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SG1-Functionalized Peptides as Precursors for Polymer−Peptide Conjugates: A Straightforward Approach

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ABSTRACT: We report here a straightforward route to polymer−peptide conjugates via the convenient synthesis of SG1-functionalized peptides able to initiate nitroxide-mediated polymerization (NMP). The NMP initiator SG1-functionalized peptide (SG1-GGGWIKVAV) was prepared by solid-phase peptide synthesis (SPPS) using an automated synthesizer, with a last step consisting of reaction between the carboxylic acid function of the MAMA-SG1 (BlocBuilder) alkoxyamine with the peptide terminal amine in the presence of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) as coupling agent. The resulting SG1-functionalized resin-attached peptide was used to perform the controlled NMP of styrene, leading after trifluoroacetic acid cleavage to the corresponding polystyrene−peptide conjugate. The latter was thoroughly characterized by UV spectrometry, gel permeation chromatography (GPC), ^{1}H NMR, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Introduction

Peptide or protein−synthetic polymer conjugates have received growing interest in the past decades because of their potential not only regarding biorelated applications such as drug delivery[1,2] and tissue engineering[3] but also for nanotechnologies area, with interesting properties of nanoscale self-assembly, as reported, for example, for certain peptide−polystyrene conjugates.[4] Initially, most of the studies concerned the poly(ethylene glycol) (PEG)-based bioconjugates,[2] which were efficient at ensuring an enhanced bioavailability of the polypeptide drugs. Recent advances in polymer synthesis, particularly in the field of controlled/living radical polymerization (CRP) techniques such as atom transfer radical polymerization (ATRP), nitroxide-mediated polymerization (NMP), and reversible addition−fragmentation chain transfer (RAFT), stimulated the development of novel well-defined vinyl polymer-based bioconjugates.[5−8] Besides the strategy of covalent coupling of adequately end-functionalized polymers with suitable reactive functions of the peptide chain,[9,10] a powerful approach is to initiate the polymerization directly from the resin-bound peptide. This requires the functionalization of the peptide chain-end with the suitable initiating moiety depending on the kind of CRP envisioned. In previous studies, peptide-based ATRP initiators[11,12] and RAFT agents[13,14] were successfully synthesized and used to achieve vinyl polymer−peptide conjugates. 2,2,5-Trimethyl-4-phenyl-3-azahexane-3-oxy (TIPNO)-functionalized peptide initiators were also successfully prepared by Wooley et al.[15,16] to prepare polystyrene/poly(acrylic acid)-based conjugates, proving the potency of the NMP approach for bioconjugate preparation. However, the limitation of this latter approach particularly relies on the multistep process required for both the preparation of the TIPNO functional alkoxyamine[17] and its attachment to the peptide.[15] There is consequently a need for a straightforward route to peptide-based NMP initiators to make them as attractive as ATRP or RAFT ones that can be easily obtained through reaction of 2-bromo isobuyryl bromide[16] or carboxylic-acid-functionalized trithiocarbonate[14] compounds, respectively, with peptide terminal amine. Here we present a versatile method to achieve SG1-functionalized resin-attached peptides, based on the reaction of the *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)hydroxylamine, so-called MAMA-SG1 alkoxyamine developed in our group[18] (and commercially referred as BlocBuilder) with the peptide terminal amine as the last step of the solid-phase peptide synthesis, for further preparation of polymer−peptide conjugates.

Experimental Section

Materials. Fmoc amide resin (0.7 mmol g^{-1}) was purchased from Applied Biosystems (Foster City, CA). Fmoc amino acids were from Novabiochem (Switzerland). Styrene (99%), trifluoroacetic acid (TFA, 99%), 1,2-ethanedithiol (EDT, 98%), and diisopropylethylamine (DIPEA, 99%) were purchased from Aldrich. MAMA-SG1 (BlocBuilder, >99%) was kindly provided by Arkema (France). Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP, 99.5%) was from Iris Biotech GmbH (Germany). All solvents used were of synthesis grade and used as received.

