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Synthesis and polymerization of unsaturated derivatives of thymol

Norbert Moszner, Ulrich Salz, and Volker Rheinberger

Ivoclar AG, Bendererstrasse 2, FL-9494 Schaan, Liechtenstein

Summary

The preparation of methacrylic and p-styrenesulfonic acid esters of the antibacterial agent thymol (2-isopropyl-5-methylphenol) and their characterization by IR, ^{1}H and ^{13}C NMR spectroscopy is described. The monomers are radically polymerizable and give polymers in which thymol is covalently attached to the polymer backbone by ester links.

1. Introduction

Substituted phenols like alkylated or chlorinated phenols show antimicrobial activity and are used as disinfectants or preservatives for industrial products (pharmaceuticals, cosmetics, paints) [1-3]. For improved microbiocidal performance, such as reduced toxicity, immobilization or controlled delivery, the agents can be fixed via covalent bonds onto a polymer backbone. The common preparation methods for macromolecular microbiocides are the appropriate modification of natural or synthetic polymers and polymerization of monomeric microbiocides [4].

Thymol (2-isopropyl-5-methylphenol) is an antibacterial agent used in dentistry for example for treatment of oral infection [5]. In the present paper the synthesis and radical-initiated polymerization of 2-isopropyl-5-methylphenyl methacrylate and p-styrenesulfonate are described.

2. Experimental

Synthesis

4-Vinylbenzenesulfonyl chloride was prepared by reacting sodium p-styrenesulfonate (Aldrich) with thionylchloride [6].

2-Isopropyl-5-methylphenyl 4-vinylbenzenesulfonate (MPPSS): To a mixture of 0.5 mol 4-vinylbenzenesulfonyl chloride and 0.5 mol thymol (Fluka) a solution of 20 g NaOH in 70 ml water was added with stirring at 70 °C. After 2 hours the reaction mixture was cooled to 0 °C to precipitate the crude product, which

was taken in ether, washed with water and dried about anhydrous calcium chloride. The residue remaining upon evaporation of the solvent was twice recrystallized from ethanol, giving pale yellow crystals (m.p. 69 °C) in 47% yield.

$C_{18}H_{20}O_3S$ (316.42) Calc.: C 68.33 H 6.37 S 10.13
Found: C 68.21 H 6.35 S 10.09

IR (KBr) 1178 (s-SO_2) and 1379 cm^{-1} (as-SO_2).

2-Isopropyl-5-methylphenyl methacrylate (MPPMA): Thymol (0.36 mol), triethylamine (TEA, 0.39 mol) and N,N-dimethylaminopyridine (DMAP, 0,7 g) were dissolved in 1.1 l anhydrous toluene and stirred at 10 °C. Then a solution of 0.43 mol methacryloyl chloride (Fluka) in 180 ml toluene was added over a period of 1h. After 2h stirring at room temperature, the reaction mixture was filtered, the toluene solution washed with water and dried over calcium chloride. After evaporation of toluene, the crude product was fractionally distilled through a Vigreux column, yielding a transparent liquid (b.p. 60 °C at 0.05 mbar) in 55% yield.

$C_{14}H_{18}O_2$ (218,30) Calc.: C 77.02 H 8.31
Found: C 76.93 H 8.25

IR (film) 1737 (C=O) 1637 cm^{-1} (C=C).

Dimethylformamide (DMF), and 2,2-azobisisobutyronitrile (AIBN) were purified as described previously [7]. Methylethylketone (MEK) was dried by refluxing over P_2O_5 and distilled before use.

Polymerization

The polymerization reactions were carried out in sealed glass tubes containing a given amount of AIBN dissolved in DMF. Subsequently, the monomer was introduced. The tubes were degassed through three freeze-thaw cycles (liquid nitrogen) before they were placed in a constant-temperature bath (60 °C). Homopolymerizations were terminated by the addition of excess methanol. The monomer conversion was calculated from the gravimetrically determined yields of the dried polymers. The polymers were repricipitated from THF/methanol and dried under vacuum to constant weight.

Measurements

^1H NMR measurements were recorded on an EM 390 (Perkin-Elmer, 90 MHz) using hexamethyldisilane (HMDS) as the standard. ^{13}C NMR spectroscopic measurements were performed with a AC 300F spectrometer (Bruker, 300 MHz) using $CDCl_3$ or dimethylsulfoxide-d_6 as a solvent. An FT-IR spectrometer 1600 (Perkin-Elmer) was used to record IR spectra. The number-average molecular weights of polymers were determined by GPC using a isocratic pump IsoChrom (Spectra-Physics) and THF as a eluent, an detector RI-4 (Varian) and colums calibrated with polystyrene standards. Differential scanning calorimetry (DSC) measurements were performed by using a Perkin-Elmer DSC-7 thermal analyzer. Scanning rates of 10 °C/min were used.

