Thermoresponsive dendronized polymers with tunable lower critical solution temperatures†

Wen Li,[a] Afang Zhang*[ab] and A. Dieter Schlüter[a]

Received (in Cambridge, UK) 7th July 2008, Accepted 12th August 2008
First published as an Advance Article on the web 23rd September 2008
DOI: 10.1039/b811464a

A series of first (PG1) and second generation (PG2) dendronized polymers were synthesized which exhibit fast and sharp phase transitions with negligible hystereses in aqueous solutions and apparent lower critical solution temperatures (LCSTs) in the range of 33–49 °C.

Responsive behavior is rather typical for biomacromolecules and has been mimicked in fields ranging from advanced artificial devices, smart surfaces and sensors to medicine and biomineralization.[1] It presents a substantial scientific and engineering challenge with a considerable application potential.[2] An interesting class of stimuli-responsive materials are thermoresponsive synthetic polymers.[3] They start to collapse close to their lower critical solution temperatures (LCSTs) due to dehydration of the chains, and subsequently form aggregates. The LCST of a polymer is not only dependent on the balance of the hydrophilic and hydrophobic units, with the more hydrophilic polymers commonly showing higher LCSTs than the more hydrophobic ones, but also on how these units are incorporated into the molecular structure. The most often investigated thermoresponsive polymers contain polyethylene glycol (PEG), oligoethylene glycol (OEG), or poly(*N*-isopropylacrylamide) (P*N*iPAM) units.[4] Their generally high biocompatibility makes them especially attractive research targets. These structural motifs have not only been used in homo- but also in more complex hybrid polymers.[5] Much attention has been paid recently to develop novel thermoresponsive macromolecules with dendritic, hyperbranched, and star structures.[6] The transitions of all these materials are often broad and associated with considerable hystereses, which are less attractive features as far as applications are concerned. Therefore, developing novel thermoresponsive polymers with sharp and fast transitions in both heating and cooling remains an important challenge.

Dendronized polymers are composed of a linear backbone surrounded by dendrons at each repeating unit.[7] The dendronization reduces the attainable backbone conformations and, in the extreme case, renders a random coil polymer into a cylindrically shaped, rigid molecular object with a more or less stretched backbone in the interior. If the dendrons were themselves thermoresponsive, they would be forced into close proximity in such a polymer, and we set out to explore whether this unique structural feature could lead to fast and sharp transitions. Furthermore, the hydrophilicity–hydrophobicity balance in dendronized polymers could in principle be easily tuned by changing generation, interior, or peripheral groups. We recently reported two examples of thermoresponsive dendronized polymers.[8] Although they show fast and sharp transitions around their LCSTs, the corresponding temperatures (in the range of 63–65 °C) are too high to be attractive for applications in bio-related fields.

We here present the design and synthesis of a series of first (**PG1**) and second generation (**PG2**) dendronized polymers (Fig. 1) which comprises three structural variables that allow tuning the LCST almost at will. They comprise the choice of either a methoxy or an ethoxy terminal substituent, the length of the outmost OEG segment (y = 1 or 2), and the dendron generation (G1 or G2). The polymer structures were designed based on the calculated hydrophilicity values ($\log P$, with $P = [\text{solute}]_{n\text{-octanol}}/[\text{solute}]_{\text{water}}$) by Ghose's increment method, whereby the smaller the $\log P$, the more hydrophilic the polymer should be.[9]

The synthetic procedures for the corresponding dendrons and macromonomers are delineated in Scheme 1. First, the methoxy-terminated dendrons and macromonomers will be discussed. Williamson etherification of methyl gallate with tosylated diethylene glycol monomethyl ether (Me-DEG-Ts)