Synthesis of SG1-Gly Alkoxyamine. MAMA-SG1 (1.0 g, 2.6 mmol), amide-protected glycine hydrochloride (0.44 g, 4 mmol, 1.5 equiv), PyBOP (2.1 g, 4 mmol, 1.5 equiv), and dichloromethane (10 mL) were introduced in a round-bottomed flask, and the dispersion was deoxygenated for 20 min by argon bubbling. DIPEA (1.35 mL, 7.8 mmol, 3 equiv) was then added with a syringe through a septum. The mixture was stirred at room temperature for 1.5 h. The mixture was then washed with successively a 5 wt % hydrochloric acid (HCl) solution, NaCl-saturated aqueous solution, $NaHCO_3$-saturated solution, NaCl-saturated

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solution, and finally HCl 5 w% solution, then dried on magnesium sulfate, and filtrated. After evaporation of dichloromethane, the product was precipitated in ethyl acetate (yield: 45%, 0.51 g). ^{1}H NMR ($CDCl_3$, δ): 1.09 (s, 9H, C−C(CH_3)$_3$), 1.22 (s, 9H, N−C−(CH_3)$_3$), 1.31 (t, 3H, O−CH_2−CH_3), 1.35 (t, 3H, O−CH_2−CH_3), 1.55 (s, 3H, C−CH_3), 1.75 (s, 3H, C−CH_3), 3.38 (d, J(H,P) 28 Hz, 1H, N−CH−P), 3.95−4.35 (m, 6H, P−(O−CH_2−CH_3)$_2$, NH−CH_2−CO). ^{31}P NMR ($CDCl_3$, δ): 27.78. ESI-MS: m/z 436.3 $[M-H]^-$ (negative ion mode), m/z 438.3 $[M + H]^+$ and m/z 460.3 $[M + Na]^+$ (positive ion mode). For the following of the kinetics by ^{31}P NMR, the reaction was performed directly inside the NMR tube in $CDCl_3$, in the same relative amounts of reactants and coupling agents, as mentioned above (0.25 g MAMA-SG1 scale).

Synthesis of SG1-Functionalized GGGWIKVAV Peptide Alkoxyamine. Stepwise elongation of the peptide was carried out on Fmoc amide resin (0.25 mmol, 0.7 mmol.g^{-1}) using the Fmoc/*t*-Bu chemistry with an automated synthesizer (model 433A, Applied Biosystems).[19] Trifunctional amino acids tryptophan and lysine were side-chain-protected with Boc. *N*-α-Amino groups were deprotected by treatment with 18 and 20% piperidine/*N*-methylpyrrolidone for 3 and 8 min, respectively. The Fmoc-amino acid derivatives were coupled (20 min) as their hydroxybenzotriazole active ester in *N*-methylpyrrolidone (four-fold excess). The 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/hydroxybenzotriazole (HBTU/HOBt) coupling agents in combination with diisopropylethylamine (DIPEA) were used. The reaction between the last glycine residue of the peptide and the MAMA-SG1 (three-fold excess) was performed using the PyBOP coupling agent (three-fold excess) and the DIPEA (three-fold excess) for 2 h. The obtained SG1-functionalized peptide was kept on the resin for further NMP initiation. A fraction was cleaved from resin, for peptide analysis, with TFA (1 mL, 13 mmol) in the presence of EDT (50 μL, 0.6 mmol). After resin filtration, the peptide was precipitated in diethyl ether and dried under vacuum. ESI-MS m/z 1192.6 $[M+H]^+$ and m/z 596.8 $[M+2H]^{2+}$ (M = 1191.7 g·mol^{-1}, $C_{55}H_{94}N_{13}O_{14}P$, loss of *t*-Bu group next to the nitrogen of the aminoxy). ^{31}P NMR ($CDCl_3$ + TFA, δ): 29.58.

