ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 5, pp. 788–791. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © C.F. Lu, C. Xie, Z.X. Chen, G.C. Yang, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 5, pp. 800–803.

Synthesis of New Soluble Dendrimers on Poly(ethylene glycole) Sublayer

C. F. Lu, C. Xie, Z. X. Chen, and G. C. Yang

Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules
& School of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, China
e-mail: lucf@hubu.edu.cn

Received September 21, 2007

Abstract—A rational method of synthesis was developed for new soluble dendrimers on poly(ethylene glycole) sublayer with a high density of functional groups applying 2,4,6-trichloro-1,3,5-triazine as a dendron and piperazine as linker and functional group carrier. The density of functional groups in the synthesized soluble dendrimers calculated from the elemental analysis for chlorine was 2.19 mmol of NH groups per 1 g of polymer. These new water-soluble dendrimers can be used not only as convenient soluble polymer sublayers but also for efficient trapping in purification of reaction products from impurities.

DOI: 10.1134/S1070428009050248

Recently the importance grew of the use of polymer sublayers, especially in the automated synthesis and combinatorial chemistry. Soluble polymer sublayers possess certain advantages over insoluble polymers with respect to the easy analysis and process monitoring and especially in establishing homogeneous conditions most feasible for bimolecular processes [1].

We successfully used in our laboratory poly(ethylene glycol) (PEG) as a polymer sublayer [2–5]. However due to the fact that each PEG molecule has only two functional groups for adding reagents, namely, the terminal hydroxy groups, PEG possesses a low density of functional groups, and this significant disadvantage limits its efficient application as a soluble polymer sublayer.

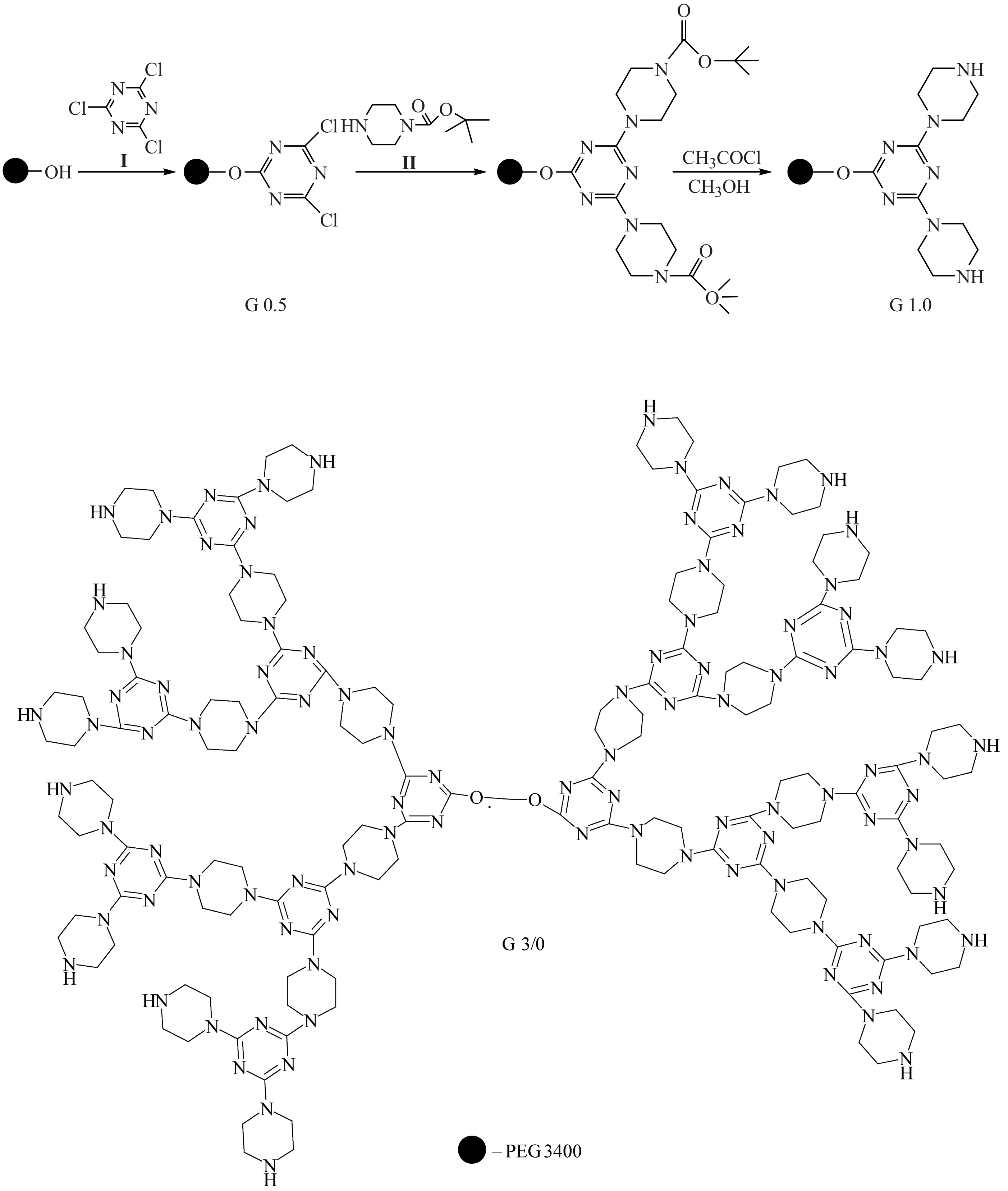
Attempts were made to increase the density of functional groups on PEG by chemical modification [6, 7]. Our team also carried out a research aiming to develop two types of soluble polymer sublayers with a high density of the functional groups, dendrimers on PEG sublayer [8, 9]. The number of functional groups on the periphery of a dendrimer increases from generation to generation resulting in the growth of the number of functional groups with the growing size of the dendrimer. Besides the spherical form of large dendrimers makes it possible to apply simple purification methods. These two factors can make dendrimers useful sublayers for organic synthesis. The additional advantage of soluble dendrimers is the possibility to investigate the intermediates on the sublayer by standard analytical methods, like NMR, IR spectroscopy, and mass spectrometry, due to the highly ordered and repeating structural element of dendrimers.