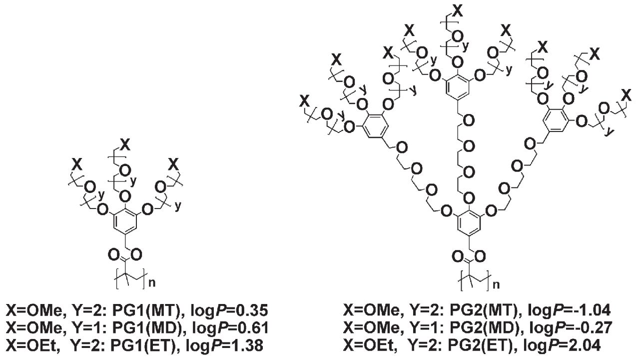
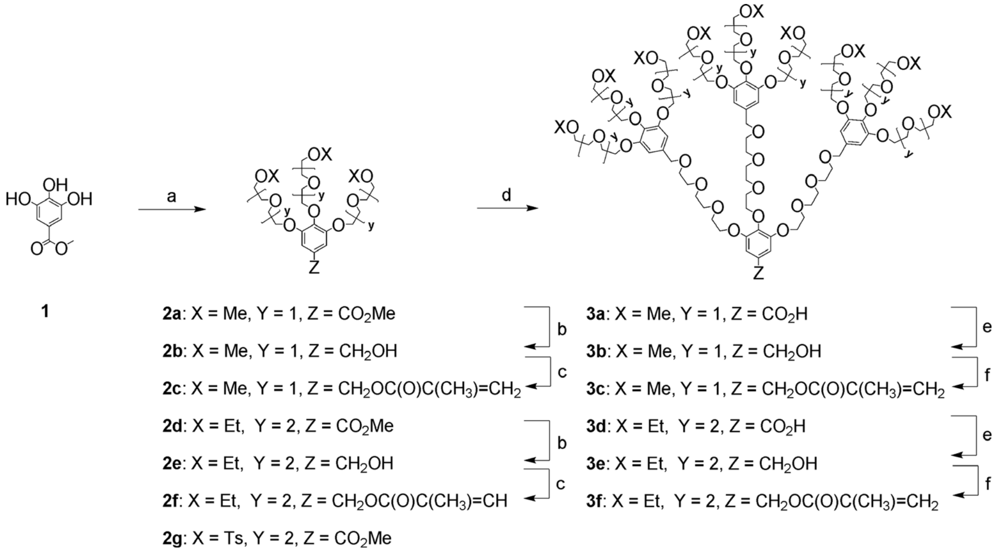


Fig. 1 Chemical structures of the dendronized polymers: **PG1(MT)** and **PG2(MT)** reported in the earlier work,[8] as well as **PG1(MD)**, **PG2(MD)**, **PG1(ET)** and **PG2(ET)** from the present work. For the $\log P$ values, see main text. For the nomenclature: **MT**, **MD** and **ET** stands for methoxytriethyleneoxy, methoxydiethyleneoxy and ethoxytriethyleneoxy, respectively.

---

[a] *Institute of Polymers, Department of Materials, ETH Zurich, Wolfgang-Pauli-Strasse 10, HCI G 525, Zurich, 8093, Switzerland. E-mail: zhang@mat.ethz.ch; Fax: (+41) 44-6331390*
[b] *School of Materials Science and Engineering, Zhengzhou University, Daxue Beilu 75, Zhengzhou, 450052, China*

† Electronic supplementary information (ESI) available: Experimental procedures and details. NMR spectra of new compounds and polymers. See DOI: 10.1039/b811464a



2a: X = Me, Y = 1, Z = CO_2Me
2b: X = Me, Y = 1, Z = CH_2OH
2c: X = Me, Y = 1, Z = $CH_2OC(O)C(CH_3){=}CH_2$
2d: X = Et, Y = 2, Z = CO_2Me
2e: X = Et, Y = 2, Z = CH_2OH
2f: X = Et, Y = 2, Z = $CH_2OC(O)C(CH_3){=}CH$
2g: X = Ts, Y = 2, Z = CO_2Me

3a: X = Me, Y = 1, Z = CO_2H
3b: X = Me, Y = 1, Z = CH_2OH
3c: X = Me, Y = 1, Z = $CH_2OC(O)C(CH_3){=}CH_2$
3d: X = Et, Y = 2, Z = CO_2H
3e: X = Et, Y = 2, Z = CH_2OH
3f: X = Et, Y = 2, Z = $CH_2OC(O)C(CH_3){=}CH_2$