Synthesis of Peptide−Polystyrene Conjugate. The SG1 resin peptide (180 mg) and styrene (5.6 g, 53.8 mmol) were introduced in two-necked round-bottomed flasks, fitted with septum, condenser, and deoxygenated for 20 min by argon bubbling. The mixture was then heated to 120 °C under stirring (ramp from room temperature to 120 °C: ∼20 min). At different polymerization times (t = 0 corresponding to the starting ramp temperature), samples were extracted from the mixture. For each sample, the resin was filtered and washed with tetrahydrofuran (THF). TFA (1 mL) and EDT (50 μL) were then added to the resin, and the mixture was stirred overnight for cleavage. After filtration and washing with THF, the polystyrene−peptide conjugate (in the filtrate) was precipitated in cold methanol.

Analytical Techniques. ^{31}P NMR (121.59 MHz) and ^{1}H NMR (300 MHz) analyses were performed on a Bruker Advance300 spectrometer in $CDCl_3$. Electrospray ionization mass spectrometry (ESI-MS) analyses were performed using a mass spectrometer 3200 QTRAP (Applied Biosystems SCIEX, Concord, ON, Canada) equipped with a pneumatically assisted electrospray ionization source. The sample was dissolved in methanol and then diluted (dilution factor 1/1000) in a methanolic solution of ammonium acetate (3 mmol L^{-1}). The sample solution was infused in the ionization source at a 5 μL min^{-1} flow rate. Ionization was performed in either positive or negative mode under the following conditions: electrospray voltage (ISV): 5500 V (or −4200 V); orifice voltage (OR): 20 V (or −20 V); nebulizing gas flow pressure (air): 20 psi. The mass spectrum was obtained using a quadrupole mass analyzer. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis was performed using a Bruker Autoflex I mass spectrometer (Bruker Daltonics, Leibzig, Germany) equipped with a nitrogen laser emitting at 337 nm, a single-stage pulsed ion extraction source, and dual microchannel plate detectors. Data acquisition was performed in the reflectron mode. Positive ion mode was used for all analyses, using a pulse frequency of 10 Hz and an accelerating voltage of 19 kV. The PS−peptide (30 μL) solution at 2 g·L^{-1} in CH_2Cl_2/TFA (95/5 v/v) was mixed with 40 μL of matrix (trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]-malonitrile, DCTB) at 10.3 g·L^{-1} in THF and 1 μL of this mixture was placed on the target for analysis. Analyses performed with different salts showed that the observed peaks could be assigned to polymer molecules adducted with residual Na^+ cations. UV spectra were recorded in dichloromethane between 240 and 350 nm on a Cary 50 Varian spectrometer. Polymer molecular weights and polydispersities were determined by gel permeation chromatography (GPC) on a system comprising a Waters 515 HPLC pump equipped with three Styragel columns used in series, HR 3 (4.6 mm ×300 mm, 5 μm bead size, separation between 500 and 30 000 g·mol^{-1}), HR 4 (4.6 mm ×300 mm, 5 μm bead size, separation between 5000 and 600 000 g·mol^{-1}), and HR 5 (4.6 mm ×300 mm, 5 μm bead size, separation between 2000

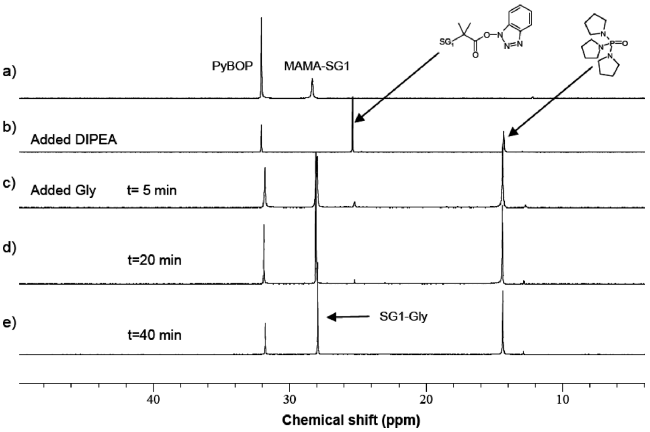
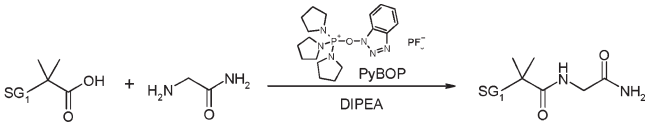


