

## Synthesis and radical polymerization of novel vinyl monomers having the imidazoline and pyrimidine moiety

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### Summary

Alkylation of the methylene bridged tetrahydropyrimidine derivatives by chloromethylstyrene produces the bridged bis(4-vinylbenzyl)-1,4,5,6,-tetrahydropyrimidinium salts in high yields. Similar procedures are used to prepare 2-imidazolium derivatives. The quaternary salts which support functional side groups of potential biomedical interest are characterized by means of spectroscopic methods. These monomers are readily polymerized free radically in solution of dimethyl formamide at moderate temperatures. The soluble and insoluble polymers containing 2-imidazolium and 1,4,5,6-tetrahydropyrimidinium salts were found to exhibit antibacterial activities against *Escherichia coli*.

### Introduction

The development of functional polymeric system has opened the route to new materials showing wide range of applications [1-7]. In this sense, there has been a growing interest in the use of multifunctional polymeric systems such as controlled release delivery systems, macromolecular catalysts, protecting groups, supports in organic synthesis, separation media, materials for biomedicine etc. were designed by several research groups. These systems can take the form of either soluble polymers to which the functional group may be attached by some form of suitable linkage or biodegradable microspheres in which the functional group is incorporated. A fundamental prerequisite that needs to be established is to prepare polymeric systems with potential application.

Recently much interest has been focused on the chemistry of heterocycles such as 2-imidazolines and 1,4,5,6-tetrahydropyrimidine derivatives, because when properly substituted they show variety of physiological activities[8-14]. A facile synthesis of 1-substituted-2-imidazolines and 1,4,5,6-tetrahydropyrimidines from *N,N*-dimethylformamide dimethylacetal and corresponding diamines have been developed [15]. These heterocycles readily react with alkyl halides (R=Me; Et; CH<sub>2</sub>Ph etc. ) to give quaternary salts, which can be converted into tetraminoalkenes[16].

Therefore the main objective of this study was forwarded to the synthesis and the study of free radical polymerization of the vinylbenzyl monomers attached to heterocyclic moieties such as reduced pyrimidine or imidazole. First, these compounds have been synthesized and characterized with, <sup>1</sup>H NMR, <sup>13</sup>C NMR, FT-IR, and elemental analysis. Then, polymerization and copolymerization were carried out using azoisobutyronitrile (AIBN) as radical initiator. The corresponding polymers were found to exhibit antibacterial activity against gram-negative bacteria.

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## Experimental

All reactions, including polymerization, were carried out under an argon or nitrogen atmosphere by using standard schlenk or vacuum line techniques. Melting points were determined on a Koffler apparatus and were uncorrected. Fourier Transform Infrared spectra (FT-IR) were recorded on a Ati Unicam Matson 1000 model FT-IR spectrometer. Elemental analyses were carried out on a Hewlett-Packard Model 185 analyzer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a Bruker AC 80 MHz FT-NMR. Thermal Analysis was performed on Shimadzu Network system 50 at a heating rate of  $10^\circ\text{C}/\text{min}$ . in nitrogen. All the reagents and solvents were purified and dried using standard procedures.

### *Preparation of the 1,1'-dimethylenebis(2-imidazolium) dichloride (1a)*

1,1'-Dimethylenebis(2-imidazoline) (3.6 g; 21.6 mmol) and 4-vinylbenzyl chloride (43.2 mmol) was stirred in 20 mL THF at  $20^\circ\text{C}$  for 8 h. Diethyl ether (2x10 mL) was added and the solid formed was filtered off. The solid was washed with diethyl ether (2x20 mL), dried under vacuum, white crystals of **1a** were obtained.

A similar procedure was used to obtain **1b**, **2a** and **2b**. Physical parameters are given in Table 1.

