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Synthesis of large building blocks for dendritic polyethers

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Summary Building blocks containing multi-aryl ethers linkage in larger size for rapid building larger dendrimers were prepared with 3,5-di(4-hydroxy-phenoxy)benzyl alcohol (**1**) as branch monomer and 1,3,5-tri(4-hydroxy-phenoxy)benzene (**2**) as core molecule. Two generation of dendritic polyethers (**12** and **15**) were obtained by Fréchet convergent approach with 3,5-diphenoxybenzyl bromide (**3**) as starting molecule. They were characterized firstly by ^{1}H-NMR, ^{13}C-NMR, and MS.

Introduction

Dendrimers appeared in past decade brought chemists new hopes for the synthesis of macromolecules with well defined structure not only with its geometric beauty but also distinctive properties(1),(2). Among many of its characteristics, tailor-made size and inner cavity are two aspects which attract chemists in different fields. The former feature supplies molecules with different size from micro to nano-scale while the latter supplies with properties of including guest molecules(3). Using building blocks with larger size would certainly build large size of dendrimers more rapidly in a few repeated steps and thus obtained dendrimers would be expected to have large inner cavity which may rest guest molecules with large size. Polyether dendrons developed by Fréchet group, which synthesized by convergent method(4), were once coupled to a less compact hypercore to construct high molecular weight dendrimers (5). Xu and Moore successfully applied a strategy of which combining the nonlinear character of dendrimer syntheses to a linear increase in monomer size as function of generation, to rapid preparation of large-size phenylacetylene dendrimers (6).

In this paper, branch monomer and core cell, 3,5-di(4-hydroxy-phenoxy)benzyl alcohol (**1**) and 1,3,5-tri(4-hydroxy-phenoxy)benzene (**2**), with size relatively larger than Fréchet-type(4) were prepared. 3,5-Diphenoxybenzyl bromide (**3**) was used as starting dendritic compound. Fréchet' convergent approach (4) was applied for synthesis of dendrimers. Thus obtained dendrimers containing aryl ether linkages in structure might behave high thermo- and chemical stability, and chemical modification of outer surfaces in violent condition (suppose sulfonating) might be performed.

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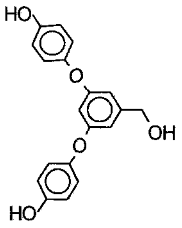

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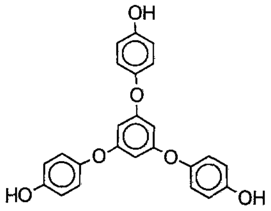

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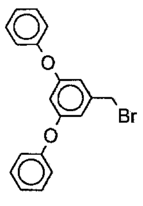

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Experimental

General

Pyridine was distilled after drying under refluxing over CaH_2. Bromobenzene and 4-bromoanisole were redistilled. Methyl 3,5-dihydroxybenzoate (**4**) was prepared under standard esterifying procedure with the corresponding acid, m.p.: 169-170°C. Other commercial reagents were used without further purification.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian WM 200MHz spectrometer with TMS as external standard. Mass Spectra was recorded on a Finnigan Mat 90. Analytical TLC was performed on commercial Merck plates precoated with silica gel GF254.

Preparation of the Building Blocks

Methyl 3,5-di(4-methoxy-phenoxy)benzoate (**5**): To a solution of 3.36g of **4** (0.02mole) in 40ml of new distilled dry pyridine was added 1.17g of 80% NaH (2×0.019mole) under dry nitrogen stream. The temperature was raised to nearly refluxing after the mixture was stirred overnight at room temperature. A 14.9g portion of 4-bromoanisole (0.08mole) was added rapidly to the mixture and 1.5g of CuCl powder followed at once. The reaction mixture was brought to reflux and hold at refluxing for 12hr under nitrogen. After cooling, the mixture was poured into 200ml of water and acidified with hydrochloric acid. The product was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed. Excess bromoanisole was distilled off under reduced pressure. The residue was purified by flash liquid chromatography, 1:5 ethyl acetate / petroleum ether as elution solvent. The product was recrystallized in methanol to give 2.5g of colorless crystal. Yield 33%, m.p.: 100.0°C. Anal. Calcd for $C_{22}H_{20}O_6$: C 69.46; H 5.30; Found: C 69.32; H 5.24.