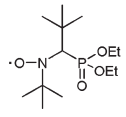
Figure 1. Monitoring of the kinetics of coupling between *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)hydroxylamine (MAMA-SG1) and glycine with benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) as coupling agent (in the presence of diispropylethylamine (DIPEA) by ^{31}P NMR (in $CDCl_3$): (a) reference MAMA-SG1+PyBOP; (b) reference MAMA-SG1+PyBOP+DIPEA base; (c)MAMA-SG1+PyBOP+DIPEA base+Gly after (c) 5, (d) 20, and (e) 40 min.

Scheme 1. Model Reaction between *N*-(2-Methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)-hydroxylamine (MAMA-SG1) and Glycine Using Benzotriazol-1-yl-oxytripyrrolidinophosphonium Hexafluorophosphate (PyBOP) As Coupling Agent (Glycine Is under Amido-Protected Form)



MAMA-SG1 Gly SG1-Gly

SG1:



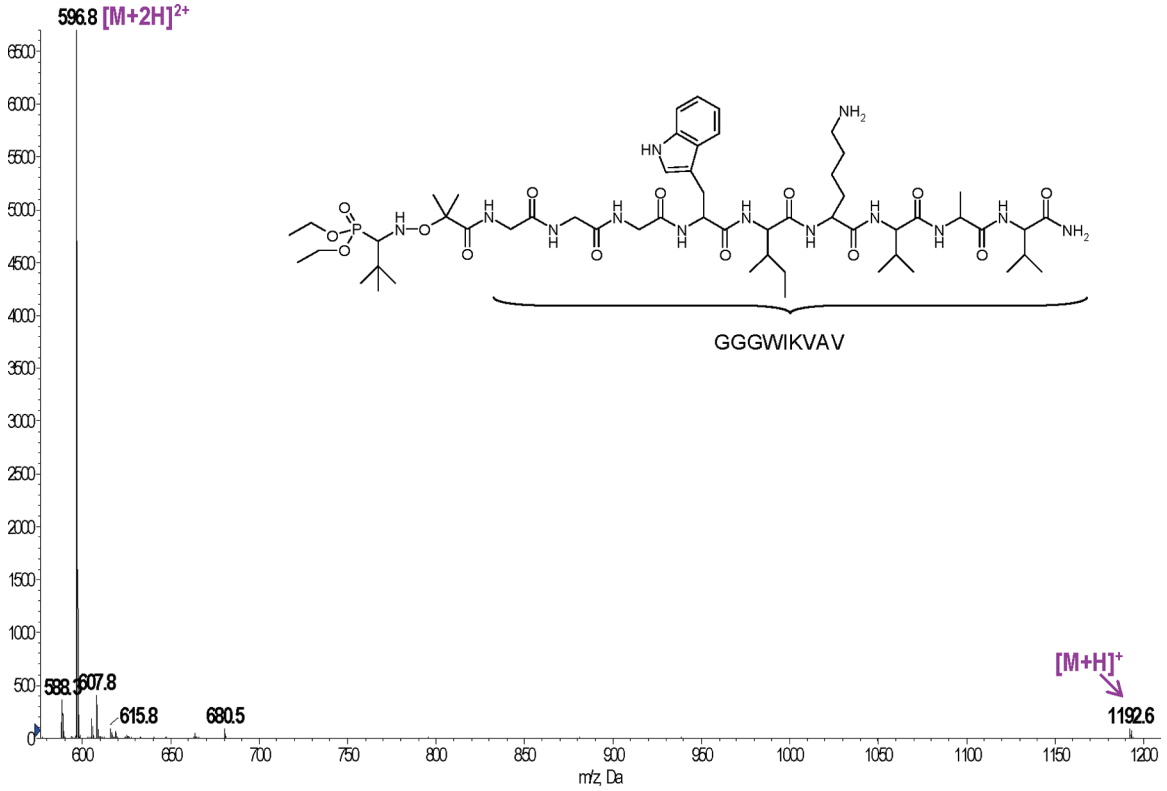
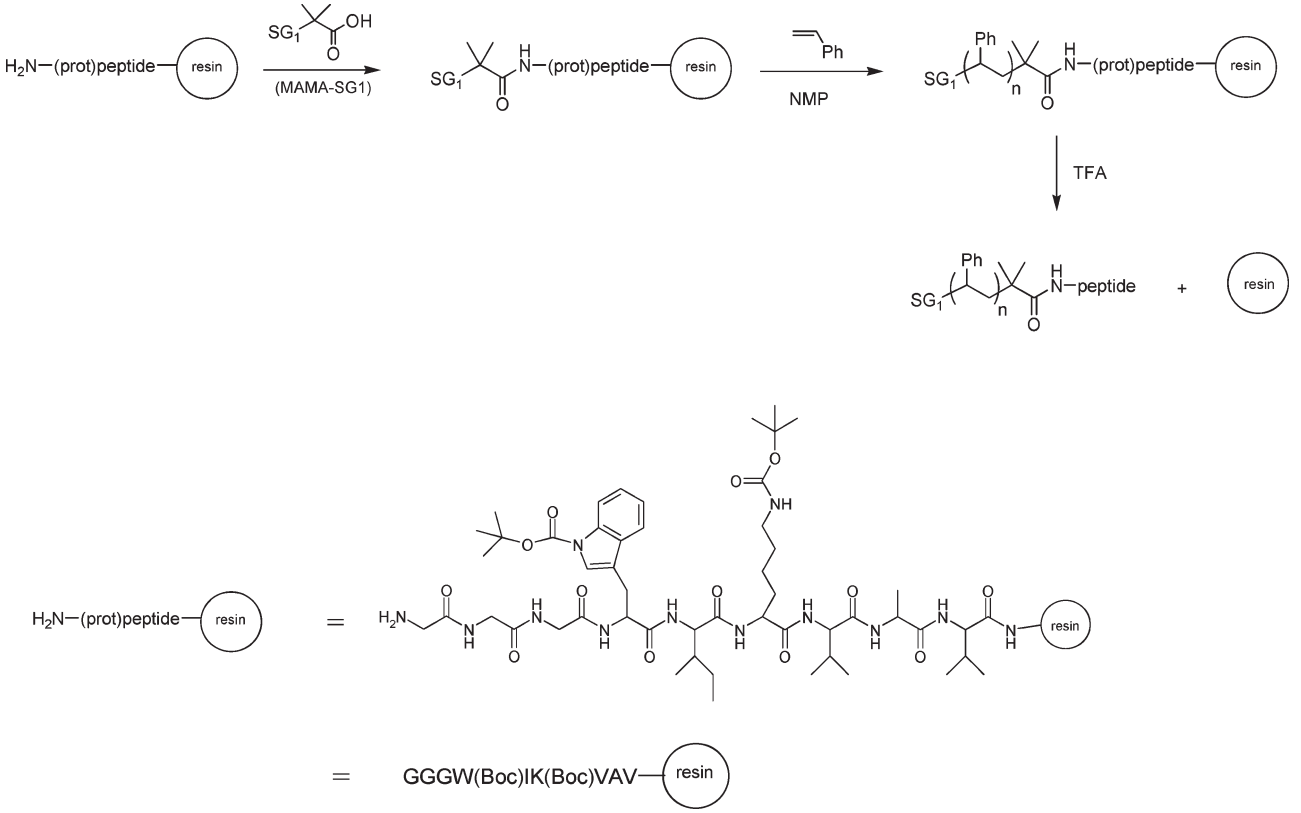