Hydrolysis of the polymers was conducted in buffer solution (pH 2,78) at 37 °C. The release of thymol was investigated by HPLC of filtrated portions of the hydrolysis solution.

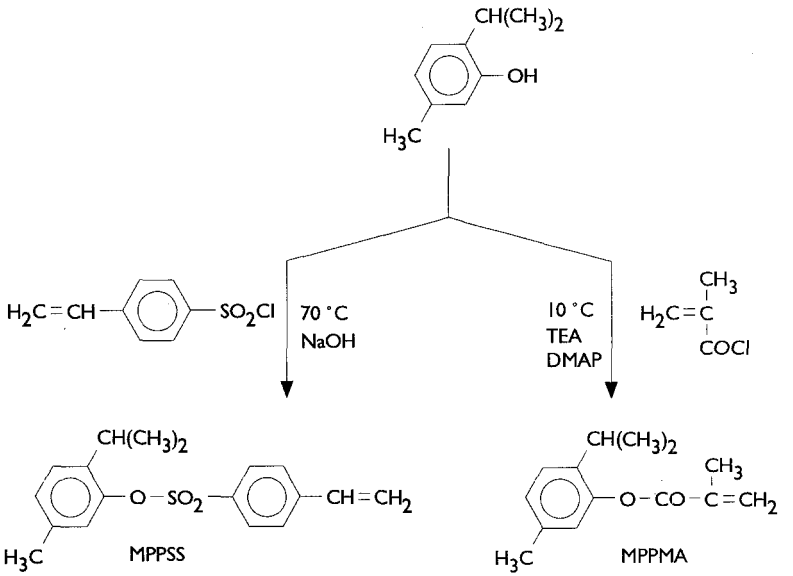
Biological tests

Antimicrobial effects of polymeric thymol derivatives were determined by a suspension test. The polymers (0.2 g) were suspended in water and injected with the test organism (Streptococcus mutans). After a certain time, the

survival rates were determined by the agar plate method.

Results and discussion

The monomeric thymol derivatives MPPSS and MPPMA were prepared from the appropriate acid chlorides and Thymol as shown in the following scheme:



The characterization of monomers was carried out by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and elemental analyses. The ^{1}H NMR spectral data, presented in Table 1 support the expected structure of prepared monomers. Also results of elemental analysis and ^{13}C NMR data (Table 2) support the proposed structures. For assigment of the observed ^{13}C signals chemical shift increments

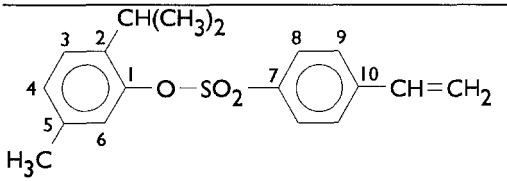
Table 1. ^{1}H NMR shift data of MPPSS und MPPMA

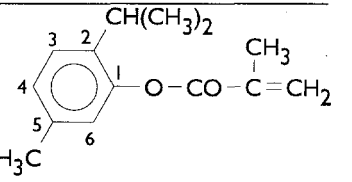
Monomer	Chemical shifts (intensity, multiplicity) [1]					
	$CH_2=$	$=CH-$/ $=C(CH)_3-$	$>C(CH_3)_2$	Ar-CH<	CH_3-Ar	Ar-H
MPPSS	5.47 (1H,d)	6.73	0.95 (3H,s)	3.00	2.27	6.97-7.97
	5.90 (1H,d)	(1H,dd)	1.10 (3H,s)	(1H,hept)	(3H,s)	(7H,m)
MPPMA	5.75 (1H,s)	2.08	1.18 (3H,s)	2.98	2.31	6.85-7.24
	6.35 (1H,s)	(3H,s)	1.22 (3H,s)	(1H,hept)	(3H,s)	(3H,m)

[1] Shift value in ppm down field from internal HMDS

Table 2. ^{13}C NMR shift data of MPPSS and MPPMA

C-Atom	Chemical shifts[1] MPPMA[2] obs.	CH_n (DEPT)	calc.[4]	MPPSS[3] obs.
1	148.2	C	148.9	146.8
2	122.8	CH	121.8	122.6
3	136.0	C	135.3	136.7
4,5	126.4	CH	125.9,	126.5,
	127.0	CH	127.6	126.8
6	137.0	C	138.6	138.5
Ar-CH_3	20.8	CH_3	21.4	20.8
$>C(CH_3)_2$	23.0	CH_3	24.0	23.1
$-CH(CH_3)_2$	27.3	CH	34.3	26.6
$CH_2=$	127.0	CH_2	128.0	118.3