### *Copolymerization of 2a and Styrene (P2a')*

Styrene was washed with 0.5% NaOH solution to remove the polymerization inhibitors, then rinsed with distilled water to eliminate all traces of the NaOH. Molecular sieves were added to the monomer, and stored at  $4^\circ\text{C}$ . Prior to polymerization, the monomers styrene and **1 - 2** were purified by distillation and crystallization in methanol, respectively. Copolymers were prepared in DMF solution via free radical polymerization initiated by AIBN. In a sealed tube comonomer **2a** (0.10 mol) in DMF styrene (0.39 mol) and AIBN (6mmol) were added (total concentration of 2,5-3,5  $\text{mol}/\text{dm}^3$ ). Copolymerization of **2a** and styrene was carried out with various ratios of **2a**. The temperature was kept at  $80^\circ\text{C}$  for 48h in order to obtain high conversion. Charging of the reagents, styrene and one of the monomers in DMF and AIBN into an ampule and sealing of the ampule were done according to the method given in the literature [17]. The tube was opened after polymerization, and its contents were poured into a large amount of diethyl ether (150 mL) to precipitate the polymer. The resulting polymers were collected by decantation. The solid product dried in vacuum at room temperature overnight. The FT-IR spectrum shows the disappearance of the band at  $1640\text{ cm}^{-1}$  which is a typical band for  $\text{C}=\text{C}$  (Figure 1). The copolymer composition was evaluated from the nitrogen content. Results and experimental parameters were cited in Table 3.

The other copolymers **P2b'**, **P1a'** and **P1b'** were synthesized similarly by adjusting the ratio of functional comonomers.

### *Synthesis of Cross-linked Copolymers*

The polymerization inhibitors were removed from the monomers as described above. Divinylbenzene (DVB; Aldrich, 55% isomeric mixture) was distilled twice at  $40^\circ\text{C}$  under reduced pressure prior to the polymerization. The cross-linked polymer was prepared in DMF solution via free radical polymerization initiated by AIBN. The ampule charged with proper amounts of monomers, a solution of **2** (0.10 mol) in DMF, DVB (0.01mol; technical 55wt%) and AIBN (6 mmol), was immersed in an oil bath preheated to  $105^\circ\text{C}$  and a nitrogen atmosphere was maintained throughout the reaction. The reaction mixture was poured into a large volume of diethyl ether (150mL) and the polymer was recovered by

filtration, washed several times with diethyl ether, redispersed in toluene and coagulated in diethyl ether. The product was then dried in vacuum oven at 100°C. The chemical composition of the cross-linked copolymers were determined by elemental analysis of nitrogen. Fourier transform infrared spectroscopy (FT-IR) was also used to probe the chemical structure of the monomers and the polymers.

*Escherichia coli B* was cultivated as given in the literature [18]. In the glass tube was placed 40 mL of bacterial suspension containing a prescribed amount of polymers. The mixture was stirred at 300 rpm at 30°C. After a prescribed time aliquot portions (0.5 mL) of the treated cell suspensions were removed and quickly mixed with 4.5 mL physiological saline, and then decimal serial dilution were prepared from this. From this dilutions, the surviving bacteria were counted on nutrient media by the spread-plate method. Following the inoculation, the plates were incubated at 37 °C, and the colonies were counted after 42 h. The counting was done in quintuplicate every time. Average results obtained are given in Tables 3 and 4.

## Results and discussion

1,1'-Dimethylene-3,3'-di(vinylbenzyl)imidazolium dichloride, **1a**, 1,1'-trimethylene-3,3'-di(vinylbenzyl)imidazolium dichloride, **1b**, 1,1'-dimethylene-3-3'-di(vinylbenzyl)-1,4,5,6-tetrahydropyrimidinium dichloride, **2a** and 1,1'-trimethylene-3-3'-di(vinylbenzyl)-1,4,5,6-tetrahydropyrimidinium dichloride **2b**, were selected as the active species. The monomers **1** and **2** were synthesized in good yields exploiting 4-vinylbenzyl chloride according to Scheme 1. The starting heterocycles were obtained by cyclizing the diamines with *N,N*-dimethylformamide dimethylacetal [15].

As expected, 2-imidazolines and 1,4,5,6-tetrahydropyrimidines are good nucleophiles. Thus, they were alkylated cleanly at N-3 with a slight excess of vinylbenzyl chloride in THF to give the quaternary salts **1** and **2**. The salts, which are hygroscopic crystalline solids were characterized by elemental analysis and NMR spectroscopy (Tables 1 and 2).

