SYNTHESIS OF CROSSLINKED POLYACRYLAMIDE GEL CONTAINING SALICYL ALDEHYDE FRAGMENTS*

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The synthesis of 5-methacryloylamidosalicyl aldehyde is described. It yielded potassium Λ - and Δ -bis-[N-(5-methacryloylamidosalicylidene)-s-valinato] cobaltate (+3) (I) and cupric N-(5-methacryloylamidosalicylidene)-s-valinate (+2) (II). Copolymerization of I and II with acrylamide and N,N'-methylene-bis-acrylamide, followed by decomposition of the complexes, yielded hydrophilic polymers containing salicyl aldehyde fragments chemically bound to the polymeric matrix. The capacities of the polymers obtained with respect to the carbonyl group were determined.

THIS paper relates to the synthesis of hydrophilic crosslinked polymers based on acrylamide and containing salicyl aldehyde fragments. As the starting material we took N-methacryloyl derivative of aminosalicyl aldehyde. Papers have been published with descriptions of derivatives of 3-aminosalicyl [1] and 5-aminosalicyl [2] aldehydes with respect to the carbonyl group, although the foregoing aldehydes have not been isolated in the free state, since they undergo immediate transformation to insoluble polymeric products [1, 2]. We met with no success in attempts to acylate the reduction product of 5-nitrosalicyl aldehyde with methacrylic acid anhydride. We are therefore proposing the following route for the synthesis of 5-methacryloylaminosalicyl aldehyde:



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Compounds I-V are stable crystalline substances. Good yields ($\sim 80\%$) were obtained at all the stages, and no further purification of products is required. The use of screening groups (mesil and ethylene acetal groups) opens the way



FIG. 1. ORD curves: 1- for the mixture of Λ -VI, acrylamide, N,N'-methylene-bis-acrylamide, ammonium persulphate in water; 2- for the gel obtained from these same components.

FIG. 2. ORD curves: 1- for the polymeric film immediately after its preparation; 2- for the polymeric film after it has remained in water for 24 hr; 3- ditto, after being in water for 3-8 days.

to catalytic reduction of the nitro group in compound II under very mild conditions. Hydration must be brought to an end immediately after absorption of the theoretical amount of hydrogen, since exhaustive hydration (7 hr) results in the removal of both protective groups and in the formation of 2-hydroxy-5-aminophenylcarbinol. In the PMR spectrum the latter has a characteristic singlet in the 2.35 ppm region (CD₃OD as solvent, hexamethyldisiloxane (HMDS) as the external standard). Hydrolysis of compound IV likewise proceeds under mild conditions. A factor of importance here is the order of removal of screening groups. If one starts with acid hydrolysis, followed by alkaline, the desired product V fails to appear (thin layer chromatography (TCL) on silica gel in the presence of a tracer).

The direct use of 5-methacryloylaminosalicyl aldehyde itself for copolymerization with acrylamide and N,N'-methylene-bis-acrylamide is impracticable for the following reasons: a) phenolic oxygen is an inhibitor of radical reactions; b) the aldehyde is insoluble in water. We therefore synthesized potassium bis-[N-(5-methacryloylaminosalicylidene)-s-valinato]cobaltate (+3) (VI) which dissolves readily in water, and cupric N-(5-methacryloylaminosalicylidene)-s-valinate (VII), which dissolves in pyridine mixed with water. In these solvents the acrylamide forms gels in presence of the cross agent (N,N'-methylene-bis-acrylamide). Identical ORD curves were obtained for a mixture of components A-VI, acrylamide, N,N'-methylene-bis-acrylamide, ammonium persulphate in water, and the gel obtained by adding to this mixture a small amount of N,N,N',N'-tetramethylethylenediamine (Fig. 1); this means that no racemization of the complex takes place during polymerization. Moreover, prolonged retention in water did not reduce the optical activity of polymeric films prepared from the foregoing components (Fig. 2), which evidences the incorporation of VI in the polymer chain. It should be noted that similar films based on potassium Λ -bis-[N-salicylidene-svalinato]cobaltate (+3) containing no groups capable of copolymerization suffer a complete loss of their optical activity after remaining in water for 30-40 min.