Here we report on the synthesis of one more soluble dendrimer on the PEG sublayer as shown on the Scheme.

2,4,6-Trichloro-1,3,5-triazine was selected as dendron because of its appropriate reactivity and chemoselectivity of the chlorine atoms in the reactions of compound **I** at various temperatures [10]. Therefore it was possible to reduce the number of cross-links by controlling the reaction conditions. The piperazine was employed as a linker and functional groups carrier in dendrimer formation. Besides the piperazine is a secondary amine therefore the use of dendrimer with piperazine for linker is potentially more valuable than a dendrimer with ethylenediamine as linker at the use of the dendrimer for trapping of protons.

The efficient density of functional groups in the dendrimer was estimated using the elemental analysis for chlorine. The effective and theoretical density of the

Scheme.



● – PEG 3400

Functional groups density of dendrimers on PEG sublayer, mmol per 1 g of polymer

Dendrimer	G 0.5	G 1.0	G 1.5	G 2.0	G 2.5	G 3.0
Cl content, %	3.7	0.2	6.0	0.5	8.1	1.1
Effective density	1.04	1.00	1.69	1.51	2.63	2.19
Theoretical density	1.08	1.03	1.78	1.64	2.92	2.55

functional groups are presented in the table. It is seen that the effective density is less than theoretical. The functional groups density decreases with the growing size of the substrate molecule. This phenomenon may be ascribed to the combination of steric strain due to the short distance between the polar functional groups and intramolecular hydrogen bonds with the growing number of generations. Still the functional groups density of dendrimer G 3.0 on PEG sublayer (2.19 mmol NH per 1 g of polymer) is considerably higher than that of commercial PEG 3400 (0.59 mmol NH per 1 g of polymer).

One of important factors in the liquid-phase organic synthesis is the attaining the compromise between the functional groups density of the sublayer and the general solubility of the system. Therefore we investigated also the solubility of dendrimers on PEG sublayer and found that they were soluble in many solvents, like DMF, H_2O, etc. We also studied the thermal stability of dendrimers by thermogravimetric analysis and revealed that these dendrimers were stable at heating up to ~450°C. The good thermal stability of these dendrimers shows that they are usable in many organic syntheses both at room temperature and at heating.

Note in conclusion that we developed new soluble dendrimers on PEG sublayer with a high functional groups density. These dendrimers are suitable for application in liquid-phase organic synthesis and in the combinatorial chemistry as good substrates on soluble polymer sublayers. Moreover, they can be used for efficient trapping for purification of reaction products due to the enhanced number of the active functional NH groups. Therefore the synthesis of these dendrimers is promising, and their applications will be described in further publications.