Scheme 1 Synthesis procedures for G1 and G2 macromonomers **2c**, **2f** and **3c**, **3f**. *Reagents and conditions*: (a) Me-DEG-Ts or Et-TEG-Ts, K_2CO_3, KI, DMF, 80 °C, 24 h (83–87%); (b) LAH, THF, −5 to 25 °C, 3 h (91–92%); (c) MAC, triethylamine (TEA), 4-dimethylaminopyridine (DMAP), DCM, 0–25 °C, 3 h (92%); (d) KI, 15-crown-5, NaH, THF, r.t., 24 h (48–50%); (e) (i) *N*-methylmorpholine, ethyl chloroformate, THF, −15 °C, 1 h; (ii) $NaBH_4$, −5 to 25 °C, 4 h (81–82%); (f) MAC, TEA, DMAP, DCM, 0–25 °C, 5 h (83–85%).

gave **2a**, whose reduction with lithium aluminum hydride (LAH) furnished the corresponding dendron alcohol **2b**, which was reacted with **2g**[8] to give the G2 dendron acid **3a**. From this acid, **3b** was obtained by its reduction according to Kokotos' protocol.[10] The corresponding G1 and G2 macromonomers **2c** and **3c** were prepared by esterification of the respective alcohols **2b** and **3b** with methacryloyl chloride (MAC). By similar procedures, the ethoxy-terminated analogs **2f** and **3f** were obtained from the corresponding dendron alcohols. All macromonomers were obtained as completely colorless, water-soluble liquids, whose fluidity is reminiscent of glycerol. The high synthesis efficiency is illustrated by overall yields for **2c**, **2f**, **3c** and **3f** of 73, 70, 26 and 25%, respectively, starting from methyl gallate. All new compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, and correct values from combustion analysis. Typical ^{1}H NMR spectra are shown in the supplementary information to illustrate the high purities achieved.

The macromonomers were polymerized by conventional free radical techniques, and the conditions and typical results are summarized in Table 1. The molar masses were determined by GPC using DMF (0.1 wt% LiBr) as eluent and universal calibration. Polymerization of this kind of liquid macromonomers in bulk normally affords polymers with much higher molar masses than in DMF solution.[8] Thus, DMF seems to be an unfavorable solvent at first glance. However, the polymerization of **2c** always led to gelation in bulk or even in concentrated DMF solution. Therefore, its polymerization needed to be done in slightly dilute DMF solution (56 wt%) and stopped at an early stage in order to avoid gelation. This is the reason for the low conversion of 28%. The other polymerizations did not lead to gelation and bulk conditions, which are advantageous for achieving high molar mass polymers from macromonomers,[11] could be applied.

All polymers are water-soluble at room temperature, but collapse from water and their aqueous solutions turn turbid when heated up to the LCST. The LCSTs were measured and the thermoresponsive behavior investigated by turbidity measurements using UV/Vis spectroscopy. Typical phase transition curves are shown in Fig. 2(a). For comparison, the transition curves for **PG1(MT)** and **PG2(MT)** from ref. 8 are also included. It is interesting to note how strongly the transitions depend on slight structural changes and how sharp ($\leq$0.8 °C) they are in addition to their unprecedented reversibility. Also, the hystereses are very small ($\leq$0.6 °C). Though it would be tempting to correlate the transitions' sharpness with molecular structure, we feel that more examples are needed before serious conclusions can be drawn.[5c,6d] The

Table 1 Conditions for and results from the polymerization of the macromonomers **2c**, **2f**, **3c** and **3f**

	Polymerization conditions[a]				GPC results[d]			
Entries	Monomer	[Monomer][c]/mol L^{-1}	*t*/h	Yield (%)	$10^{-5}M_n$	DP$_n$[e]	PDI	LCST/°C
1	**2c**[b]	1.10	4.0	28	4.5	843	1.90	43.3
2	**2f**	1.56	3.0	68	7.2	1023	3.15	33.2
3	**3c**	0.56	24.0	61	5.9	303	2.63	48.5
4	**3f**	0.44	24.0	62	3.4	139	3.14	36.0

[a] All polymerizations were carried out at 60 °C in bulk with AIBN as initiator (concentration 0.5 wt% based on monomer). [b] In DMF. [c] The values were obtained by calculation from the monomer density (1.1 g mL^{-1} for both G1 and G2 monomers). [d] All GPC measurements were done in DMF (0.1 wt% LiBr) as eluent at 45 °C. [e] DP$_n$ = number-average degree of polymerization.