Methyl 3,5-di(4-hydroxy-phenoxy)benzoate (**6**): A suspension solution of 5.0g of **5** in 50ml of 1:1 acetic acid / HBr(48%) was refluxed for 2hr with vigorous stirring. Crystal formed after cooling was separated to give 4.4g of 3,5-di(4-hydroxy-phenoxy)benzoic acid. The obtained intermediate was esterified in 60ml of methanol in which 0.5ml of concentrated H_2SO_4 was added. The product thus obtained was recrystallized with benzene containing small amount of ethanol. Yield 85%, m.p.: 168.5 ~170.0°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 3.50 (s, 3H, CH_3), 4.44 (s, 2H, PhOH), 6.36-6.44 (t, 1H, ArH), 6.44-6.64(Abq, 8H, PhH), 6.80-6.86(d, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ (ppm) 168.35, 161.92, 155.42, 149.81, 133.72, 122.95, 117.92, 112.83, 112.19, 53.63; Anal. Calcd for $C_{20}H_{16}O_6$: C 68.17, H 4.58; Found: C 68.48, H 4.66.

3,5-Di(4-hydroxy-phenoxy)benzyl alcohol (**1**): To a suspension of 0.2g of $LiAlH_4$ (5.2mmole) in 20ml of dry diethyl ether was added dropwisely a solution of 0.5g of **6** (1.4mmol) in 20ml of ether. The mixture was brought to reflux for 2hr after dropping finished. Water was then added to the cooled mixture with vigorous stirring and then diluted HCl to dissolve the precipitate. The product was extracted with ether. After dried over Na_2SO_4, the extracts was condensed to give a liquid which crystallized afterward. The crude product was recrystallized with methanol-water (2:1) mixed solvent. Yield 92%. m.p.: 141.0-143.0°C. ^1H NMR (DMSO-d_6) δ (ppm) 4.36(s, 2H, $ArCH_2$), 6.22(s, 1H, ArH), 6.42(s, 2H, ArH), 6.62-6.92(Abq, 8H, PhH); EI-MS: M^+ 324; Anal. Calcd for $C_{19}H_{16}O_5$: C 70.36, H 4.97; Found: C 70.56, H 5.08.

Methyl 3,5-Diphenoxybenzoate (**7**): The procedure was similar to that for **5**. The reactants were bromobenzene and methyl 3,5-dihydroxybenzoate. Crystal. Yield 47%. m.p.: 93.5~94.5°C. ^1H NMR ($CDCl_3$) δ (ppm) 3.86 (s, 3H, CH_3), 6.88-6.92(t, 1H, ArH), 7.00-7.45 (m, 12H, ArH and PhH); ^{13}C NMR ($CDCl_3$) δ (ppm) 166.07, 158.82, 156.23, 132.84, 130.01, 124.12, 119.39, 113.88, 113.41, 52.35; Anal. Calcd for $C_{20}H_{16}O_4$: C 74.99, H 5.04; Found: C 75.06, H 4.86.

3,5-Diphenoxybenzyl alcohol (**8**): To a suspended solution of 0.33g of lithium aluminum hydride (8.8mmole) in 20ml of dry diethyl ether was added dropwisely a solution of 2.8g of **7** (8.8mmol) in 40ml of ether. After the addition finished, the mixture was brought to reflux for 2hr. Water was then added slowly to the cooled mixture with vigorous stirring to decompose excess of $LiAlH_4$ and following dilute HCl to dissolve white precipitate. The product was extracted with ether. The extracts was dried over Na_2SO_4 and condensed to give a liquid which crystallized over night. Yield 97%. TLC pure. m.p.: 47.5~48.5°C; Anal. Cacd for $C_{19}H_{16}O_3$: C 78.04, H 5.52; Found C 78.27, H 5.43.

