[8] R. Kanazawa, T. Tokoroyama, *Synthesis* **1976**, 526.
[9] A. O. Stewart, R. M. Williams, *J. Am. Chem. Soc.* **1985**, *107*, 4289.
[10] ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.01$ (s, 9H; $SiMe_3$), 0.93 (m_c, 2H; CH_2SiMe_3), 1.87 (dd, $^3J(H,H) = 10.5$, $^2J(H,H) = 13.5$ Hz, 1H; 3″-H_{ax}), 1.90 (s, 3H; CH_3CON), 2.03, 2.06, 2.08, 2.09, 2.13, 2.15 (s, 27H; 9 CH_3CO), 2.60 (dd, $^3J(H,H) = 5.5$, $^2J(H,H) = 13.5$ Hz, 1H; 3″-H_{eq}), 3.44 (d, $^2J(H,H) = 11.5$ Hz, 1H; 1″-H_{ax}), 3.59 (dd, $^3J(H,H) = 7.5$, 10.5 Hz, 1H; 2′-H), 3.52–3.58

(m, 1H; OCH_2CH_2Si), 3.64 (dt, $^3J(H,H) = 3.5, 10.0$ Hz, 1H; 5-H), 3.71 (dd, $^3J(H,H) = 3.0, 10.5$ Hz, 1H; 3'-H), 3.81 (t, $^3J(H,H) = 9.5$ Hz, 1H; 4-H), 3.80–3.91 (m, 4H; 5'-H, 5''-H, 6'-H_a, 6''-H), 3.89 (d, $^2J(H,H) = 11.5$ Hz, 1H; 1''-H_{eq}), 3.92–3.99 (m, 1H; OCH_2CH_2Si), 4.02–4.13 (m, 2H; 6-H_a, 6'-H_b), 4.10 (dd, $^3J(H,H) = 6.0$, $^2J(H,H) = 12.0$ Hz, 1H; 9''-H_a), 4.35 (d, $^2J(H,H) = 7.5$ Hz, 1H; 1'-H), 4.38–4.43 (m, 2H; 6-H_b, 9''-H_b), 4.49 (d, $^2J(H,H) = 8.0$ Hz, 1H; 1-H), 4.88 (dd, $^3J(H,H) = 8.0, 9.5$ Hz, 1H; 2-H), 5.21 (t, $^3J(H,H) = 9.5$ Hz, 1H; 3-H), 5.15–5.23 (m, 2H; 4''-H, 8''-H), 5.25 (dd, $^3J(H,H) = 2.0, 6.5$ Hz, 1H; 7''-H), 5.29 (dd, $^3J(H,H) = 1.5, 3.0$ Hz, 1H; 4'-H), 5.32 (d, $^3J(H,H) = 9.0$ Hz, 1H; NH); $[\alpha]_D^{20} = -6.6$ ($c = 0.5$ in $CHCl_3$); MS (DCI): m/z (%) = 1098.3 (100) $[M + NH_3 + H]^+$.

[11] R. R. Schmidt, P. Zimmermann, *Angew. Chem.* **1986**, *98*, 722; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 725.

[12] M. Bartra, F. Urpi, J. Vilarrasa, *Tetrahedron Lett.* **1987**, *28*, 5941.

Self-Assembly of a Mesogenic Polyamide: Induction and Significant Stabilization of a Liquid-Crystalline Phase through Complexation of a Phenylbenzoic Acid with a Polymer Backbone Derived from 2,6-Bis(amino)pyridine Units**

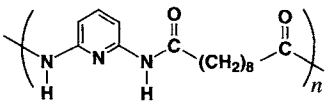
Takashi Kato,* Yasuo Kubota, Toshiyuki Uryu, and Seiji Ujiie

The use of specific interactions for the design and preparation of molecular materials such as liquid crystals has attracted attention because of their potential as dynamically functional molecular systems.[1] For liquid-crystalline polymers, specific intermolecular forces such as hydrogen bonding,[1-4] ionic,[5] and charge transfer interactions[6] have been used for several years for the formation of mesogenic structures. Thus, for instance, the first hydrogen-bonded supramolecular mesogenic polymer, which consists of different and independent molecular components, was prepared from a stilbazole and a polyacrylate containing a benzoic acid group in the side chain.[2] Two bifunctional complementary components were used for the formation of the first main-chain supramolecular mesogenic polymer.[3] Since then, a wide variety of hydrogen-bonded supramolecular polymers that exhibit mesomorphic behavior have been prepared by self-assembly processes.[4] Recently we have shown that 2,6-bis(acylamino)pyridine can be used as a molecular component for supramolecular liquid-crystalline materials through the formation of double hydrogen bonds.[7] These complexes exhibit only monotropic mesophases with relatively narrow temperature ranges. Aminopyridines have been used frequently as versatile molecular units for the control of molecular aggregation.[3, 8]