By copolymerization of IV and VII with acrylamide and N.N'-methylenebis-acrylamide followed by decomposition of the complexes we obtained polymers VIII and IX respectively containing free functions of salicyl aldehyde. The presence of these fragments was confirmed by qualitative reactions to the carbonyl group (yellow colouring with amines and amino acids and red colouring with 2,4-dinitrophenylhydrazine and to the phenol group (blue colouring with FeCl₃), these reactions being typical for salicyl aldehyde. Quantitative determinations of carbonyl groups were based on reactions with NH₂OH·HCl. Values obtained for capacities of the polymers in respect to carbonyl groups were similar (0.121-0.130 for VIII and 0.136-140 mmole/g of dry polymer for IX), the theoretical capacities being identical (0.173-0.174 mmole/g), providing evidence that hydrolysis of the amide bond did not take place under conditions of decomposition of the cobalt complex (dilute acetic acid, $FeSO_4 \cdot 7H_2O$, $60-70^\circ$, 24 hr). On the other hand, decomposition of the copper complex takes place under very mild conditions, under the action of dilute hydrochloric acid or with a solution of disodium salt of EDTA at room temperature.

Polymers VIII and IX swell readily in water and in pyridine-water mixtures, but do not swell in alcohol, $CHCl_3$, CCl_4 , DMF or ether. The chemical properties of the obtained hydrophilic gels are now being investigated.

The absorption spectra and ORD curves were recorded with a Hitachi EPS-3 spectrophotometer and Jasco-ORD/UV-5 instrument; Hitachi-Perkin-Elmer R-20 and Perkin-Elmer R-1? and RYa-2308 instruments were used for the PMR spectra. A Radiometer TTT-1c instrument was used for the potentiometric titration.

5-Nitro-2-methanesulphonyloxybenzaldehyde(I). To a suspension of 15 g (0.09 mole) of 5-nitrosalicyl aldehyde in 100 ml of absolute pyridine was added dropwise, whilst stirring, 10 ml (15 g, 0.125 mole) of methanesulphonyl chloride. This led to dissolution of the 5-nitrosalicyl aldehyde. After the total amount of methanesulphonyl chloride had been added, the reaction mixture was once again stirred for 15 min and was decanted into water. The deposit that separated out was filtered, washed water and dried over P_2O_5 . Yield of I 21.1 g (95.5%); m.p. 98-99° (CCl₄).

Ethylene acetal of 5-nitro-2-methanesulphonyloxybenzaldehyde(II). Into a flask fitted with a Dean-Stark attachment were placed 21·1 g (0.086 mole) of I, 10 ml (11·2 g, 0.18 mole) of ethylene glycol, 100 ml of benzene and 0·4 ml of 85% H₃PO₄. The mixture was boiled until the evolution of water stopped, and was then decanted into water. The benzene layer was separated, washed with a small amount of water, and dried over MgSO₄. Benzene was distilled cff and the residue was recrystallized twice from alcohol. Yield of II 17·7 g (72%), m.p. $89\cdot5-90\cdot5^{\circ}$ (EtOH). Found, %: C 41·45, H 3·64, N 4·84. C₁₀H₁₁NO₇S. Calculated, %: C 41·52, H 3·81, N 4·84. PMR spectrum, ppm (pyridine-D⁵ as solvent, external standard HMDS): 2·95 c. (OSO₂CH₃), 3·40 c. (OCH₂CH₂O), 5·85 c. (OCHO), 7·81 m. (ArH).

Ethylene acetal of 5-amino-2-methanesulphonyloxybenzaldehyde(III). A solution of 5 g of II in 100 ml of absolute methanol was hydrated at atmospheric pressure and room temperature in the presence of 1.25 g of 5% Pd/Al₂O₃. After absorption of the theoretical amount of hydrogen the reaction was stopped, and the catalyst was filtered and washed with ethanol. After drying in air 3.52 g of III (80%) was obtained. The purity of the product was verified by TLC using silica gel (eluent – petroleum ether : acetone = 1 : 1). PMR spectrum (solvent – CD₂OD, external standard HMDS), ppm: 2.85 c. (OSO₂CH₃), 3.72 c. (OCH₂CH₂O), 5.70 c. (OCHO), 6.2-7.2 m. (ArH).

