

## Tertiary Amino Polymers by Polyaddition of 2,2'-Alkylenediiminodiethanethiols to 1,4-Bismethacryloylpiperazine

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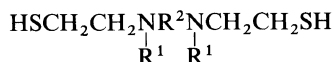
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(Received November 30, 1992)

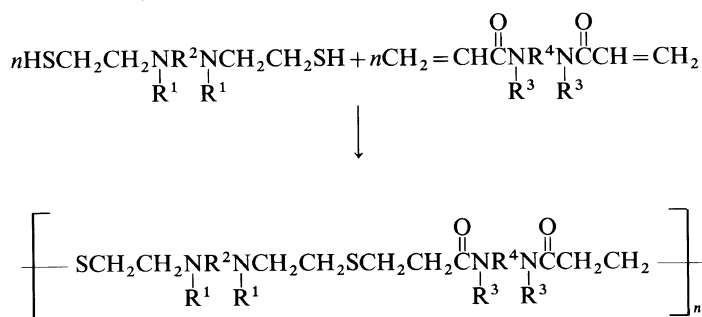
**ABSTRACT:** The synthesis of poly(methacrylamido-thioetheramine)s by thermal polyaddition of 2,2'-alkylenediiminodiethanethiols to 1,4-bismethacryloylpiperazine is reported. These products show less pronounced hydrolytic behavior in acidic aqueous solution than the corresponding poly(acrylamido-thioetheramine)s. They were characterized by viscometric measurements, elemental analyses, Fourier transform infrared spectrophotometer, nuclear magnetic resonance and differential scanning calorimeter.

**KEY WORDS** Amino Polymers / 2,2'-Alkylenediiminodiethanethiols / 1,4-Bismethacryloylpiperazine / Polyaddition / Hydrogen-Transfer Polyaddition / Poly(amidothioetheramine)s /

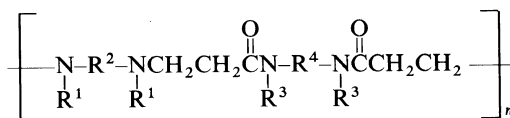
In a previous paper<sup>1</sup> we have reported on a new family of *tert*-aminomercaptans, namely 2,2'-alkylenediiminodiethanethiols:



which can act as monomers in a variety of hydrogen-transfer polyaddition reactions.<sup>2-4</sup> For example, in aqueous or alcoholic solution they give poly(amidothioetheramine)s by polyaddition to bisacrylamides<sup>4</sup>:



These polymers bear *tert*-amino groups in their main chain, and are being studied as biomaterials, as well as selective metal-ions complexing agents, being structurally related to poly(amidoamine)s, whose interest on these respects is well documented<sup>5-9</sup>:



Several attempts have been made in the past in order to substitute bismethacrylamides

for bisacrylamides in the above polyadditions, with disappointing results (E. Ranucci, unpublished). No reaction at all was observed with amines, and only low-molecular weight, poorly characterizable products were obtained with 2,2'-alkylenediiminodiethanethiols, under the same conditions leading to poly(amidoamine)s<sup>7)</sup> and poly(amidothioetheramine)s,<sup>4</sup> respectively.

Both poly(amidoamines) and poly(amidothioetheramines) are fairly easily degradable in aqueous media.<sup>10</sup> Degradation is thought to occur prevalingly *via* hydrolytic cleavage of the amidic bonds. A relatively fast degradation in aqueous media is a serious drawback for most applications. The substitution, as monomers, of bismethacrylamides for bisacrylamides might provide a way for obtaining less degradable *tert*-amino polymers having on other respects similar chemical properties. It is well known, in fact, that poly(methacrylates) are much less easily degradable than the corresponding poly(acrylates).

Therefore, we thought it interesting to relate here on the successful thermal polyaddition of typical 2,2'-alkylenediiminodiethanethiols, namely 2,2'-(1,4-piperazinediyl)diethanethiol **I**, 3,6-dimethyl-3,6-diazaoctane-1,8-dithiol **II**, and 2,2'-(1,4-diazepine-1,4-diyl)diethanethiol **III** to 1,4-bismethacryloylpiperazine **IV**.

## EXPERIMENTAL

### Measurements

Viscometric measurements were performed with an Ubbelohde viscometer at 30°C. Molecular weight measurements were performed in CHCl<sub>3</sub> at 30°C with a Perkin Elmer Model 115 vapor-pressure osmometer. Infrared spectra were performed with an FTIR Jasco 5100 spectrophotometer. Elemental analyses were performed by Redox Laboratory (Cologno Monzese, Italy). <sup>1</sup>H NMR spectra were run at 60 MHz on a EM 360A Varian spectrometer in CDCl<sub>3</sub>, using TMS as internal reference. Thermograms were obtained with a

Perkin Elmer DSC7 calorimeter. Typical experiments were performed at a scanning rate of 20°C min<sup>-1</sup>.