EXPERIMENTAL

All organic solvents were dried by standard procedures. Poly(ethylene glycol) and compounds on PEG sublayer were heated in a vacuum at 80°C before use to remove the moisture traces. IR spectra were recorded on a spectrophotometer IR-Spectrum one (PE), ^{1}H NMR spectra were registered on a spectrometer Varian AS 300 from solutions in $CDCl_3$, internal reference TMS. Thermogravimetric analyses were performed on a Perkin-Elmer analyzer. The qualitative analysis for chlorine was carried out as described in [11].

***tert*-Butyl piperazine-1-carboxylate (I)**. A solution of 32.73 g (0.15 mol) of di-*tert*-butyl dicarbonate in 50 ml of anhydrous CH_2Cl_2 was added dropwise within 20 min to a stirred solution of 25.0 g (0.3 mol) of anhydrous piperazine in 300 ml of anhydrous CH_2Cl_2. The separated precipitate was filtered off and washed with dichloromethane (3 × 100 ml). The solvent was removed in a vacuum, the colorless oily residue was dissolved in 300 ml of water and filtered to remove the insoluble bis(*tert*-butoxycarbonyl) derivative. The water filtrate was saturated with K_2CO_3 and extracted with ethyl ether (3×100 ml). The solvent was removed in a vacuum. Yield 21.3 g (64%), viscous oily substance of sufficient purity. IR spectrum, ν, cm^{-1}: 3321, 1710. ^{1}H NMR spectrum, δ, ppm: 1.47 s [9H, $C(CH_3)_3$], 2.80–2.90 m (2H, $HNCH_2$), 3.08–3.17 m (2H, CH_2NBoc).

The removal of protective Boc-group. General procedure. In 30 ml of ethyl acetate was dissolved 35.5 ml (0.05 mol) of acetyl chloride, and the solution was added dropwise to a solution of 8.3 mmol of polymer protected with N-Boc-group in 56 ml of methanol; thus formed a solution of 5 mol l^{-1} of HCl in methanol. The mixture was stirred at room temperature for 40 min. On completion of the reaction to the solution was added triethylamine to pH 7. The solution was concentrated in a vacuum, and the residue was recrystallized from cold ethyl ether (100 ml Et_2O per 1 g of polymer), washed with cold ethyl ether (3 × 100 ml) to give the product with removed protective Boc-group.

Dichlorotriazine on PEG sublayer (G 0.5). To 40 ml of benzene containing 1 mg of 1,10-phenanthroline as indicator was added under nitrogen atmosphere 2 ml of 5 M butyllithium solution in hexane. The bright-orange solution obtained was titrated with a solution of 10.0 g of PEG 3400 in 100 ml of benzene till yellow color in the final point indicating a slight excess of PEG. This solution was added dropwise to a solution of 5.42 g (29 mmol) of trichlorotriazine in 150 ml of benzene, and the reaction mixture was stirred at room temperature for 1 h. On evaporating the solvent the residue was dissolved in 200 ml of CH_2Cl_2 and washed with water (3×25 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in a vacuum; the residue was recrystallized from 500 ml of cold Et_2O and washed with cold Et_2O (3 × 100 ml). We obtained 10.10 g (94%) of G 0.5 that was subjected to TLC (eluent EtOAc–petroleum ether, 1 : 4) to prove that it contained no low-molecular reagents. IR spectrum, ν, cm^{-1}: 2884, 1530, 1111. ^{1}H NMR spectrum, δ, ppm: 3.4–3.6 m (1H, PEG), 3.8–4.0 m ($PEG–OCH_2CH_2OC_3N_3Cl_2$). Cl 3.7%.

Dendrimer on PEG sublayer (G 1.0). In 200 ml of acetonitrile was dissolved 10.0 g of dendrimer G 0.5 and 6.04 g (32.4 mmol) of substituted piperazine **II**, to the mixture was added 3.43 g (32.4 mmol) of Na_2CO_3, and the reaction mixture was boiled at stirring for 12 h. On evaporation of the solvent the residue was dissolved in 200 ml of CH_2Cl_2 and washed with water (3×50 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in a vacuum; the residue was recrystallized from 500 ml of cold Et_2O and washed with cold Et_2O (3 × 100 ml). We obtained N-Boc-protected polymer. IR spectrum, ν, cm^{-1}: 1710, 1530. ^{1}H NMR spectrum, δ, ppm: 1.47 s [9H, $C(CH_3)_3$], 2.8–2.9 m (2H, $NHCH_2$), 3.02–3.15 m (2H, CH_2NBoc), 3.4–3.7 s (1H, PEG).