Ethylene acetal of 5-methacrylcylamino-2-methanesulphonyloxybenzaldehyde(IV). To a solution of 3.25 g of III in 30 ml of absolute pyridine was added, while stirring at room temperature, 5 ml of methacrylic acid anhydride. The mixture was left standing for 2 hr at 100 m temperature, and was then diluted with water and extracted with chloroform. The extract was dried over MgSO₄, chloroform and pyridine were evaporated off under low pressure. The residue took the form of a viscous oil on trituration with alcohol. 3.47 g of IV (~80%) was obtained. M.p. 115.5-116.5° (water : alcohol=1:1). Found, %: C 51.47, H 5.24. N 4.37. C₁₄H₁₇NO₆S. Calculated, %: C 51.38, H 5.20, N 4.28.

5.Methacryloylaminosalicyl aldehyde (V). A solution of 1.5 g of IV in 200 ml of an EtCH- $H_2O-1 \times KOH$ mixture (12:4:3) was stirred for 48 hr at room temperature, after which a 1 \times solution of HCl was added till an acid reaction was obtained, water was then added, followed by extraction with chloroform. The extract was dried over MgSO₄. After distilling cff chloroform 0.82 g (83%) of V was obtained; m.p. 115°. Found, %: C 64·19, H 5·C4, N 6·92. $C_{11}H_{11}NO_3$. Calculated, %: C 64·39, H 5·37, N 6·83. PMR-spectrum (CH₃OD solvent, internal standard, HMDS), ppm: 2·00 c. (CH₃), 5·58 c. and 5·90 c. (=CH₂), 6·9-9·1 m (A1H), 10·16 c (CHO).

Potassium bis- $[N-(5\cdot mcthacryloylaminosalicylidene)-3$ -valinato]cobaltate (+3) (VI) was prepared from Co(CH)₃, V and s-valine in water [3]. Diasteremers were separated chromatographically on anhydrous aluminium oxide (eluent -96% ethanol). Further purification was carried out on Sephadex IH-20, elution with an alcohol-benzene mixture (3:1). Yield of VI. 2t%.

For the A-ss-iscmer found, %: C 51.09, H 5.22, N 7.37. $C_{32}H_{36}N_4O_8CoK \cdot 3H_2O$. Calculated, %: C 50.79, H 5.55, N 7.41.

For the \triangle -ss-iscmer found, %: C 51.97, H 5.52, N 7.75. $C_{32}H_{36}N_4O_8CoK \cdot 2H_2O$. Calculated, %: C 52.03, H 5.42, N 7.59.

The UV spectra and CRD curves for Λ -VI and Δ -VI are displayed in Fig. 3. The absolute configuration of the dissterceners was fixed by comparing CRD curves with the respective-

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ORD curves of the Λ - and Δ -bis-[N-salicylideneglycinato]cobaltate (+3) ions having known absolute configurations [3]. Further corroboration of the correct assignment of the absolute configurations is the fact that $R_{f\Lambda-ss} > R_{f\Delta-ss}$ on Al_2O_3 [4]. PMR-spectra (CD₃OD solvent, internal standard, HMDS), ppm: Λ -ss: 1·18 d. (CH₃CHCH₃), 1·95 c. (H₃C-C), 2·1-2·9 m. (β -CH), 4·48 d. (α -CH), 5·47 c. and 5·86 c. (H₂C=), 6·4-8·0 m. (ArH), 8·50 c. (-CH=N); Δ -ss: 1·24 t. (CH₃CHCH₃), 1·94 c. (CH₃-C), 2·3-3·0 m. (β -CH), 4·35 d. (α -CH), 4·80 c. and 4·95 c. (H₂C=), 6·6-7·8 m. (ArH), 8·40 c. (-CH=N).



FIG. 3. ORD curves and UV spectra of VI in water: 1-ORD for the Λ -(ss)-isomer; 2-ORDfor Λ -(ss); 3-UV-spectrum of Λ -ss; 4-UV spectrum of Λ -ss.