3,5-Diphenoxybenzyl bromide (**3**): To a mixture of 4.9g of **8** (0.017mole) and 7.0g of CBr_4 (0.021mole) dissolved in a minimum amount of dry tetrahydrofuran was added 5.5g of triphenylphosphine (0.021mole). The reaction mixture was stirred for 20min under nitrogen. Water was then added and extraction was applied by using CH_2Cl_2 (2×50ml). The combined extracts was dried and evaporated to dryness. The crude product was then purified by flash chromatography, eluting with 7:1 petroleum / ethyl acetate to give colorless crystal in large pieces. Yield 95%, m.p. 43.5~44.5°C. ^1H NMR ($CDCl_3$) δ (ppm) 4.39 (s, 2H, $ArCH_2Br$), 6.65-6.85 (m, 3H, ArH), 7.05-7.22 (m, 6H, PhH), 7.35-7.48 (m, 4H, PhH); ^{13}C NMR ($CDCl_3$) δ (ppm) 158.92, 156.25, 140.56, 129.93, 123.98, 119.44, 113.38, 108.78, 32.59; FAB-MS, M/Z 354, 355, 356, 357; Anal. Calcd for $C_{19}H_{15}O_2Br$: C 64.24, H 4.26; Found: C 64.47, H 4.06

1,3,5-Tri-(4-methoxy-phenoxy)-benzene (**10**): A 0.7g portion of Na in pieces was added into 20ml of anhydrous methanol solution of 4.0g of 4-methoxyphenol (32mmol). The solvent was evaporated to dryness after Na disappeared. The 40ml of dry pyridine was added and the stirred mixture was then brought to reflux. To the mixture 2.5g of tribromobenzene and 0.2g of CuCl were added rapidly. The reaction mixture was kept refluxing for 10hr under N_2. The cooled mixture was poured into 100ml of water and HCl was added until acidified. The product was extracted with 3×50ml portions of dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated. The black oil thus obtained was purified by flash chromatography to give 1.5g of liquid with light yellow color. Yield 42%. ^{1}H NMR ($CDCl_3$) δ (ppm) 3.78 (s, 9H, OCH_3), 6.09 (s, 3H, core ArH), 6.80-7.00 (Abq, 1,4-PhH, 12H); Anal. Cacld for $C_{27}H_{24}O_6$: C 72.96, H5.44; Found: C 72.25, H5.51.

1,3,5-Tri-(4-hydroxy-phenoxy)-benzene (**2**): A suspension solution of 1.4g of **10** in 30ml of 1:1 acetic acid / HBr(48%) was refluxed for 2hr under vigorous stirring. The reaction mixture was extracted with ether and the extract was washed with an aqueous solution of $NaHCO_3$ and finally with brine. Ether was evaporated after dried with anhydrous Na_2SO_4. Light red residue was left and purified by flash chromatography using ethyl acetate / petroleum as elution solvent. The crystal product (0.9g) with light pink was given. Yield 70%. m.p.: 143.0-146.0°C. ^{1}H NMR (CD_3OD) δ (ppm) 6.12 (s, 3H, core ArH), 6.75-6.92 (Abq, 12H, 1,4-ArH); EI-MS M^+ 402; Anal. Calcd for $C_{24}H_{18}O_6$: C 71.63, H 4.51; Found: C 71.14, H 4.52.

Preparation of Dendrimers

Dendron **13**: A mixture of 1.64g of **3** (4.6mmol), 0.7g of **1** (2.2mmol), 0.76g of K_2CO_3 (5.5mmol) in acetone was brought to refluxing with vigorous stirring under protection of N_2. The reaction was maintained for 10hr. Most of the acetone was distilled off. The residue was partitioned with CH_2Cl_2 and water. The organic phase was washed three times with water and dried over anhydrous $MgSO_4$ and condensed to dryness. The crude product was purified with flash liquid chromatography to give stick liquid. Yield 94%. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.38 (s, 2H, $ArCH_2OH$), 5.0 (s, 4H, Ar`CH_2O), 6.5-7.5 (m, 37H, PhH, ArH); Anal. Calcd for $C_{57}H_{44}O_9$: C 78.43, H 5.08; Found: C 78.51, H 5.11.