Then the protective Boc-group was removed. We obtained 8.53 g (81%) of G 1.0 that was subjected to TLC (eluent EtOAc–petroleum ether, 1:4) to prove that it contained no low-molecular reagents. IR spectrum, ν, cm^{-1}: 3321, 2884, 1530, 1140, 1111. ^{1}H NMR spectrum, δ, ppm: 1.9–2.1 m (NH), 2.7–2.8 m (1H, CH_2), 3.1–3.2 m (1H, CH_2), 3.4–3.6 s (1H, PEG), 3.8–4.0 m (1H, $PEG–OCH_2CH_2OC_3N_3$). Cl 0.2%.

Dendrimer on PEG sublayer (G 1.5). A mixture of 4.67 γ (25.3 mmol) of compound **I** and 6.0 ml (25.3 mmol) of diisopropylethylamine was added to 100 ml of $CHCl_3$ and it was stirred at 0°C. 8.0 g of dendrimer G 1.0 was dissolved in 50 ml of $CHCl_3$, and this solution was added dropwise to the above mixture maintaining the temperature below 5°C for 1 h, then the reaction mixture was stirred for 4 h at room temperature and afterwards it was washed with water (3 × 50 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in a vacuum; the residue was recrystallized from cold Et_2O and washed with cold Et_2O (3 × 100 ml). Yield 7.66 g (83%) of G 1.5 that was subjected to TLC (eluent EtOAc–petroleum ether, 1 : 4) to prove that it contained no low-molecular reagents. IR spectrum, ν, cm^{-1}: 2884, 1530, 1111, 1071. ^{1}H NMR spectrum, δ, ppm: 3.2–3.3 m (1H, CH_2), 3.4–3.6 m (1H, PEG), 3.8–4.0 m (1H, $PEG–OCH_2CH_2OC_3N_3$). Cl 6.0%.

Dendrimers G 2.0 and G 3.0 on PEG sublayer were synthesized analogously to dendrimer G 1.0 on PEG sublayer, and dendrimer G 2.5 on PEG sublayer, similarly to dendrimer G 1.5 on PEG sublayer.

The study was carried out under a financial support of National Foundation for Natural Sciences of China (№ 20772026).

REFERENCES

1. Toy, P.H. and Janda, K.D., *Acc. Chem. Res.* 2000, vol. 33, p. 546.
2. Chen, Z.X., Yue, G.Z., Lu, C.F., and Yang, G.C., *Synlett.* 2004, vol. 7, p. 1231.
3. Chen, Z.X., Yang, G.C., Zhang, Z.J., and W,ang D., *Synthesis*. 2001, p. 1483.
4. Zhang, H.Q., Yang, G.C., Chen, J.N., and Chen, Z.X., *Synthesis*. 2004, p. 3055.
5. Chen, Z.X., Yang, G.C., and Zhang, Z.J., *Synth. Commun.* 2003, vol. 33, p. 729.
6. Knischka, R., Lutz, P.J., Sunder, A., Mulhaupt, R., and Frey, H., *Macromolecules*, 2000, vol. 33, p. 315.
7. Fishman, A., Farrah, M.E., Zhong, J.H., Paramanantham, S., Carrera, C., and Lee-Ruff, E., *J. Org. Chem.* 2003, vol. 68, p. 9843.
8. Lu, C.F., Xie, C., Chen, Z.X., and Yang, G.C., *React. Funct. Polym.* 2006, vol. 66, p. 952.
9. Xie, C., Lu, C.F., Chen, Z.X., and Yang, G.C., *Chin. J. Chem.* 2006, vol. 24, p. 585.
10. Gustafson, G.R., Baldion, C.M., O'Donnell, M.E., and Sheldon, A., *Tetrahedron,* 1998, vol. 54, p.v4051.
11. *Lanzhou University. Quantitive Microanalysis of Organic Compaunds*, Beijing: Science Press, 1978.