[4] *Metal-Ion Separation and Preconcentration: Progress and Opportunities* (Eds.: A. H. Bond, M. L. Dietz, R. M. Rogers), Oxford University Press, New York, **1999**.
[5] S. Shinkai, H. Koreshi, K. Ueda, T. Arimura, O. Manaba, *J. Am. Chem. Soc.* **1987**, *109*, 6371.
[6] P. Thuéry, M. Nierlich, B. Souley, Z. Asfari, J. Vicens, *J. Chem. Soc. Dalton Trans.* **1999**, 2589.
[7] a) P. C. Leverd, P. Berthault, M. Lance, M. Nierlich, *Eur. J. Inorg. Chem.* **1998**, 1859; b) P. C. Leverd, I. Dumazet-Bonnamoour, R. Lamartine, M. Mierlich, *Chem. Commun.* **2000**, 494.
[8] T. N. Lambert, L. Dasaradhi, V. J. Huber, A. Gopalan, *J. Org. Chem.* **1999**, *64*, 6097.
[9] a) P. D. Beer, M. G. B. Drew, D. Hesek, M. Kan, G. Nicholson, P. Schmitt, P. D. Sheen, G. Williams, *J. Chem. Soc. Dalton Trans.* **1998**, 2873; b) P. Schmitt, P. D. Beer, M. G. B. Drew, P. D. Sheen, *Tetrahedron Lett.* **1998**, *39*, 6383.
[10] L. Deshayes, N. Keller, M. Lance, A. Navaza, M. Nierlich, J. Vigner, *Polyhedron* **1994**, *13*, 1725.
[11] A. Dejean, P. Charpin, G. Folcher, P. Rigny, A. Navaza, G. Tsoucaris, *Polyhedron* **1987**, *6*, 189.
[12] a) D. C. Moody, R. A. Penneman, K. V. Salazar, *Inorg. Chem.* **1979**, *18*, 208; b) D. C. Moody, A. J. Zozulin, K. V. Salazar, *Inorg. Chem.* **1982**, 3857.
[13] A. Navaza, F. Villian, P. Charpin, *Polyhedron* **1984**, *3*, 143.
[14] a) R. D. Rogers, L. K. Kurihara, M. M. Benning, *Inorg. Chem.* **1987**, *26*, 4346; b) R. D. Rogers, A. H. Bond, W. G. Hipple, A. N. Rollins, R. F. Henry, *Inorg. Chem.* **1991**, *30*, 2671.
[15] D. L. Clark, D. W. Keogh, P. D. Palmer, B. L. Scott, C. D. Tait, *Angew. Chem.* **1998**, *110*, 173; *Angew. Chem. Int. Ed.* **1998**, *37*, 164.
[16] *The Porphyrin Handbook* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, Boston, **2000**.
[17] a) O. Bilsel, S. N. Milam, G. S. Girolami, K. S. Suslick, D. Holten, *J. Phys. Chem.* **1993**, *91*, 7216; b) G. S. Girolami, P. A. Gorlin, S. N. Milam, K. S. Suslick, S. R. Wilson, *J. Coord. Chem.* **1994**, *32*, 173.
[18] a) J. L. Sessler, S. J. Weghorn, *Expanded*, *Contracted and Isomeric Porphyrins*, Elsevier, New York, **1997**; b) A. Jasat, D. Dolphin, *Chem. Rev.* **1997**, *97*, 2267.
[19] A. K. Burrell, G. Hemmi, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1991**, *113*, 4690.
[20] a) J. L. Sessler, T. D. Mody, V. Lynch, *Inorg. Chem.* **1991**, *31*, 529; b) J. L. Sessler, T. D. Mody, M. T. Dulay, R. Espinoza, V. Lynch, *Inorg. Chim. Acta* **1996**, *246*, 23.
[21] J. L. Sessler, A. Gebauer, M. C. Hoehner, V. Lynch, *Chem. Commun.* **1998**, 1835.
[22] T. J. Marks, D. R. Stojakovic, *J. Chem. Soc. Chem. Commun.* **1975**, 28.
[23] G. R. Choppin. *Radiochim. Acta* **1983**, *32*, 43.
[24] J. L. Sessler, S. J. Weghorn, V. Lynch, K. Fransson, *J. Chem. Soc. Chem. Commun.* **1994**, 1289.
[25] S. J. Weghorn, Dissertation, The University of Texas at Austin, USA, TX, **1994**.
[26] H. Falk, H. Flödl, *Monatsh. Chem.* **1988**, *119*, 247.