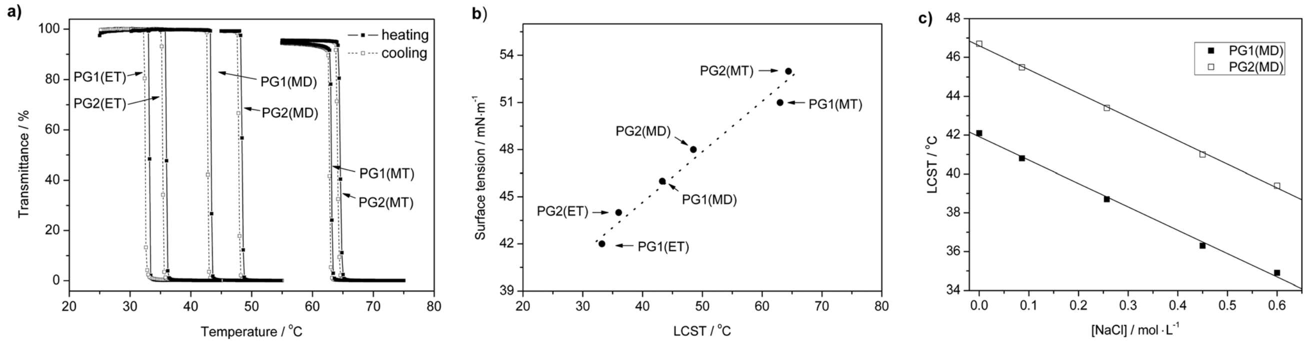


Fig. 2 Plots of transmittance (a) and surface tension (b) *vs.* temperature for 0.25 wt% aqueous solutions of **PG1(ET)**, **PG2(ET)**, **PG1(MD)**, **PG2(MD)**, **PG1(MT)** and **PG2(MT)**. (c) LCST dependence of **PG1(MD)** and **PG2(MD)** on NaCl concentration in PBS (pH 7.0). The linear lines in (b) and (c) are a guide to the eye.

LCSTs for **PG1(ET)**, **PG2(ET)**, **PG1(MD)**, **PG2(MD)**, **PG1(MT)** and **PG2(MT)** are 33, 36, 43, 48, 63 and 64 °C, respectively. The log *P* values for these polymers are qualitatively in line with this structure/LCST relation. The following conclusions as to the dependence of LCST on structure can be drawn: (i) LCSTs of **PG1** are lower than the corresponding **PG2**, (ii) ethoxy-substituted polymers have always lower LCSTs than their methoxy counterparts, (iii) the OEG segments with $y = 1$ have lower LCSTs than those with $y = 2$. The change of terminal groups from methoxy into ethoxy shows a stronger effect on LCST than either alternation of dendron generation or the length of OEG.

In order to substantiate the above correlation of hydrophilicity values with LCST, surface tension measurements were performed using the pendent drop method,[12] and the results are plotted in Fig. 2(b). Surface tension mirrors the hydrophilicity of a polymer, with a larger value indicating higher hydrophilicity. As expected, for the various polymers investigated, the LCSTs increase with the surface tension values.

In view of potential applications of these polymers in biomedical areas, the phase transitions of **PG1(MD)** and **PG2(MD)** in phosphate buffer solutions (PBS) in the presence of NaCl were examined with UV/Vis spectroscopy. The results are plotted in Fig. S1 in ESI,† and the LCST dependence on concentration of NaCl is shown in Fig. 2(c). These plots suggest buffer conditions and salt additions show a very small influence on the phase transitions' sharpness of both polymers, while the LCSTs decrease linearly with the increase of salt concentration.

In conclusion, we have demonstrated that a novel class of dendronized polymers based on OEG dendrons shows fast and sharp thermal transition around their LCSTs. The hystereses between heating and cooling processes are very small. The LCSTs can be varied between 33 to 49 °C by changing three structural parameters, all of which are synthetically easy to be implemented: (i) terminal methoxy group *vs.* ethoxy, (ii) length of the outermost ethyleneoxy chain ($y = 1$ or 2), (iii) dendron generation. This range of LCSTs is highly attractive for applications in the biomedical and actuator materials. The collapse and aggregation mechanism is presently under investigation.[13]

We thank Prof. L. Gauckler (ETH Zurich) for suggesting the surface tension measurements. I. Akartuna and M. Colussi are thanked for their kind help with the surface tension and GPC measurements, respectively. This work was supported by ETH Research Grant ETH-1608-1. A. Z. thanks for the financial support from the National Natural Science Foundation of China (Nos. 20374047 & 20574062).