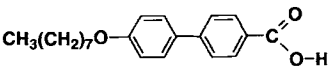
[*] Dr. T. Kato
Department of Chemistry and Biotechnology, Graduate School of Engineering
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113 (Japan)
Fax: Int. code +(3)3818-4868
e-mail: kato@chiral.t.u-tokyo.ac.jp
Y. Kubota, Prof. T. Uryu
Institute of Industrial Science, The University of Tokyo
Roppongi, Minato-ku, Tokyo 106 (Japan)
Dr. S. Ujiie
Department of Material Science, Shimane University
Matsue, Shimane 690 (Japan)

[**] This work was supported by the Ministry of Education, Science, Sports, and Culture (Grant-in-Aid for Scientific Research in Priority Areas of "New Polymers and Their Nano-Organized Systems" (No. 277/08246101) for T. K.).

Our aim is to obtain a nylon with heterocyclic units in the backbone that is capable of molecular recognition and self-organization through the incorporation of the bifunctional pyridine, and we report here on a novel form of self-assembly of a main-chain polymer, which leads to a greatly stabilized mesophase through complexation of a phenylbenzoic acid with a 2,6-bis(amino)pyridine unit in the polymer backbone. The 2,6-bis(amino)pyridine unit was incorporated into a polymer main chain to enable the polymer to recognize hydrogen-bonding molecules on its backbone. Polyamide **1** was prepared by low-temperature polycondensation of 2,6-bis(amino)pyridine and sebacoyl chloride in solution. The polymer is nonmesogenic. On heating the polymer, glass and melting transitions were observed at 118 and 222 °C, respectively. 4-(4'-(Octyloxy)phenyl)benzoic acid (**2**) exhibits a smectic C phase between 179 and 250 °C, and a subsequent nematic phase up to 259 °C.



1



2

We expected that **1** and **2** would form a supramolecular complex.[7, 8] The 1:1 complex from **1** and **2** (equimolar amounts of aminopyridine and carboxylic acid moieties) was prepared by direct mixing in the molten state. Microscope studies and differential scanning calorimetry (DSC) measurements gave no indications of transition behavior for each of the single components, rather the complex behaved as one single macromolecular component. The complex exhibited a melting transition at 212 °C. After melting, birefringence, which suggests the existence of a mesophase, was observed under a polarizing microscope. Significantly, the mesophase was stable up to 350 °C; thereafter, the polymer slowly decomposed. The results of X-ray diffraction measurements for the complex support the existence of the mesophase. Figure 1 shows X-ray diffraction patterns of the crystalline state (A) and of the mesomorphic state (B). The peak due to the layer spacing at 31.5 Å and several peaks in the

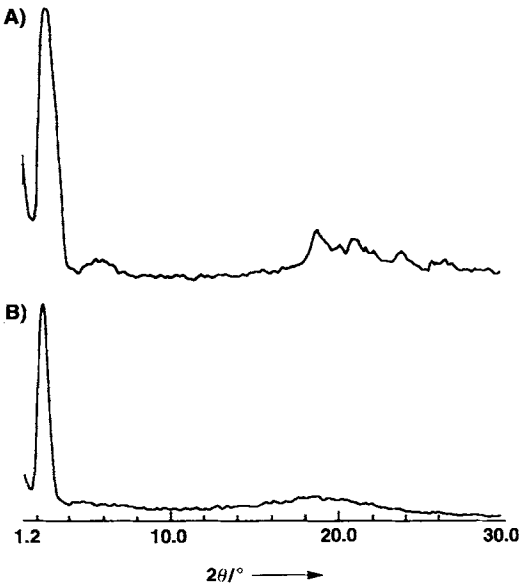


Figure 1. X-ray diffraction patterns of the complex formed from **1** and **2** at 100 °C (A) and at 290 °C (B).

  0570-0833/97/3615-1617 $ 17.50+.50/0