Dendron **14:** To a mixture of 3.0g of **13** (3.44mmol) and 2.1g of CBr_4 (6.88mmol) which dissolved in minimum amount of dry tetrahydrofuran was added 1.6g of PPh_3 (6.88mmol) under N_2. After stirred for 30 min, water was added to quench the reaction. To the mixture CH_2Cl_2 was added to extract products. The organic phase was washed with water and dried and evaporated to dryness. The residues was purified by flash chromatography. The product was obtained as solid. Yield 96%. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.36 (s, 2H, $ArCH_2Br$), 5.01 (s, 4H, Ar`$CH_2O$), 6.55-7.05 (m, 17H, ArH, Ar`H), 7.05-.50 (m, 20H, PhH); ^{13}C NMR ($CDCl_3$) δ (ppm) 159.72, 158.73, 156.27, 154.93, 149.43, 140.18, 139.95, 129.71, 123.69, 120.99, 119.18, 115.90, 111.69, 108.30, 106.78, 69.60, 32.66; FAB-MS, M/Z 934, 935, 936, 937; Anal. Calcd for $C_{57}H_{43}O_8Br$: C 73.16, H 4.63; Found: C 73.14, H 4.55.

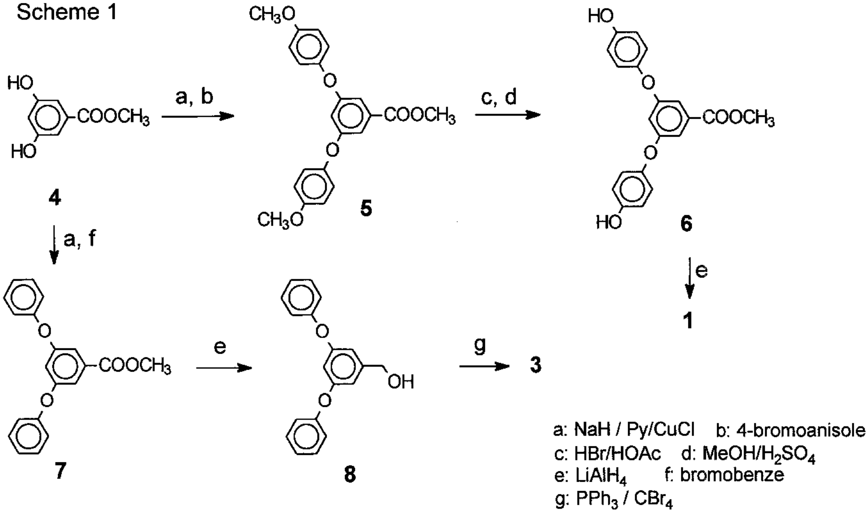
First generation of dendrimer (**12**): The procedure was same as that for **13** with reactants mole ratios as 3:1 (**3**:**2**). Solid. Yield 90%. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.92(s, 6H, $ArCH_2O$), 6.20 (s, 3H, core ArH), 6.60-6.68 (t, 3H, ArH), 6.76-6.83 (d, 6H, ArH), 6.84-7.00 (m, 12H, ArH), 7.00-7.24 (m, 18H, PhH), 7.28-7.46 (t, 12H, PhH); ^{13}C NMR ($CDCl_3$) δ (ppm) 69.72(CH_2O), 100.97, 160.34(Core 1,3,5 ArC), 111.90, 120.91, 139.99, 154.90(core 1,4 ArC), 119.22, 123.71, 129.77, 156.33(monomer PhC), 108.32, 115.89, 149.53, 160.34(monomer ArC); FD-MS: 1226; Anal. Calcd for $C_{81}H_{60}O_{12}$: C 79.39, H 4.94; Found: C 79.02, H 5.23.

Second generation of dendrimer **(15)**: The reaction between **14** and **2** was similar to the procedure for **12** with reactants mole ratios as 3:1 (**14**:**2**). The solvent was changed to tetrahydrofuran. Yield 20%. ^{1}H NMR ($CDCl_3$) δ (ppm) 4.86(s, 6H, $ArCH_2O$), 4.92(s, 12H, $ArCH_2O$), 6.18(s, 3H, core ArH), 6.40-6.74(m, 27H, monomer 1,3,5ArH), 6.74-7.22(m, 72H, PhH, 1,4ArH), 7.25-7.60(t, 24H, PhH); ^{13}C NMR ($CDCl_3$) δ (ppm) 69.73, 69.79(CH_2O), 100.76, 160.38(Core 1,3,5 ArC), 110.08, 120.97, 139.68, 154.93(core 1,4 ArC), 119.23, 123.73, 129.79, 156.31(monomer PhC), 108.31, 106.43, 115.91, 149.40, 149.67, 158.80, 159.83 (monomer ArC); FD-MS: 2975. Anal. Calcd for $C_{195}H_{144}O_{30}$: C 78.93, H 4.89; Found: C 77.76, H 5.11.