### Monomers

2,2'-Alkylenediiminodiethanethiols **I—III** were prepared as previously described.<sup>1,4</sup> 1,4-Bismethacryloylpiperazine **IV** was prepared as previously described in the case of 1,4-bisacryloylpiperazine,<sup>11</sup> by substituting methacryloylchloride for an equimolecular quantity of acryloylchloride. It could be also prepared as follows. Anhydrous piperazine (8.61 g, 0.1 mol) and methacrylic acid (17.22 g, 0.2 mol) were dissolved in dry, alcohol-free chloroform (300 ml). The solution was cooled at 0–5°C by means of an external bath, and *N,N'*-dicyclohexylcarbodiimide (42 g, 0.21 mol) was added at once while stirring. The reaction mixture was stirred at 0–5°C for 2 h, then the cooling bath was removed and stirring was continued for 1 h while rising to room temperature. The product was isolated by filtering off the precipitated dicyclohexylurea, evaporating the solvent, and recrystallizing the residue from *n*-heptane–ethylacetate 2 : 1.

By both procedures yields were about 75%, mp 114°C (uncorrected).

*Anal.* Calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.84%; H, 8.16%; N, 12.60%. Found: C, 68.44%; H, 8.21%; N, 12.51%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.1 (s, 6H, C–CH<sub>3</sub>); 3.8 (s, 8H, N–CH<sub>2</sub>CH<sub>2</sub>–N); 5.3–5.6 (m, 4H, CH<sub>2</sub>=C). IR (cm<sup>-1</sup>): 2970 (ν<sub>C–H</sub> CH<sub>3</sub>); 2860 (ν<sub>C–H</sub> CH<sub>2</sub>); 1610 (ν<sub>C=O</sub>, ν<sub>C=C</sub>); 1440 ppm (ν<sub>C–N</sub>).

### Polymers

*Polymer (V).* A mixture of **I** (4.128 g, 0.02 mol) and **IV** (4.446 g, 0.02 mol) was carefully purged with nitrogen and melted by gentle heating under a nitrogen atmosphere. The mixture was then maintained at the selected temperature (see the text) under nitrogen with occasional stirring. The reaction mixture was then cooled to room temperature, dissolved in dichloromethane, and reprecipi-

tated with *n*-pentane. This procedure was repeated twice, then the product was dried to constant weight at room temperature and 0.1 mm Hg. Yield 7.8 g (91%).

*Anal.* Calcd for  $(C_{20}H_{36}N_4O_2S_2)_x$ : C, 56.04%; H, 8.46%; N, 13.07%; S, 14.96%. Found: C, 55.51%; H, 8.51%; N, 13.21%; S, 15.23%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.1–1.45 (6H, d, C-CH<sub>3</sub>); 3.72 (8H, m, CON-CH<sub>2</sub>CH<sub>2</sub>-NCO); 2.5–3.2 (22H, m, all other H). IR ( $cm^{-1}$ ): 2970 ( $\nu_{C-H}$  CH<sub>3</sub>); 2860 ( $\nu_{C-H}$  CH<sub>2</sub>); 1610 ( $\nu_{C=O}$ ); 1440 ( $\nu_{C-N}$ ).

*Polymers VI–VII* were prepared at 120°C in the same way as **V** by substituting **II** (5.288 g, 0.02 mol) and **III** (4.408 g, 0.02 mol) for **I**, respectively. The products were isolated in the same way as **V**.

*Polymer VI.* Yield 70%; *Anal.* Calcd. for  $(C_{24}H_{46}N_4O_2S_2)$ : C, 59.22%; H, 9.52%; N, 11.51%; S, 13.17%. Found: C, 58.99%; H, 9.73%; N, 11.32%; S, 13.01%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.0–1.9 (14H, m, C-CH<sub>2</sub>-C and CCH<sub>3</sub>); 2.1 (6H, s, N-CH<sub>3</sub>); 3.72 (8H, m, CON-CH<sub>2</sub>CH<sub>2</sub>-NCO); 2.5–3.2 (22H, m, all other H). IR ( $cm^{-1}$ ): 2970 ( $\nu_{C-H}$  CH<sub>3</sub>); 2860 ( $\nu_{C-H}$  CH<sub>2</sub>); 1610 ( $\nu_{C=O}$ ); 1440 ( $\nu_{C-N}$ ).