Figure 2. Electrospray ionization mass spectrometry (ESI-MS) spectrum of the SG1-functionalized peptide SG1-GGGWIKVAV (after loss of the *t*-Bu group due to trifluoroacetic acid (TFA) cleavage from the resin, $M = 1191.7\ g \cdot mol^{-1}$).

Scheme 2. Strategy of Preparation of SG1-Functionalized Resin Peptide for Nitroxide-Mediated Polymerization (NMP) Initiation; (Prot)peptide: GGGW(Boc)IK(Boc)VAV, with the *N*-Boc-Protected Lysine and Tryptophan ($M = 1099.35\ g \cdot mol^{-1}$); Peptide: GGGWIKVAV ($M = 885.09\ g \cdot mol^{-1}$)



and $4 \times 10^6\ g \cdot mol^{-1}$)), an oven at 30 °C, and two detectors, UV/vis (Waters 486) and RI (Waters 2414). THF was the mobile phase, with a flow rate of 1 $mL.min^{-1}$. Calibration was based on polystyrene standards.

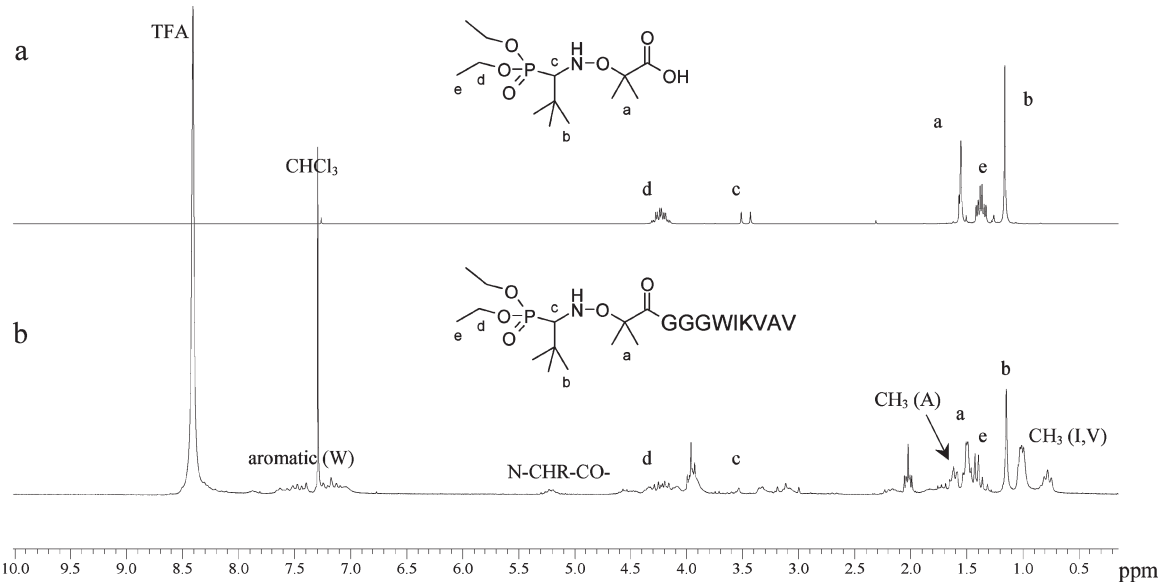


Figure 3. ^{1}H NMR ($CDCl_3$, 2 vol % trifluoroacetic acid (TFA)) spectra of *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)hydroxylamine (MAMA-SG1) after 1.5 h in TFA as a reference (a) and SG1-GGGWIKVAV functionalized peptide after TFA cleavage (b).