[27] J. L. Sessler, D. Seidel, V. Lynch, *J. Am. Chem. Soc.* **1999**, *121*, 11257.
[28] While experimental difficulties limit the accuracy of these measurements, extinction coefficients [$dm^3\,mol^{-1}\,cm^{-1}$] of $\varepsilon = 120000$ for the main transition at 531 nm and $\varepsilon = 40000$ for the Q-like transition at 830 nm were recorded.
[29] a) Crystallographic parameters for **6** (dark prisms grown from vapor diffusion of CH_2Cl_2 and hexanes): orthorhombic, space group *Pbcn*, $a = 9.0295(2)$, $b = 17.1213(4)$, $c = 24.7737(6)$ Å, $Z = 4$, $R1 = 0.0365$, $wR2 = 0.0612$, $V = 3829.9$ Å^3. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at $-150\,^\circ C$ using a Oxford Cryostream low temperature device. The structure was refined by full-matrix least-squares on F^2 to 0.0612, with $R(F)$ equal to 0.0242 and a GOF = 1.009. The complex lies on a crystallographic twofold rotation axis at 0,*y*,¼. The twofold axis passes through the uranium atom and bisects the bipyrrole and the tetrapyrrole moieties. b) The crystallographic parameters for [Et_3NH][**7**] (red-green dichromic rods, of dimension $0.08 \times 0.08 \times 0.12$ mm^3, were grown from vapor diffusion of CH_2Cl_2 and hexanes): monoclinic, space group $P2_1/c$, $a = 15.099(2)$, $b = 22.742(3)$, $c = 14.353(1)$ Å, $\beta = 110.857(4)^\circ$, $V = 4606(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.501$ mg m^{-3}. The data were collected at 203 K on a Bruker P4/CCD diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). A total of 18883 (5694 independent and $2\theta_{max} = 45^\circ$) reflections were collected using a combination of ϕ and ϑ scans. The structure was solved using direct methods, and refined against F^2 to convergence, with $R(I > 2\sigma) = 0.0925$ and $wR(I > 2\sigma) = 0.1371$ for 5694 reflections and 550 L.S. parameters. The final residual electron density was 0.89 e Å^{-3}. Hydrogen atom positions were idealized and refined using a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149932 (**6**) and -150148 ([Et_3NH][**7**]). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[30] D. L. Clark, S. D. Conradson, S. A. Ekberg, N. J. Hess, M. P. Neu, P. D. Palmer, W. Runde, C. D. Tait, *J. Am. Chem. Soc.* **1996**, *118*, 2089.
[31] J. M. Combers, C. J. Chisholm-Brause, G. E. Brown, Jr., G. A. Parks, S. D. Conradson, P. G. Eller, I. R. Triay, D. E. Hobart, A. Meijer, *Environ. Sci. Technol.* **1992**, *26*, 376.
[32] L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**, p. 644.
[33] a) P. Thuéry, N. Keller, M. Lance, J.-D. Vigner, M. Nierlich, *New J. Chem.* **1995**, 619; b) P. Thuéry, N. Keller, M. Lance, J.-D. Vigner, M. Nierlich, *Acta Crystallogr. Sect. C* **1995**, *51*, 801.
[34] a) J. L. Sessler, S. J. Weghorn, Y. Hiseada, V. Lynch, *Chem. Eur. J.* **1995**, *1*, 56; b) S. J. Weghorn, J. L. Sessler, V. Lynch, T. F. Baumann, J. Sibert, *Inorg. Chem.* **1996**, *35*, 1089; c) J. L. Sessler, A. Gebauer, A. Guba, M. Scherer, V. Lynch, *Inorg. Chem.* **1998**, *37*, 2073.