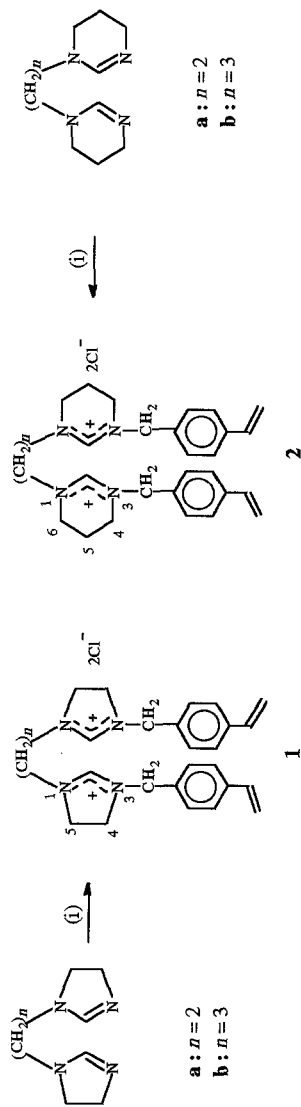
**Table 1** .Yields, m.p.s (b.p.) and analytical data for the compounds **1** and **2**.

Compound No	m.p. (°C)	Yield (%)	$\nu$ (C=N) $\text{cm}^{-1}$	Found (Required) (%)		
				C	H	N
<b>1a</b>	292-295*	78	1735	66.4 (66.24)	6.9 (6.84)	11.9 (11.88)
<b>1b</b>	288-290*	82	1732	66.9 (66.80)	7.1 (7.06)	11.7 (11.54)
<b>2a</b>	260-262*	85	1712	67.6 (67.33)	7.4 (7.26)	11.4 (11.22)
<b>2b</b>	254-256*	72	1710	67.9 (67.83)	7.6 (7.46)	11.1 (10.91)

\* With decomposition

The elemental analysis data for the monomers are in agreement with the theoretical values. The FT-IR spectra indicated the formation of C=N band, as well as C=C band. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were consistent with the proposed structures.

In the  $^1\text{H}$  NMR spectra C-2 resonances were relatively broad and diagnostic ( $\delta = 8.4 - 9.5$  ppm). The analysis of the NMR (Table 2). After preliminary tests of radical polymerizability, monomers **1** and **2** were homo polymerized and copolymerized in DMF at



**Scheme 1.** Synthetic route for the preparation of comonomers **1** and **2**; *Reagents and conditions*: (i) THF, 4-vinylbenzyl chloride, 20°C.

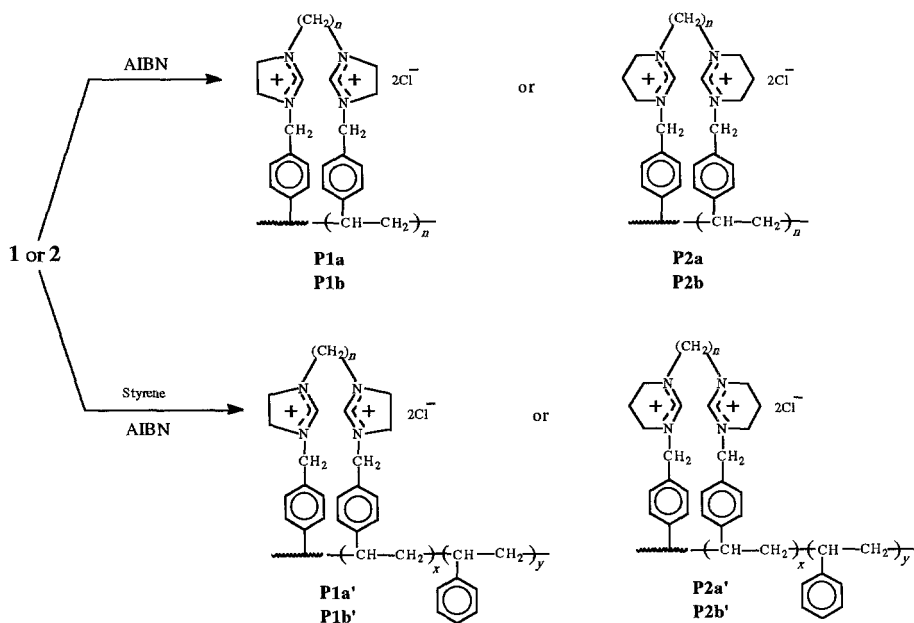
**Table 2.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data, with assignments for **1** and **2**.<sup>†</sup>