Notes and references

1 A. P. Feinberg, *Nature*, 2007, **447**, 433.

2 (*a*) C. H. Alarcon, S. Pennadam and C. Alexander, *Chem. Soc. Rev.*, 2005, **34**, 276; (*b*) T. Muraoka, K. Kinbara and T. Aida, *Nature*, 2006, **440**, 512; (*c*) A. Kumar, A. Srivastava, I. Y. Galaev and B. Mattiasson, *Prog. Polym. Sci.*, 2007, **32**, 1205.

3 (*a*) R. Yerushalmi, A. Scherz, M. E. van der Boom and H.-B. Kraatz, *J. Mater. Chem.*, 2005, **15**, 4480; (*b*) H. Mori, H. Iwaya, A. Nagai and T. Endo, *Chem. Commun.*, 2005, 4872; (*c*) A. Kumar, A. Srivastava, I. Y. Galaev and B. Mattiasson, *Prog. Polym. Sci.*, 2007, **32**, 1205; (*d*) H. Lee, J. A. Lee, Z. Poon and P. T. Hammond, *Chem. Commun.*, 2008, 3726.

4 For example, see: (*a*) Y. Li, B. S. Lokitz and C. L. McCormick, *Angew. Chem., Int. Ed.*, 2006, **45**, 5792; (*b*) X. Zhang, J. Li, W. Li and A. Zhang, *Biomacromolecules*, 2007, **8**, 3557.

5 (*a*) G. Chen and A. S. Hoffman, *Nature*, 1995, **373**, 49; (*b*) C. Li, N. Gunari, K. Fischer, A. Janshoff and M. Schmidt, *Angew. Chem., Int. Ed.*, 2004, **43**, 1101; (*c*) J.-F. Lutz, O. Akdemir and A. Hoth, *J. Am. Chem. Soc.*, 2006, **128**, 13046.

6 (*a*) Y. Z. You, C. Y. Hong, C. Y. Pan and P. H. Wang, *Adv. Mater.*, 2004, **16**, 1953; (*b*) Z. Jia, H. Chen, X. Zhu and D. Yan, *J. Am. Chem. Soc.*, 2006, **128**, 8144; (*c*) Y. Haba, C. Kojima, A. Harada and K. Kono, *Angew. Chem., Int. Ed.*, 2007, **46**, 234; (*d*) Y. Zhou, D. Yan, W. Dong and Y. Tian, *J. Phys. Chem. B*, 2007, **111**, 1262; (*e*) D. W. Chang and L. Dai, *J. Mater. Chem.*, 2007, **17**, 364.

7 (*a*) A. D. Schlüter and J. P. Rabe, *Angew. Chem., Int. Ed.*, 2000, **39**, 864; (*b*) A. Zhang, L. Shu, Z. Bo and A. D. Schlüter, *Macromol. Chem. Phys.*, 2003, **204**, 328; (*c*) A. D. Schlüter, *Top. Curr. Chem.*, 2005, **245**, 151.

8 W. Li, A. Zhang, K. Feldman, P. Walde and A. D. Schlüter, *Macromolecules*, 2008, **41**, 3659.

9 V. N. Viswanadhan, A. K. Ghose, G. R. Revankar and R. K. Robins, *J. Chem. Inf. Comput. Sci.*, 1989, **29**, 163.

10 G. Kokotos, *Synthesis*, 1990, 299.

11 A. Zhang, B. Zhang, E. Wächtersbach, M. Schmidt and A. D. Schlüter, *Chem.–Eur. J.*, 2003, **9**, 6083.

12 For example, see: (*a*) J. Zhang and R. Pelton, *Langmuir*, 1996, **12**, 2611; (*b*) V. P. Gilcreest, K. A. Dawson and A. V. Gorelov, *J. Phys. Chem. B*, 2006, **110**, 21903; (*c*) U. T. Gonzenbach, A. R. Studart, E. Tervoort and L. J. Gauckler, *Langmuir*, 2007, **23**, 1025.

13 B. Screenath, M. Ballauff, W. Li, A. Zhang and A. D. Schlüter, in preparation.