Narrow Molecular Weight Distribution Precursors for Polymer–Drug Conjugates**

Antony Godwin, Markus Hartenstein, Axel H. E. Müller,* and Stephen Brocchini*

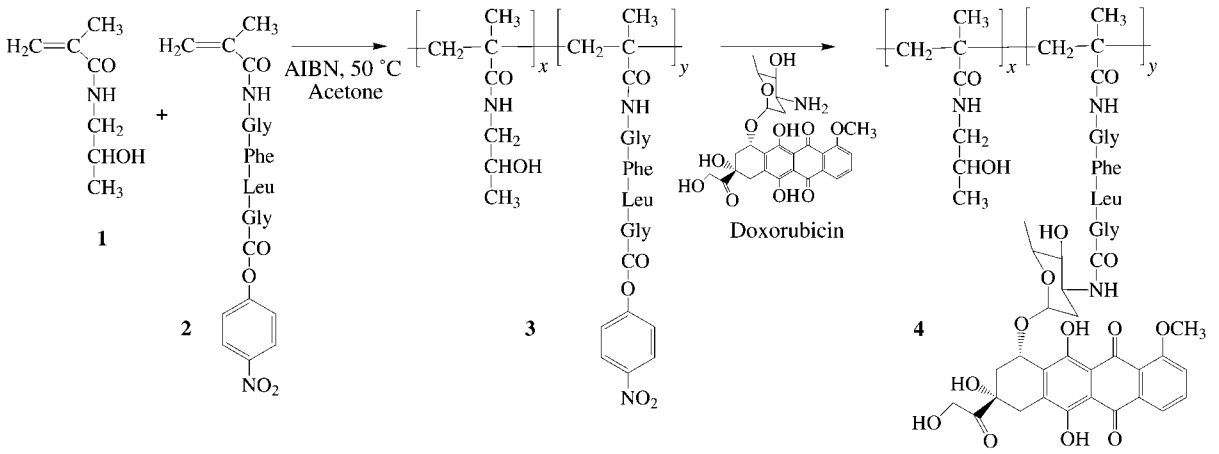
Polymer–drug conjugates derived from copolymers of *N*-(2-hydroxypropyl)-methacrylamide (HPMA) can be prepared from a copolymer precursor such as **3** (Scheme 1).[1] This methodology has been used for the development of conjugate **4** which is currently undergoing Phase II trials in the UK for the treatment of cancer.[2]

To exploit more widely the biological advantages of large molecule therapeutics[1, 3a] and to examine more thoroughly how structure, molecular weight,[4] and solution properties correlate with biological profile[3] it is essential to develop preclinical conjugates that have 1) narrow molecular weight

[*] Prof. Dr. A. H. E. Müller, M. Hartenstein
Universität Bayreuth
Makromolekulare Chemie II
95440 Bayreuth (Germany)
Fax: (+49) 921-55-3393
E-mail: Axel.Mueller@uni-bayreuth.de
Dr. S. Brocchini, A. Godwin
School of Pharmacy
University of London
29–39 Brunswick Square, London, WC1N 1AX (UK)
Fax: (+44) 207-753-5931
E-mail: Stephen.Brocchini@ulsop.ac.uk

[**] We are grateful for funding from the EPSRC and the School of Pharmacy (A.G.) and Mr. Derek Marley for conducting the atomic absorption analysis.

  0044-8249/01/11303-0614 $ 17.50+.50/0



Scheme 1. Preparation of a polymer–drug conjugate **4** from a copolymer precursor **3** derived from **1** and **2**. AIBN = azobisisobutyronitrile.