*Polymer VII.* Yield 76%. *Anal.* Calcd. for  $(C_{21}H_{38}N_4O_2S_2)$ : C, 56.98%; H, 8.65%; N, 12.66%; S, 14.49%. Found: C, 56.94%; H, 8.70%; N, 12.60%; S, 14.39%.  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.0–1.8 (8H, m, CH<sub>3</sub>C and C-CH<sub>2</sub>-C); 3.72 (8H, m, CON-CH<sub>2</sub>CH<sub>2</sub>-NCO); 2.1–3.2 (22H, m, all other H). IR ( $cm^{-1}$ ): 2970 ( $\nu_{C-H}$  CH<sub>3</sub>); 2860 ( $\nu_{C-H}$  CH<sub>2</sub>); 1610 ( $\nu_{C=O}$ ); 1440 ( $\nu_{C-N}$ ).

The influence of radical inhibitors was

determined by performing the polymerization reactions at 120°C exactly as previously described, but adding the required amounts of 4-methoxyphenol before heating. The products were isolated and characterized without further purification, and the results compared with those obtained in the absence of inhibitor.

The influence of the monomer's ratio was studied by performing each experiment, corresponding to a given ratio, in a separate ampoule. After 5 days, the content of each ampoule was dissolved in enough chloroform to give a 0.2% solution, and the intrinsic viscosity determined.

The variation of intrinsic viscosity *versus* time was studied by running several polymerizations with 1:1 monomers' ratio in separate ampoules. The content of each ampoule was treated, at proper time, as in the previous case.

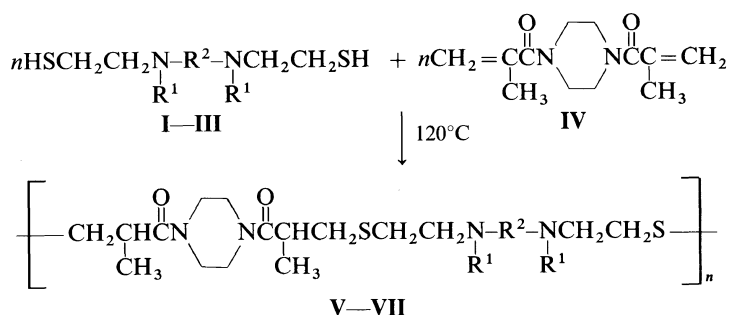
The stability of **IV** towards storage at high temperatures was tested by maintaining **IV** (1 g) in molten state at 120°C under a nitrogen atmosphere for 4 days. The product was then analyzed (mp and mixed mp, NMR spectra). No alteration could be detected.

The degradation experiments of polymers were performed in a 0.5M acetate buffer pH 4.98, on 0.29 g dl<sup>-1</sup> solutions, at 30°C, with an Ubbelohde viscometer, following dropping of flow time of the solution at intervals.

## RESULTS AND DISCUSSION

### Synthesis

The reaction:



**Table I.** Poly(amidothioetheramine)s

No.	Structure of the repeating unit	$\bar{M}_n^a$	$[\eta]^b$	Solubility <sup>c</sup>
V		3600	0.17	B, D, E, F, <sup>d</sup> H, I, <sup>d</sup> M, <sup>d</sup> N, O, P <sup>d</sup>
VI		3300	0.12	B, C, D, E, F, <sup>d</sup> H, I, L, M, N, O, P
VI		2400	0.09	B, C, D, E, F, <sup>d</sup> H, I, L, M, N, O, P

<sup>a</sup> Number average molecular weight from osmometric measurements in chloroform.

<sup>b</sup> Intrinsic viscosity in chloroform at 30°C (dl g<sup>-1</sup>).

<sup>c</sup> Solvents tried: Water (A); acetate buffer pH 4.86 (B); phosphate buffer pH 6.88 (C); chloroform (D); methanol (E); isopropanol (F); ethyl ether (G); acetone (H); ethyl acetate (I); *n*-heptane (L); toluene (M); DMSO (N); DMF (O); acetonitrile (P).

<sup>d</sup> Soluble near boiling point.

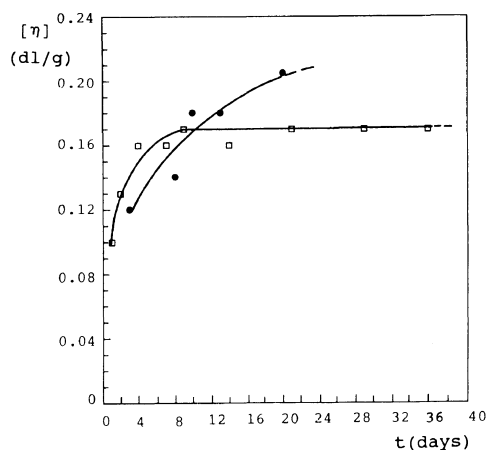
takes place in the molten state, without added solvents or catalysts. An inert atmosphere must be maintained throughout the polymerization time in order to avoid oxidation of the thiol groups.