Results and Discussion

Study of the Reactivity of the MAMA-SG1 Alkoxyamine with Amines. Our strategy for preparation of polymer−peptide conjugates relies on the transformation of the terminal amine of the resin bound peptide with MAMA-SG1 alkoxyamine via its carboxylic acid moiety. This yields an SG1-terminated peptide that can initiate NMP. In a preliminary study, we first checked that the MAMA-SG1, through its carboxylic acid function, could efficiently react with the last amino acid residue (namely glycine) of the synthesized peptide. Indeed, the carboxylic acid function of the MAMA-SG1 is rather hindered, which renders the reactions with amino-containing compounds difficult with classical coupling agents.[20] A particularly efficient one, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP, 1.5 equiv), was then tested for the reaction between MAMA-SG1 (1 equiv) and glycine amino-acid residue (1.5 equiv) as a model (Scheme 1) in the presence of DIPEA (3 equiv) as a base. The coupling kinetics could be nicely monitored by ^{31}P NMR, performing the reaction directly in the NMR tube (in $CDCl_3$). The reaction proceeds through the quantitative formation of an activated benzatriazol ester of the MAMA-SG1 ($\delta \sim 25$) under basic conditions and a phosphine (δ 14.2), as shown in Figure 1b, followed by the nucleophilic attack of the amine of the glycine, leading to the desired SG1-Gly alkoxyamine (δ 27.8), in nearly quantitative yields after only 20 min (Figure 1d). Bigger scale reaction was performed to purify the product, which was identified by ^{1}H NMR and ESI-MS as being the expected alkoxyamine. It is to point out that the reaction of MAMA-SG1 with a more hindered amine, namely, *t*-butyl amine, was shown to be as fast and quantitative as that with glycine, showing the efficiency of the PyBOP coupling agent.

Synthesis of the SG1-Functionalized Peptide (SG1-GGGWIKVAV). The previous results regarding the high and fast coupling efficiency between MAMA-SG1 and the Gly amino acid residue with PyBOP as coupling agent prompted us to perform the coupling of the MAMA-SG1 on a resin-attached model peptide as the last step of the peptide synthesis (Scheme 2, first step). We chose GGGWIKVAV, which contains the IKVAV laminin-derived sequence described as a cell adhesion promoter. This strategy allows the preparation of the SG1-functionalized peptide able to initiate NMP.

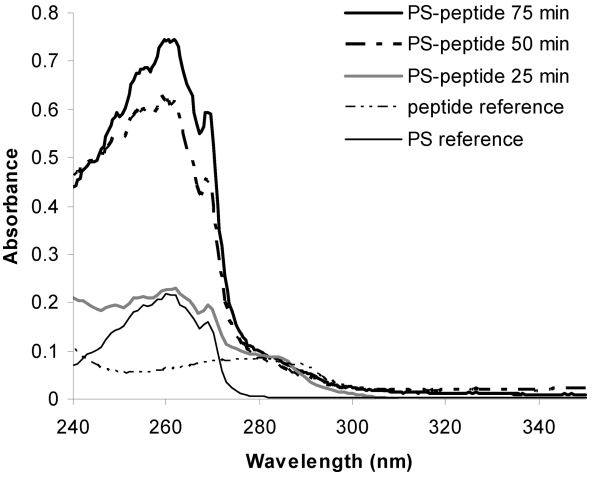


Figure 4. UV spectra in dichloromethane of the polystyrene-GGGWIKVAV peptide conjugates obtained at different times of polymerization (bulk, 120 °C). Each sample was obtained after resin washing with THF, TFA cleavage, filtration, and precipitation in methanol. (UV spectra of SG1-GGGWIKVAV peptide and standard polystyrene are given as a reference.)