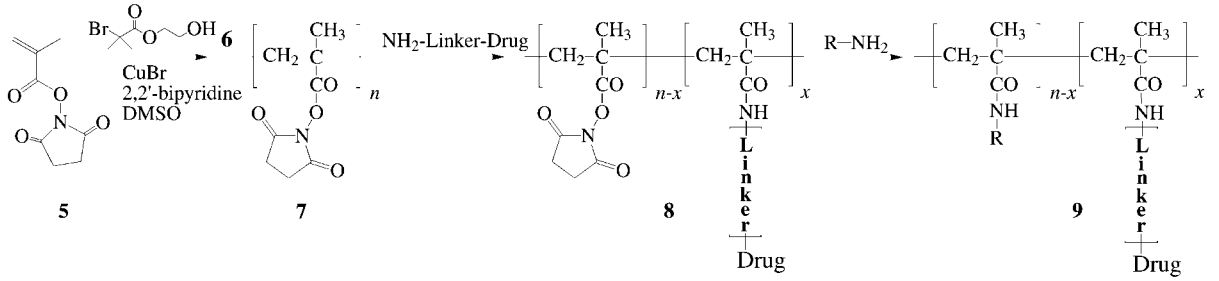
distribution (MWD), 2) the same molecular weight characteristics, and 3) uniform pendent chain structure. To address these issues we have prepared a narrow MWD homopolymeric precursor **7** (Scheme 2) by atom-transfer radical polymerization (ATRP) of **5** with **6**.[5] We have also begun to examine the reactions of **7** with amines to determine if this precursor can be used to prepare families of conjugates.

Although the use of active ester homopolymers is known for preparing functionalized polymers,[6] the preparation of a narrow MWD active ester homopolymeric precursor (for example, **7**) to give water-soluble copolymer conjugates has not been examined. Preparation of narrow MWD methacrylamide copolymers (for example, **3**) is currently not feasible, so the only way to obtain narrow MWD conjugates is by tedious fractionation procedures. By using only the homopolymeric precursor **7**, different stoichiometries of various solubilizing and drug-conjugating pendent chains will give families of conjugates with the same absolute molecular weight characteristics. This is not possible with copolymer precursors (for example, **3**) because each structurally distinct conjugate requires a different copolymer precursor, and each precursor is typically prepared by precipitation free-radical polymerization which results in conjugates with different molecular weights.

We selected *N*-methacryloxysuccinimide **5**[7] (m.p. 102–104 °C) because these esters can be more hydrolytically stable than other commonly used active esters.[8] Narrow MWD ($\bar{M}_w/\bar{M}_n = 1.1-1.2$; $\bar{M}_w$ = weight-averaged molar mass, $\bar{M}_n$ = number-averaged molecular mass) polymer **7** was prepared in both THF and acetone, but premature precipitation of the polymer frequently occurred to limit the preparation of a wide range of molecular weights.[9] Maintaining a homogeneous reaction mixture seemed the most systematic long-term strategy to prepare polymers at molecular weights which give prolonged circulation times in blood.[1–3]

Several polymerizations were conducted in DMF (110–130 °C) using monomer concentrations spanning 33–91 wt % in order to maintain solution homogeneity. Although polymer **7** is soluble in DMF,[7] this solvent is not considered optimal for ATRP because of its possible competitive chelation of copper ions.[10] The concentration of monomer **5** relative to DMF was critical for the outcome of the polymerization. A 50 % yield of polymer **7** was isolated at 61 wt % of monomer **5** while no polymer was isolated when the reaction was conducted at 33 wt %. The reaction mixture solidified at monomer concentrations above 75 wt % ($M_{target} \leq 18300\ g\,mol^{-1}$). To probe for competing thermal initiation[11] monomer **5** was stirred alone in DMF at 80 and 110 °C for 8–24 h. This resulted in the formation of some polymer of broad MWD ($\bar{M}_w/\bar{M}_n > 1.5$).

The experiments in DMF suggested that a homogeneous copper-mediated polymerization of **5** in a polar organic solvent was possible. DMSO was examined as the solvent, and homogeneous, reproducible polymerization reactions occurred to give a range of molecular weights (Table 1; entries 1–5). Polymerizations were stopped after 10–15 minutes to give narrow MWD polymer **7** in good yields (80–96 %). Even after 2.5 minutes the yield was nearly 50 % (Table 1, entry 6). These reactions were carried out on a 1.8–2.5 g scale and have also been successfully conducted on a 6 g



Scheme 2. Preparation of polymer–drug conjugates **9** starting from a narrow MWD homopolymeric precursor **7**. The use of **7** as a common precursor enables the synthesis of families of conjugates **9** with similar molecular weight characteristics.

  0044-8249/01/11303-0615 $ 17.50+.50/0

Table 1. Conditions and results for the copper-mediated polymerization of monomer **5** in DMSO.