The structures of the resulting polymers, together with some characterizations, are reported in Table I. It may be observed that both intrinsic viscosities and molecular weights of the new polymers are fairly low. While, according to our characterizations, the general structure of the polymers corresponds to the expected one, we have not at present reliable data on the nature of the terminal groups. It should be noticed, however, that we are in the presence of very reactive functions, and the polymerization temperatures are high. Therefore side reactions leading to a lowering of the molecular weight may occur.

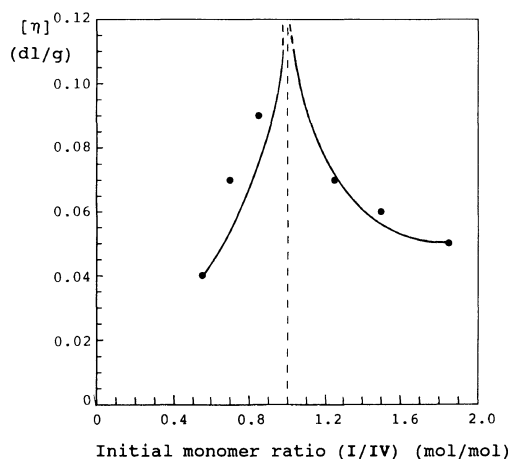
For polymer V the variation of the intrinsic viscosity *versus* reaction time of the unfractionated mixture was monitored at 100, 120, 140, and 160°C. The results are shown in

Figure 1. The highest molecular weights were obtained at 100°C, but with a low polymerization rate. Higher temperatures resulted in higher polymerization rates, but the products had lower intrinsic viscosities, and, for temperatures > 120°C, were also heavily discolored. It would appear that a polymerization temperature of 120°C represents the best compromise between reaction rate and products quality. It may be observed that in all cases the polymerization proceeds fairly slowly, by considering the reaction temperature, and the fact that the monomers are undiluted. However, even by taking into account that the reaction mechanism is probably ionic (see below), we did not think it opportune to add basic catalysts to accelerate the reaction, since tertiary amino groups are already present in **I—III**, and stronger bases, such as mineral hydroxides, might induce degradation of the resulting polymer, as it was already found in the case of poly(amidoamine)s.<sup>12</sup>

The influence of the monomers' ratio on the



**Figure 1.** Variation of the intrinsic viscosity of the raw polymerization product in the reaction of **I+IV** versus reaction time at 100 (curve ●) and 120°C (curve □). After four days the intrinsic viscosity at 140 and 160°C was 0.12 and 0.11 dl g<sup>-1</sup>, respectively. At these temperatures, longer times resulted in very heavy discoloration. Experimental conditions: solvent, chloroform; concentration, 0.25 g dl<sup>-1</sup>; temperature, 30°C.



**Figure 2.** Variation of the intrinsic viscosity of the raw polymerization product in the reaction of **I+IV** versus the initial monomers at maximum conversion. Experimental conditions: solvent, chloroform; concentration, 0.25 g dl<sup>-1</sup>; temperature, 30°C.

intrinsic viscosity of the product was studied for the polyaddition of **I** to **IV**. The reaction was performed at 120°C for 96 h. The results are shown in Figure 2. It may be observed that the intrinsic viscosity values, though always very slow, critically increase in the proximity of the 1:1 ratio, as expected for a stepwise polyaddition. The polymerization mechanism deserves comments. From one hand, all the polyaddition reactions described in Introduction presumably proceed through an ionic mechanism<sup>2-4,12</sup>; from the other hand, polymers were obtained by Marvel and his colleagues by radical polyaddition of bithiols to non activated, non conjugated dienes.<sup>13,14</sup>

We think it improbable that we are in the presence of a radical stepwise polyaddition analogous to that described by Marvel.<sup>13</sup> We have found, in fact, that the presence of variable amounts of a typical radical inhibitor, namely 4-methoxyphenol in the reaction **I+IV**→**V** has little influence on both yields and intrinsic viscosities of the resulting polymers (Table II). It may be also worthwhile

**Table II.** Comparison between polymers obtained by reaction of **I+IV** in the presence of different amounts of 4-methoxyphenol

Amount of 4-methoxyphenol	Yield	Intrinsic viscosity <sup>a</sup>
%	%	dl g <sup>-1</sup>
0	90.5	0.13
5	86.5	0.25
15	91.1	0.15

<sup>a</sup> In chloroform, at 30°C, concentration 0.29 g/dl<sup>-1</sup>.

to recall that according to literature reports,<sup>15</sup> confirmed by ourselves in the case of *N*-methacryloylpiperidine, *N,N*-disubstituted methacrylamides are inert towards radical polymerization. Moreover, during this work, we have found that **IV** is unaffected by heating at 120°C under nitrogen for 4 days. No evidence of decomposition reactions was observed running DSC thermograms up to 210°C.