[1] Shift value in ppm down field from internal HMDS; [2] Alken-CH_3 18.5, $>C=$ 136.5; [3] $=CH-$ 135.0, C-7 135.2, C-8/C-9 128.1/128.7, C-10 143.2; [4] Chemical shift increments taken from [8]

Chemical shift increments taken from [8] compiled by Pretsch et al. [8] and the DEPT (distortionless enhancement by polarization transfer) experiment [9] were used.

The polymerization of monomers MPPSS or MPPMA was carried out with AIBN in DMF or MEK at 60 °C. The results in Figure 1 and Table 3 show, that the monomers are radically polymerizable and the monomer conversion increases with the polymerization time. As expected from a normal radical polymerization, the number-average molecular weight of polymers increase with increasing concentration of monomers

The obtained polymers of MPPSS and MPPMA are soluble in toluene, acetone, tetrahydrofuran, dimethylformamide and methylene chloride. In the IR and ^1H NMR spectra of obtained polymers the signals of the vinylic $C=C$ bonds of the starting materials disappeared showing the successful polymerization. The results of spectroscopic analyses show that the polymerization of MPPSS and MPPMA yield homopolymers with pendant 2-isopropyl-5-methyl-phenyl groups. In case of poly(MPPMA) the thymol moieties are attached to the polymer backbone by easily cleavable carboxylic acid ester bond whereas in case of poly(MPPSS) the antibacterial agent is immobilized to the polymer chain through very stable sulfonate ester groups. Both polymers which are suspended in the

buffer aqueous solution did not release thymol after 20 weeks at 37 °C. In contrast to inactive poly(MPPSS), poly(MPPMA) show a antibacterial activity against Streptococcus mutans in the biological test, which is probably caused by enzymatically released thymol.

The glass transition temperatures of poly(MPPSS) or poly(MPPMA) determined by DSC analysis were 107 (M_n = 56500 g/mol) or 100 °C (38000 g/mol).

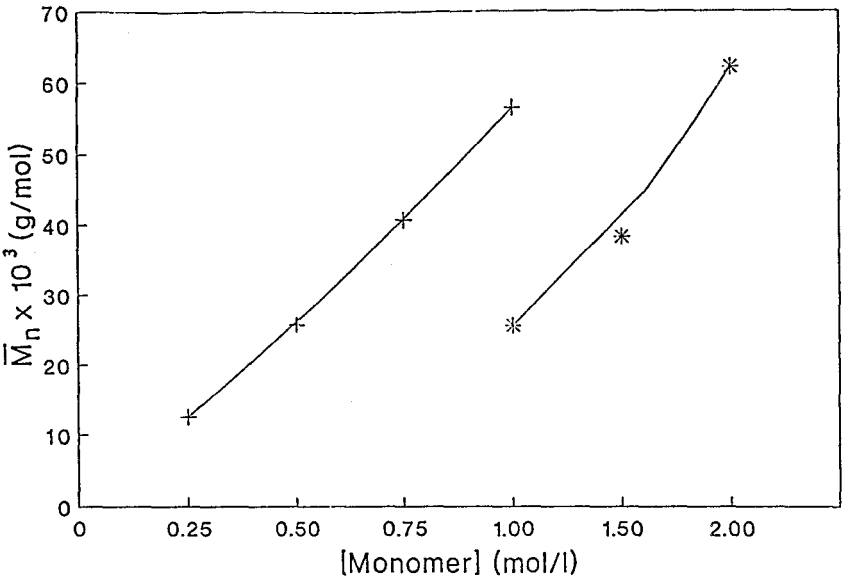


Fig. 1. Polymerization of MPPSS (+:[AIBN] = 0.02 mol/l, t_p: 8.0 h) and MPPMA (*:[AIBN] = 0.05 mol/l, t_p: 1.0 h)

Table 3. Polymerization of MPPSS (0.50 mol/l) and MPPMA (2.0 mol/l) in solution at 60 °C[1)]

Monomer	Time h	Conversion %
MPPSS	1.0	17.5
	2.0	34.4
	4.0	49.8
	8.0	85.5
MPPMA	0.5	5.9
	1.0	17.5
	1.5	31.2
	2.0	42.6

1) MPPSS: [AIBN] = 0.02 mol/l; MPPMA: [AIBN] = 0.05 mol/l

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