Entry	**5**:**6**:CuBr:bpy[a]	T [°C]	M_{target}[b]	Yield [%]	$\bar{M}_n$[c] [g mol^{-1}]	$\bar{M}_w/\bar{M}_n$	f_{app}[d]
1	10:1:1:2	100	1830	85	12300	1.17	0.12
2	20:1:1:2	80	3660	92	16800	1.15	0.20
3	50:1:1:2	100	9150	89	22600	1.20	0.36
4	100:1:1:2	100	18300	96	29000	1.14	0.61
5	150:1:1:2	110	27450	80	40700	1.13	0.54
6[e]	100:1:1:2	100	18300	49	23300	1.15	0.38

[a] Ratio of the initial monomer and initiator concentrations. [b] $M_{target} = (\mathbf{5}/\mathbf{6}) \times 183$ g mol^{-1}. [c] The molecular weight averages were obtained by GPC using DMF as the eluent (0.1% LiCl) and PMMA standards. [d] Apparent initiator efficiency calculated by: $f_{app} = (M_{target} \times \text{yield})/\bar{M}_n$). [e] Reaction stopped after 2.5 minutes by dilution with DMSO and rapid cooling.

scale. Like the polymerizations in DMF, the concentration of DMSO similarly influenced the outcome of the polymerization where 57 wt% of monomer **5** was used in the reactions listed in Table 1. Polymer **7** was isolated as a white powdery solid by diluting the reaction mixture with DMSO followed by precipitation of the polymer by adding it to a stirred solution of acetone. Atomic absorption analysis indicated the copper content to be 0.153 ppm at a concentration of 28.0 mg mL^{-1} of polymer **7** in DMF.[12]

Molecular weights were obtained by gel permeation chromatography (GPC) using poly(methyl methacrylate) (PMMA) standards and DMF eluent (0.1% LiCl was added to inhibit aggregation). The apparent number-average molecular weight ($\bar{M}_n$) of polymer **7** was consistently higher than M_{target}, and the apparent initiator efficiency (f_{app})[13] increased as the M_{target} value increased (Table 1, entries 1–5). To obtain a better indication of the absolute $\bar{M}_n$ value and to determine the degree of polymerization (DP), a sample of precursor **7** was hydrolyzed to the sodium salt of poly(methacrylic acid) (PMAA).[6a] The apparent $\bar{M}_n$ and DP values of **7** ($f_{app} = 0.59$) prior to hydrolysis was 24800 g mol^{-1} and 136, respectively ($\bar{M}_w/\bar{M}_n = 1.20$; $M_{target} = 18300$ g mol^{-1}). After hydrolysis, aqueous GPC analysis (phosphate-buffered saline solution adjusted to pH 8.5) against PMAA sodium salt standards gave $\bar{M}_n = 22000$ g mol^{-1} ($\bar{M}_w/\bar{M}_n = 1.28$). This result indicated that the absolute DP was approximately 200 and $f_{app} = 0.50$ for this sample of **7**.

Before following the general conjugation strategy in Scheme 2 (**7**→**8**→**9**) the first conjugation reaction (**7**→**8**) had to be correlated with the stoichiometry of the added amine. Precursor **7** was stirred with different stoichiometries of glycine methyl ester in anhydrous DMSO and triethylamine at 60 °C for one hour. The FT-IR spectra obtained by attenuated total reflectance from an aliquot of each reaction mixture displayed a decrease in the height of the active ester imide band at 1735 cm^{-1} that correlated with the stoichiometry of the glycine methyl ester used (Figure 1).