Compound No	2-	Ring 4,6- or 4,5-	5-	Bridge	Vinyllic		Others
					CH-	CH <sub>2</sub> -	
<b>1a</b>	8.43(s)	3.36(s)	-	4.0(s)	6.73(m)	5.23(m)	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 3.87 (s) C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 7.31 (m)
<b>1b</b>	9.30(s)	2.51(s)	-	3.42(s)	6.84(m)	5.34(m)	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 4.76 (s) C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 7.51 (m)
<b>2a</b>	9.46(s)	1.96(m)	2.51(m)	3.58(s)	6.75(m)	5.34(m)	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 4.71 (s) C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 7.50 (m)
<b>2b*</b>	9.31(s)	1.95(m)	2.39(m)	3.23(m)	6.75(m)	5.32(m)	C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 4.73 (s) C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> 7.46 (m)
<b>1a</b>	155.5	44.13	-	55.73	130.07	128.26	115.97, 137.96, 38.28, 138.54, 139.19
<b>1b</b>	160.48	42.60	-	26.91, 50.09	130.63	128.34	116.74, 135.11, 36.02, 137.88, 138.02
<b>2a</b>	155.80	44.40	20.19	58.56	130.51	128.34	116.98, 130.51, 135.5, 137.8, 139.5
<b>2b*</b>	155.25	53.00	20.11	26.44, 58.84	130.52	128.31	116.90, 130.91, 36.52, 137.88, 138.02

<sup>†</sup> Spectra recorded in CDCl<sub>3</sub>. \* Recorded in DMSO-d<sub>6</sub>, chemical shifts (δ) relative to Si(CH<sub>3</sub>)<sub>4</sub>; = 0; abbreviations: s = singlet, m = multiplet.

80°C with AIBN. The homopolymers and copolymers with styrene were soluble in dioxane and DMF, but insoluble in diethyl ether.

Copolymers from **1** and **2** were also prepared with various ratios of the comonomer. The chemical compositions of the polymers were determined by elemental analysis of nitrogen. Linear copolymers prepared free radically by using AIBN as an initiator were shown in Scheme 2. The properties of polymers were summarized in Table 3. The polymers were obtained in high yields. The nitrogen contents are in close agreement with the calculated values.



**Scheme 2.** Synthetic route for linear homopolymerization and copolymerization.

Differential scanning calorimeter (DSC) measurements using the Shimadzu System50 revealed a single glass transition temperature that varied with copolymer composition as expected. The nitrogen contents of the copolymers as evaluated by elemental analysis are in accord with the predicted model. Comparison of the thermograms of homopolymers, polystyrene and their copolymers showed polystyrene follows a single glass transition temperature (101°C), furthermore homopolymers and copolymers show a similar trend. For instance, **P1a** shows a single endothermic peak at 87°C (for others see Table 3).

On copolymerization of styrene with novel monomers, the stiffness of the chain decreases due to the presence of the pyrimidine and imidazoline units which probably prevents closer packing of the macromolecular chain, resulting in an increase of free volume and a decrease of  $T_g$ . The decrease in  $T_g$  with an increasing content of comonomers is found to be exponential. This type of decreasing trend has been reported by others [19-20]. The results signify the variation of  $T_g$  with functional comonomer content of the copolymers. Since these copolymers were completely soluble in DMF, cross-linking is not likely to be taken place.

**Table 3.** Some Properties and the antibacterial activity of the soluble linear polymers against *E.coli*<sup>a</sup>

Polymer <sup>b</sup>	Styrene in Feed %	$\eta_{inh}^c$ (dL/g)	Yield %	N %		T <sub>g</sub> (°C) <sup>e</sup>	Viable cell counts (cell/mL) <sup>f</sup>
				Found	Required		
P1a	None	0.57	94	9.9	11.8	87	2.7x10 <sup>2</sup>
P1a'	10	0.67 <sup>d</sup>	80	9.8	11.8	77	1.7x10 <sup>2</sup>
P1b	None	0.62	87	11.9	11.7	78	2.4x10 <sup>2</sup>
P1b'	10	0.56 <sup>d</sup>	77	10.2	11.7	70	1.4x10 <sup>2</sup>
P2a	None	0.45	92	10.6	11.2	103	1.1x10 <sup>1</sup>
P2a'	10	0.62 <sup>d</sup>	85	8.6	11.2	88	0.8x10 <sup>1</sup>
P2b	None	0.78	83	9.7	11.1	95	1.3x10 <sup>1</sup>
P2b'	10	0.58 <sup>d</sup>	79	8.4	11.1	69	0.9x10 <sup>1</sup>