From the above results, it may be concluded that the polymerization of **I** to **IV** is most probably a hydrogen transfer one as the

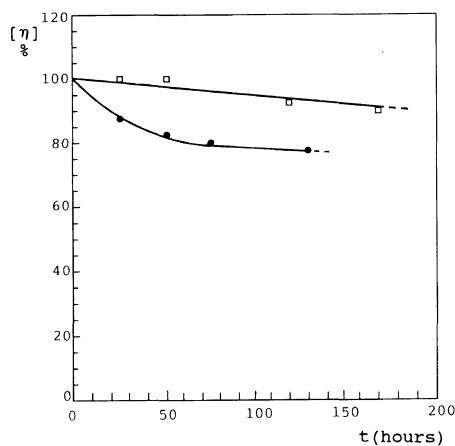
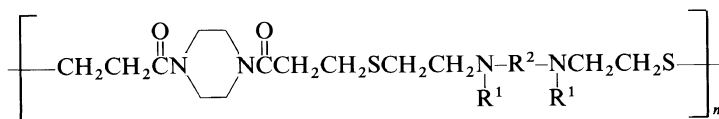
previously described cases involving bisacrylamides instead of bismethacrylamides,<sup>4</sup> and is atypical only in requiring more forcing conditions.

The polyaddition rate appears to be very slow if compared with that of the same bithiol to bis-acrylic esters. Most probably, the methyl group plays a major role on this respect both because it is an electron-donating substituent, and because increases the steric hindrance around the double bond.

#### Properties of the Polymers

Polymer **V** is a whitish fluffy powder, with softening temperature of about 80°C. Polymers **VI** and **VII** are gums. They are soluble in several solvents, and in aqueous acids (see Table I).

The molecular weights of Polymers **V**, **VI**, and **VII** are in the order of few thousands.



**Figure 3.** Degradation experiments for polymers **V** (curve □) and **VIII** (curve ●). Experimental conditions: solvent, 0.5M acetate buffer pH 4.98; concentration, 0.29 g dl<sup>-1</sup>; temperature, 30°C.

The results are shown in Figure 3. It may be observed that **V** is indeed less degradable than **VIII**, its intrinsic viscosity dropping at a lower rate. We could not perform the same

Polymer **V** was also studied for its thermal properties. Its DSC thermogram shows that no degradation occurs up to about 180°C. Above this temperature the polymer slowly begins to decompose. It has also been shown that not only monomer **IV** (see above), but also monomer **I** is stable in the same range of temperatures. Degradation experiments in aqueous solution have been performed to ascertain if the substitution of bismethacrylamides for bisacrylamides, all other structural features being the same, was indeed effective for improving hydrolytic stability in aqueous media, probably because of both steric and hydrophobic effects (see Introduction).

Polymer **V** was compared with a poly-(amidothioetheramine) **VIII** obtained by polyaddition of **I** to 1,4-bisacryloylpiperazine<sup>4</sup>:

comparison at higher pH's, at which degradation was presumably faster, because both polymers were not soluble in aqueous media at pH ≥ 6.

#### CONCLUSION

Our investigation has reasonably shown that bismethacrylamides can be used as monomers in stepwise polyadditions involving bisaminothiols as co-monomers. It is unlikely, in fact, that the polymerization reaction described in this paper is confined to the monomers mentioned above. It is more likely that it is a general one, thus providing new synthetic opportunities to basic multifunctional polymers.

Preliminary experiments indicate that the new *tert*-amino polymers may be expected to be less susceptible to hydrolytical degradation than their analogues obtained from bisacrylamides.

This property, coupled with the fact that many polymers obtained by stepwise polyaddition are endowed with functional end-groups, gives to the new polymers described in this paper the same potential of other polymers of similar structure<sup>17</sup> for surface modification of materials as well as for the preparation of functional block graft copolymers.

*Acknowledgements.* This work has been supported partially by the Italian CNR, (COMITATO TECNOLOGICO), and partially by the Italian M.U.R.S.T (40%).

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