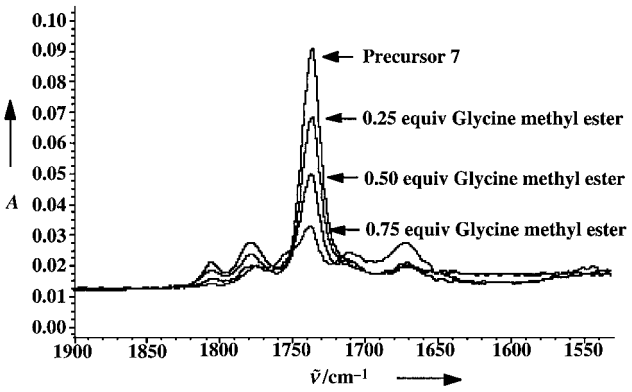
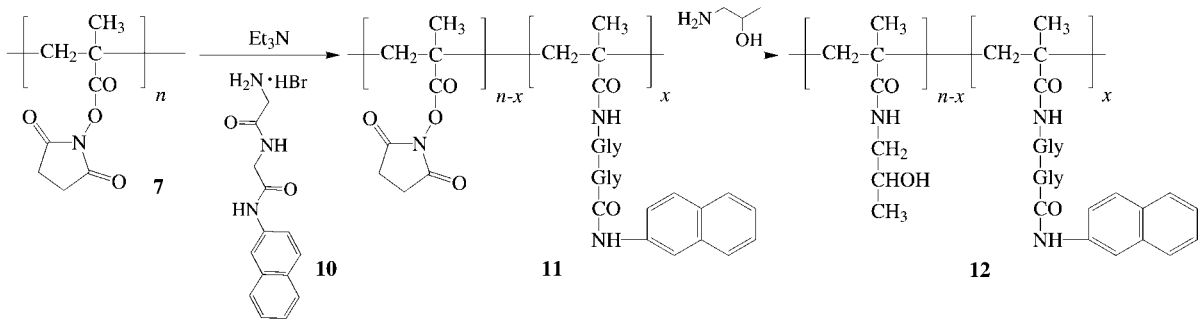


Figure 1. Superimposed IR spectra displaying the decrease in the band corresponding to the carbonyl group at 1735 cm^{-1} on conjugation of glycine methyl ester (0.25, 0.50, and 0.75 equiv) to precursor **7**. The actual decreases in peak height of 25.7, 53.7, and 74.7% correlated with the amount of added glycine methyl ester.

During the preclinical development of conjugate **4**, *p*-nitroanilide was used as a drug model and the glycine–glycine dipeptide linker was used as a control because it did not undergo lysosomal degradation.[3a,c] We used commercially available glycine-glycine-β-naphthylamide hydrobromide (**10**) as a linker–drug model to prepare model conjugates **12** (Scheme 3). To prepare a conjugate with 10% loading, 0.1 active ester group equivalents of **10** were conjugated to precursor **7**. A 10% reduction in the peak height of the IR band at 1735 cm^{-1} was observed from an aliquot of the reaction solution (Figure 2). Excess 1-amino-2-propanol (2.0 equivalents) was then added to the reaction mixture and the band at 1735 cm^{-1} disappeared. The water-soluble conjugate **12** was isolated after precipitation (acetone:diethyl ether, 1:1 (v/v)). Increasing the stoichiometry of **10** in the first reaction (namely, **7**→**11**) to 0.25 and 0.50 equivalents resulted in a corresponding decrease in the the IR band at 1735 cm^{-1}.

These preliminary experiments indicate that the narrow MWD homopolymeric precursor **7** may be used to prepare



Scheme 3. Conjugation of the drug model **10** to narrow MWD precursor **7** followed by conjugation of 1-amino-2-propanol gives the model polymer–drug conjugate **12**.

  0044-8249/01/11303-0616 $ 17.50+.50/0

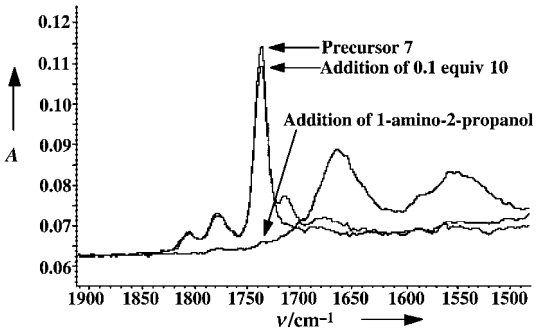


Figure 2. Superimposed IR spectra displaying the changes in the carbonyl band at 1735 cm^{-1} on addition of gly-gly-β-naphthylamide hydrobromide (**10**, 0.1 equiv) to give **11** and then on addition of excess 1-amino-2-propanol (2.0 equiv) to give the final conjugate **12**.

polymethacrylamides if competitive side reactions, for example, hydrolysis and imide formation, can be surpressed. As an example, 1-amino-2-propanol was conjugated to **7** to give a narrow MWD HPMA homopolymer (Figure 3) with only trace levels of competitive hydrolysis being observed by FT-IR spectroscopy. Controlled radical-polymerization processes, including ATRP, have successfully been used to prepare many narrow MWD polymers. One exception has been the preparation of a wide range of narrow MWD methacrylamide homo-[14] and copolymers.