<sup>a</sup>. Determined at 30°C in sterilized physiological saline. <sup>b</sup> concentration 5.0 mg/L. <sup>c</sup> Inherent Viscosity determined at 30°C for %0.4 solution in DMF, <sup>d</sup> Inherent viscosity determined at 30°C for %0.4 solution in H<sub>2</sub>SO<sub>4</sub>. <sup>e</sup> T<sub>g</sub> values determined by DSC at the heating rate of 10°C/min. <sup>f</sup> Initial cell 4.6x10<sup>5</sup> cells/mL, average results were given.

### Preparation of Cross-Linked Polymers

Terpolymerization of novel monomers, styrene and divinylbenzene by AIBN in DMF afforded the gel-type of polymers were shown in Scheme 3.

The chemical compositions, evaluated by nitrogen analysis of the cross-linked copolymers are given in Table 4.

**Table 4.** The composition and the antibacterial activity of the cross-linked copolymers against *E.coli*<sup>a</sup>

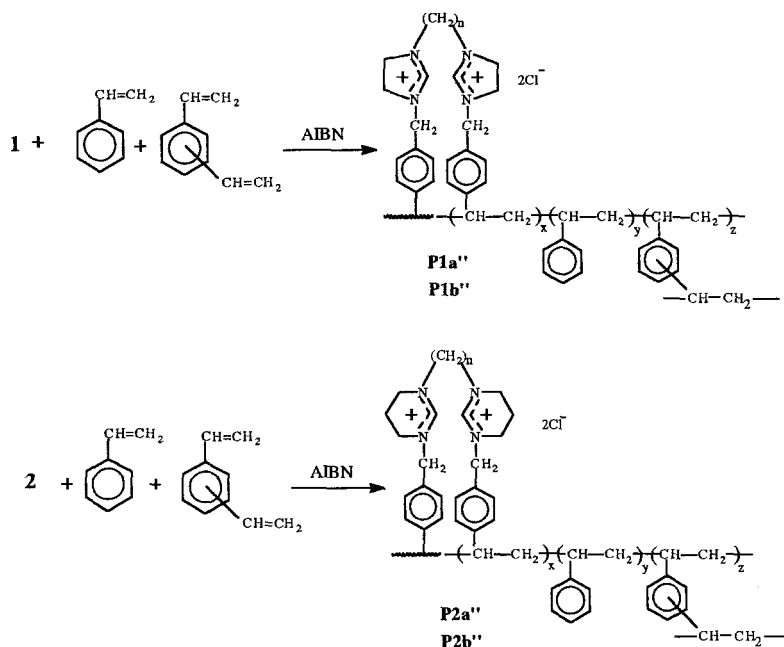
Code <sup>b</sup>	Crosslinking in mol% of DVB	Yield %	Comonomer (x) contents in mequiv/g <sup>c</sup>	Ring Subst. in %	Viable cell counts (cell/mL) <sup>d</sup>
P1a''	2	44	0.14	1.15	1.4x10 <sup>2</sup>
P1b''	2	34	0.19	2.1	3.3x10 <sup>2</sup>
P1a1''	1	51	0.18	2.0	9.2x10 <sup>2</sup>
P1b1''	2	57	0.12	1.3	1.1x10 <sup>2</sup>
P2a''	2	40	0.25	2.8	1.7x10 <sup>1</sup>
P2b''	2	33	0.43	5.1	3.8x10 <sup>1</sup>
P2a1''	4	49	0.21	2.3	9.2x10 <sup>1</sup>
P2b1''	10	29	0.34	3.9	5.6x10 <sup>1</sup>
P2a2''	10	27	0.30	3.4	3.1x10 <sup>1</sup>

<sup>a</sup> Determined at 30°C in sterilized physiological saline. <sup>b</sup> concentration 5.0 mg/L. <sup>c</sup> Determined by elemental analysis <sup>d</sup> Initial cell 4.6x10<sup>5</sup> cells/mL, average results were given.