Results and discussion

Syntheses of the building blocks involve the formation of multi-aryl ethers. Standard Ullman reaction was not suitable for the preparation of branch cell because of the presence of carboxylate. So a more mild procedure (7) by the reaction between aromatic halides and phenolate with cupric chloride as catalyst and pyridine as solvent was applied to form the multi-ether linkage in **1**, **2**. As shown in scheme 1, 3,5-diphenolate reacted with 4-bromoanisole and bromobenzene respectively to give **5** and **7** in moderate yield. The methyl groups in **5** used as protecting hydroxy groups was dealkylated by refluxing in HBr/HOAc while the carboxylate was hydrolyzed at same time. Compound **6** was obtained further by a methyl esterification. The branch monomer **1** was finally obtained by the reduction of **6** with $LiAlH_4$. The benzoate **7** was reduced to the alcohol **8** which was then brominated to afford **3**.

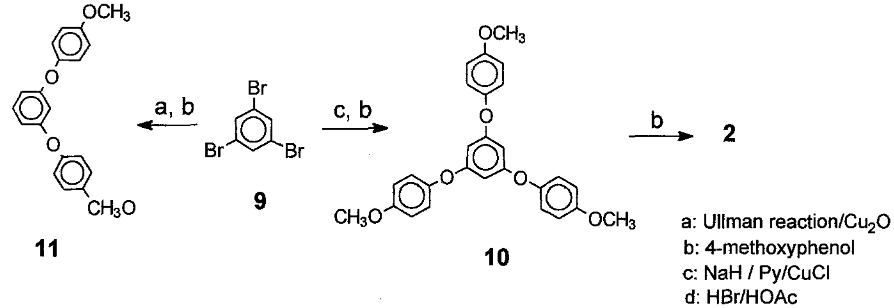
Scheme 1



a: NaH / Py/CuCl b: 4-bromoanisole
c: HBr/HOAc d: $MeOH/H_2SO_4$
e: $LiAlH_4$ f: bromobenze
g: PPh_3 / CBr_4

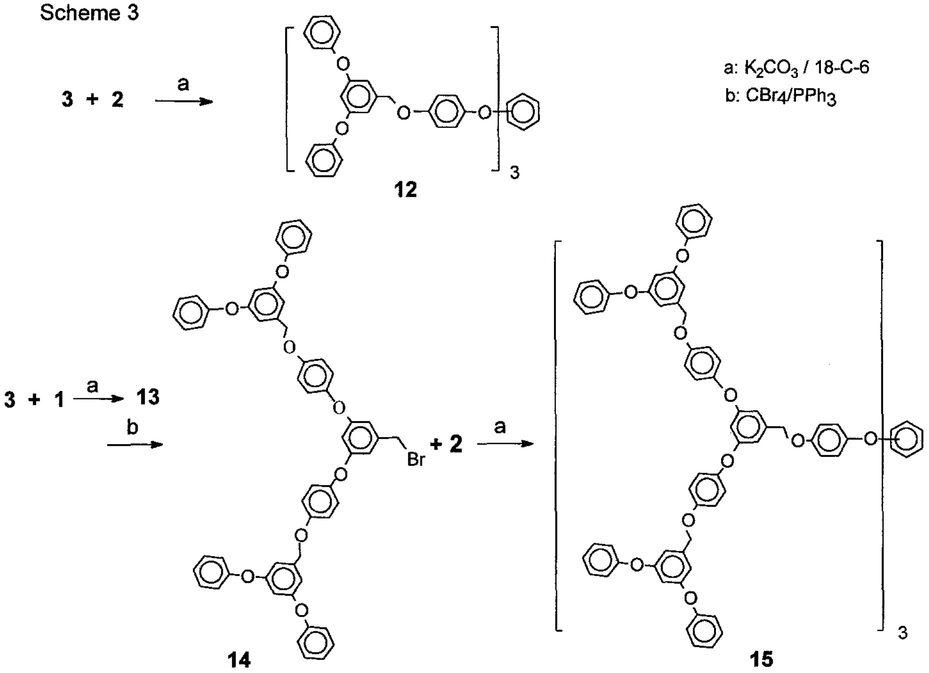
Firstly, the compound **10** was attempted to synthesize by the Ullman method which being used successful for the preparation of 1,3,5-triphenoxybenzene (8), *i.e.* by a neat reaction of tribromobenzene **9** and sodium 4-methoxyphenolate with copper powder as catalyst at around 200°C. Unfortunately the product was confirmed to be not the desired one but diphenoxybenzene **11**. Another trial by the reaction of above reactants in refluxing dimethylacrylamide with cupric oxide as catalyst also gave **11**. Since C-C coupling is a main side reaction in Ullman synthesis, the reason of the formation of **11** was not clear. A successful synthesis of **10** was based upon the same procedure as that for **5** and **7** with the reaction of **9** and 4-methoxyphenol (as shown in scheme 2). So the method seems also suitable for synthesizing multi-aryl ethers from multi-aromatic halide and phenols. Core molecule **2** was obtained after demethylation of **10**.