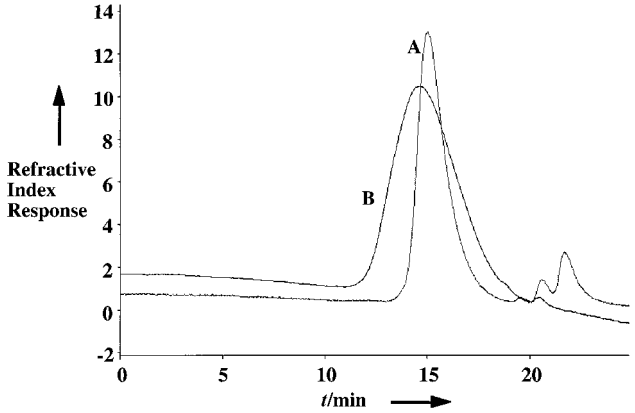


Figure 3. The gel-permeation chromatogram for the narrow MWD HPMA homopolymer (labeled A) obtained from the reaction of precursor **7** and 1-amino-2-propanol (2.0 equiv). The trace labeled B shows the HPMA homopolymer prepared by conventional free-radical polymerization.

In summary, the narrow MWD, active ester homopolymer **7** was prepared as a precursor for the efficient preparation of families of narrow MWD, water-soluble polymer–drug conjugates. This strategy may have potential for preparing narrow MWD speciality polymers for applications spanning healthcare to consumer products.

Experimental Section

7: In a typical polymerization, copper(I) bromide (31.3 mg, 0.2 mmol), 2,2′-bipyridine (bpy, 68.3 mg, 0.4 mmol), and monomer **5**[7] (2.00 g, 10.9 mmol) were added to a round-bottomed flask which was then sealed with a septum. DMSO (1.3 g) was then injected into the flask. The resulting brown mixture was gently heated until a solution had formed and then purged with argon for approximately 5 min. An argon-purged solution of 2-bromo-2-methyl-(2-hydroxyethyl) propanoate (46.1 mg, 0.2 mmol) in DMSO (0.2 g) was then injected into the mixture and the flask was heated to 100 °C in an oil bath. The reaction mixture became viscous after a few minutes and was removed from the heat after 10–15 min and rapidly cooled. The resulting crude polymeric product was then dissolved by the addition of DMSO (7–8 mL). This solution was slowly added to a stirred solution of acetone (100 mL) to precipitate polymer **7** as a white solid (1.78 g, 89 %).

12: **7** (100 mg, 0.55 mmol of reactive groups), H-Gly-Gly-β-naphthylamide · HBr · 0.6 H_2O (**10**, 19 mg, 0.06 mmol, 0.1 equiv), and a magnetic stirring bar were added to a 1.5-mL vial. The vial was sealed with a septum-centered screw-cap lid and purged with argon for approximately 2 min. Anhydrous DMSO (0.4 mL) was injected into the vial once the stirred reaction mixture was homogeneous, and a small sample of the solution was removed by syringe under argon for immediate analysis by FT-IR spectroscopy. Triethylamine (15.2 μL, 0.11 mmol, 2 salt equiv) was then added under argon to the vial and the vial was placed in an oil bath at 50 °C for 2.5 h. After cooling the solution, a sample was removed from the vial under argon for immediate analysis by FT-IR spectroscopy. The H-Gly-Gly-β-naphthylamide reaction solution was further heated with 1-amino-2-propanol (82 mg, 1.1 mmol, 2 equiv) at 50 °C for 1.25 h. A polymeric product **12** was isolated by precipitation of the DMSO reaction solution with acetone:diethyl ether (50:50) and further purified by precipitation from methanol with acetone:diethyl ether (50:50).