The FT-IR spectrum of the monomer provided compositional information, the spectra of monomer **2a** and polymer **P2a''** were compared. All polymers and copolymers showed the complete disappearance of C=C band. In the spectra in **2a** and others two peaks were observed one for the C=N unit, at 1735 cm<sup>-1</sup> and one for the C=C unit at 1658 cm<sup>-1</sup>, whereas in the case of copolymer, the peak due to C=C unit disappeared completely. A broad absorption band around 3400 cm<sup>-1</sup> is believed to be associated with the absorbed water due to hygroscopic nature of the monomer and polymer.

In addition, a peak at 2941 cm<sup>-1</sup>, essentially from aromatic C-H unit, broadened upon polymerization. Similarly, in the case of other copolymers, the same peak trend was observed. The FT-IR spectra of the cross-linked polymers were essentially identical to those of soluble linear copolymers.

Antibacterial activity of linear polymers and copolymers were given in Table 3 and 4 respectively. All polymers showed antibacterial activity against *E.coli*. However 1,4,5,6-tetrahydropyrimidinium salts showed somewhat higher activity than 2-imidazolinium salts. The antibacterial activity of these quaternary salts against gram negative bacteria was considerably greater than that of the corresponding monomeric compounds. All the polymers containing 2-imidazolinium and 1,4,5,6-tetrahydropyrimidinium salts showed strong ability to capture *E.coli* when compared with those of positively charged other polymeric materials [21-22].



Scheme 3. Synthetic route for cross-linked copolymerization.

## Conclusion

Novel series of 2 imidazolinium and 1,4,5,6-tetrahydropyrimidinium containing vinyl monomers were prepared. They were converted to linear copolymers with styrene and cross-linked copolymers with divinylbenzene and characterized. All monomers were polymerized readily in DMF by AIBN. Insoluble polymers were prepared from the terpolymerization of such monomers. Antibacterial activity against *E.coli* were tested for all polymers. Though it was found that linear polymers showed antibacterial activity, cross-linked polymers were important in this respect because they allow the combination of different molecular fragments in one polymer and thus exclude demixing process. The details of antibacterial studies of all polymers against other bacteria will be reported in the near future.

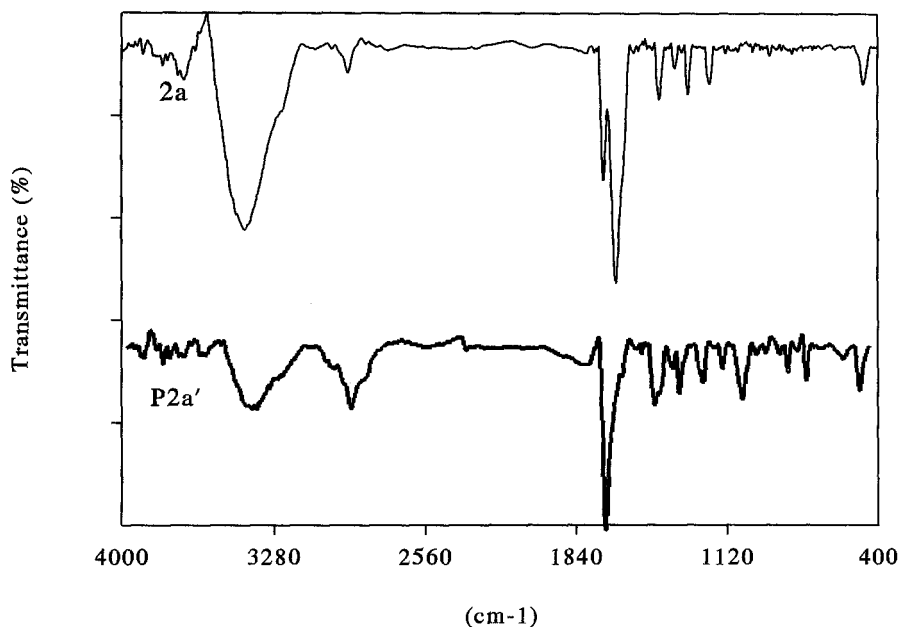


Figure 1. FT-IR Spectra of monomer 2a and polymer P2a'

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