Scheme 2



Preliminary preparation of dendrons and dendrimers were based upon well known approaches developed by Fréchet et al.(4). As revealed in scheme 3, bromide **3** was used as first generation of dendron for dendritic constructions. Thus, the reaction of **3** with branch monomer **1** in 2:1 mole ratios gave the dendron **13** which was then changed to the corresponding bromide **14** in second generation.

Scheme 3



The first generation of dendrimer **12** was obtained by the reaction of **3** with core molecule **2**. The case was not same as that for the second generation of dendrimer **15** because the reaction carried out in acetone gave complicated products which conformed not to be the expected product after separation. When the reaction solvent was changed to tetrahydrofuran, expected dendrimer **15** was obtained.

These dendrimers were characterized at present by ^1H NMR spectra and ^{13}C NMR. Figure 1 shows the ^1H NMR spectra of the second generation of dendrimer **15**. Elemental analysis showed well agreement with theoretical values for **12** and close agreement for **15**. It may indicate the presence of a small quantity of impurity in **15** that could not be removed by column liquid chromatography.

The dendrimers prepared as above undoubtedly possess more larger cavity. It seems a good alternative to rapid build large dendrimers with large building blocks. The studies of the higher generation of dendrimer as well as their properties were undergoing.

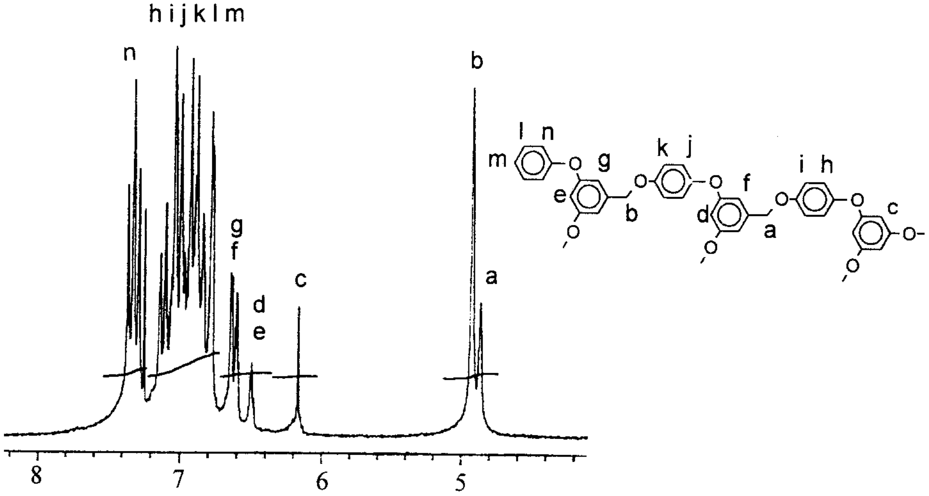


Fig.1 ^1H NMR spectrum (200MHz, $CDCl_3$) of **15**

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