Received: August 2, 2000
Revised: November 9, 2000 [Z15573]

[1] D. Putnam, J. Kopecek, *Adv. Polym. Sci.* **1995**, *122*, 55–123.
[2] a) P. Vasey, C. Twelves, S. Kaye, P. Wilson, R. Morrison, R. Duncan, A. Thomson, T. Hilditch, T. Murray, S. Burtles, J. Cassidy, *Clin. Cancer Res.* **1999**, *5*, 83–94; b) R. Duncan, L. Seymour, K. O'Hare, P. Flanagan, S. Wedge, K. Ulbrich, J. Strohalm, V. Subr, F. Spreafico, M. Grandi, M. Ripamonti, M. Farao, A. Suarato, *J. Controlled Release* **1992**, *19*, 331–346.
[3] a) R. Duncan, S. Dimitrijevic, E. Evagorou, *STP Pharma* **1996**, *6*, 237–263; b) K. Ulbrich, C. Konak, Z. Tuzar, J. Kopecek, *Makromol. Chem.* **1987**, *188*, 1261–1272; c) R. Duncan, J. Lloyd, J. Kopecek, *Biochim. Biophys. Res. Commun.* **1980**, *94*, 284–290; d) C. Pitt, J. Wertheim, C. Wang, S. Shah, *Macromol. Symp.* **1997**, *123*, 225–234.
[4] a) S. Cartlidge, R. Duncan, J. Lloyd, P. Kopeckova-Rejmanova, J. Kopecek, *J. Controlled Release* **1986**, *4*, 253–264; b) L. Sprincl, J. Exner, O. Sterba, J. Kopecek, *J. Biomed. Mater. Res.* **1976**, *10*, 953–963; c) K. Muck, O. Christ, H. Keller, *Makromol. Chem.* **1977**, *178*, 2773–2784; d) R. Ottenbrite, W. Regelson, A. Kaplan, R. Carchman, P. Morahan, A. Munson in *Polymeric Drugs* (Eds.: L. Donaruma, O. Vogl), Academic Press, New York, **1978**, pp. 263–304.
[5] a) K. Matyjaszewski, *Pure Appl. Chem. A* **1997**, *34*, 1785–1801; b) M. Sawamoto, K. Masami, *Trends Polym. Sci.* **1996**, *4*, 371–377.
[6] a) P. Strohriegl, *Makromol. Chem.* **1993**, *194*, 363–387; b) R. Arshady, *Adv. Polym. Sci.* **1994**, *111*, 1–41; c) H. Batz, G. Franzmann, H. Ringsdorf, *Makromol. Chem.* **1973**, *172*, 27–47.
[7] a) H. Batz, G. Franzmann, H. Ringsdorf, *Angew. Chem.* **1972**, *84*, 1189–1190; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1103–1104; b) P. Ferruti, A. Bettelli, A. Fere, *Polymer* **1972**, *13*, 462–464.
[8] G. Hermanson, *Bioconjugate Techniques*, Academic Press, New York, **1996**, pp. 139–140.
[9] A. Godwin, M. Hartenstein, A. H. E. Müller, S. Brocchini, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* **2000**, *41*(1), 1002–1003.
[10] K. Beers, S. Boo, S. Gaynor, K. Matyjaszewski, *Macromolecules* **1999**, *32*, 5772–5776.
[11] S. Pascual, B. Coutin, M. Tardi, A. Polton, J. Vairon, *Macromolecules* **1999**, *32*, 1432–1437.
[12] This value of 0.153 ppm of copper was obtained as an average of three separate readings from a concentration of 28.0 mg mL^{-1} of precursor **5** dissolved in DMF. This sample of precursor **5** had been isolated from one precipitation with acetone. The amount of copper observed in a sample of precursor **5** after two precipitations from DMSO into acetone was 0.067 ppm at the same concentration.
[13] Initiator efficiency f is defined in this study by the following relationship: $f = (M_{target} \times \text{yield})/M_{exp}$.
[14] M. Teodorescu, K. Matyjaszewski, *Macromolecules* **1999**, *32*, 4826–4831.

  0044-8249/01/11303-0617 $ 17.50+.50/0