Cupric N-(5-Methacryloylaminosalicylidene)-s-valinate (VII). To a solution of 0.7 g (3.43 mmole) of V and 0.43 g (3.7 mmole) of s-valine in 50 ml of an alcohol-water mixture (1:1) was added, while stirring vigorously and heating at 60°, 0.7 g (3.5 mmoles) of Cu(CH₃COO)₂·H₂O comminuted to a powder. Stirring and heating were continued for a further 1.5 hr. The reaction mixture was evaporated off under vacuum, and the obtained amorphous product was insoluble in water and alcohol. The residue was dissolved in ~20 ml of pyridine and was passed through a column containing Sephadex LH-20 (36×18 cm); clution with alcohol. After evaporation and drying under vacuum over P₂O₅ at 80° 1.5 g of VII was obtained. Found, %: C 54.90, H 5.52, C₁₆H₁₈-N₂O₄Cu·C₅H₅·N·H₂O. Calculated, %: C 54.47, H 5.40.

Separation of V from VII. A small amount of VII was dissolved in 1 ml of pyridine, and 20 ml of 2 \times HCl were added. The mixture was extracted with chloroform, and the extracts were dried over MgSO₄. After the elimination of solvent the product obtained was pure V (TLC on silica gel, using as solvent an octane-acetone mixture in 1 : 1 ratio), which substantiates the monomeric structure of VII.

Polymeric film preparation from VI, acrylamide and N,N'-methylene-bis-acrylamide. In 25 ml of water containing no CO₂ were dissolved 0.025 g $(3.31 \times 10^{-5} \text{ mole})$ of Λ -VI, 0.0522 g $(33.8 \times 10^{-5} \text{ mole})$ of N,N'-methylene-bis-acrylamide, 1.749 g $(2.36 \times 10^{-2} \text{ mole})$ of acrylamide and 0.0172 g of ammonium persulphate. The solution was decanted into a Petri dish, 2 drops of N,N,N',N'-tetramethylethylenediamine were added, after which the solution was stirred and left until polymerization ended (~ 2 hr). A translucent polymeric film of thickness 2-3 mm was obtained.

Polymerization of VI with acrylamide and N,N'-methylene-bis-acrylamide. To a solution of 2.0014 g (12.98 mmole) of N,N'-methylene-bis-acrylamide, 8.0056 g (112.6 mmole) of acrylamide, 0.6849 g (0.928 mmole) of a mixture of Λ - and Λ -VI, 0.1882 g of ammonium persulphate and 40 ml of water were added 0.2 ml of N,N,N',N'-tetramethylethylenediamine. Polymerization took place rapidly, accompanied by warm up of the mixture. After cooling the polymer was comminuted and washed with water. The complex in the polymer was reduced with an excess of FeSO₄.7H₂O in acetic acid for 24 hr at 60-70°, after which the polymer was again washed with water and placed in a saturated solution of disodium salt of EDTA to remove metal ions. Next, it was washed with water and alcohol and dried under vacuum over P₂O₅ at room temperature to constant weight. A yield of 7 g of bright yellow polymer VIII was obtained. The swelling coefficient in water was 3.5.

Polymerization of VII with acrylamide and N,N'-methylene-bis-acrylamide. To a solution of 1.0007 g (6.5×10^{-3} mole) of N,N'-methylene-bis-acrylamide, 4.0 g (5.63×10^{-2} mole) of acrylamide, 0.4294 g (9.07×10^{-4} mole) of VII and 0.0982 g of ammonium persulphate in a water-pyridine mixture (1:1) was added 0.1 ml of N,N,N',N'-tetramethylethylenediamine. Rapid polymerization accompanied by warm up of the mixture took place. After cooling the polymer was comminuted, treated to the point of loss of colouration with a saturated solution of disodium salt of EDTA, washed with water and alcohol and vacuum dried over P_2O_5 to constant weight. A yield of 4 g of a yellow polymer IX was obtained. The swelling coefficient in water was 3.8.

, Capacities of the obtained polymers. A weighed portion of polymer, about 0.5 g, was placed in a small amount of water free from CO_2 and was left standing overnight before being transferred quantitatively to a cell for potentiometric titration, where 10 ml of a 4.76×10^{-3} M solution of hydroxylamide hydrochloride was added. This was followed by titration with an NaOH solution of known concentration. After each alkali addition the mixture was kept for 20-30 min until the equilibrium was established. On the basis of the flex points on plots of pH vs. the NaOH volume we found the amount of HCl that is evolved in the reaction and is equal to the capacity of the resin.

Determination results, mmole/g of dry polymer: VII-0·121, 0·130; IX-0·136, •0·140.

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