The peptide was synthesized according the Fmoc/*t*-Bu chemistry using a Fmoc amide resin. The reaction between the MAMA-SG1 and the last glycine amine residue of the peptide (after Fmoc deprotection) with PyBOP was quantitative in <1 h, as attested by the ninhydrin test. A small amount of the obtained SG1-functionalized peptide was cleaved from resin (TFA/EDT) for characterization. ESI-MS analysis showed the presence of the expected product (Figure 2), which is characterized by the loss of the *t*-butyl group adjacent to the nitrogen of the SG1 aminoxy function. Indeed, it was previously shown in our lab that SG1-based alkoxyamines loose the *t*-Bu moiety adjacent to the nitrogen in the presence of strong acids such as TFA.[21] In Figure 3a representing the ^{1}H NMR reference spectrum of the MAMA-SG1 after 1.5 h in TFA, one single *t*-Bu proton

singlet (b, δ 1.09) is indeed observed, whereas the two *t*-Bu proton singlets of the SG1 moiety are normally clearly observed for the intact MAMA-SG1 (at δ 1.09 and 1.22). For the SG1-functionalized peptide after TFA cleavage (Figure 3b), the same unique *t*-Bu singlet was observed, confirming the total loss of the *t*-Bu adjacent to nitrogen of SG1 moiety. Furthermore, the ^{1}H NMR spectrum of the peptide showed all signals relative to the alkoxyamine moiety and the signals relative to the amino acids of the peptide, indicating the presence of the (*t*-Bu excepted) SG1-functionalized peptide and corroborating the ESI-MS analysis. Finally, the ^{31}P NMR spectrum showed one single peak at 29.6 ppm, confirming the presence of the (*t*-Bu excepted) SG1 nitroxide fragment on the peptide and a quite good compound purity. The loss of one *t*-Bu group on the SG1-functionalized peptide after TFA cleavage from resin was not problematic because we further envisioned initiation of NMP from the resin-attached peptide. Regarding experimental procedure and conjugate purity, this approach is more attractive than the one consisting of cleaving the peptide from the resin before performing NMP.

Table 1. Evolution of the Polystyrene−Peptide Molecular Weights Determined by Gel Permeation Chromatography (GPC), ^{1}H NMR, and Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) Mass Spectrometry along Polymerization[a] (Bulk, 120 °C)

polymerization time (min)	M_n [GPC] (PDI) (g·mol^{-1})	M_n [NMR] (g·mol^{-1})	M_n [MALDI TOF] (PDI) (g·mol^{-1})
25	n.d.	3200	2120 (1.05)
50	20 500 (1.32)	n.d.	n.d.
75	25 000 (1.22)	n.d.	n.d.

[a] Each sample was obtained after resin washing with THF, TFA cleavage, filtration, and precipitation in methanol.

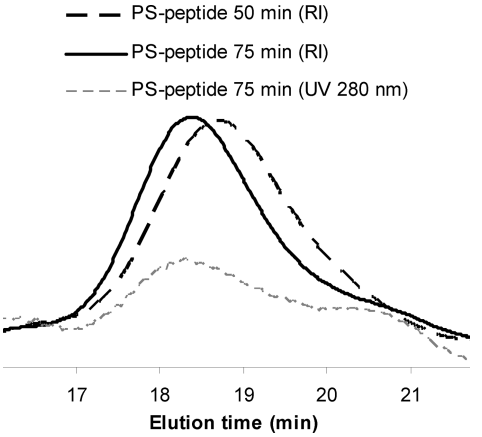


Figure 5. Gel permeation chromatography (GPC) traces (THF eluent, RI, or UV detection) of the polystyrene-GGGWIKVAV peptide conjugates obtained at different times of polymerization (bulk, 120 °C). Each sample was obtained after resin washing with THF, TFA cleavage, filtration, and precipitation in methanol.

NMP from SG1-Functionalized Peptide Bound to Resin. The NMP of styrene from the SG1 resin-attached peptide was performed in bulk at 120 °C (Scheme 2, second step). In Figure 4 are presented the UV spectra (in dichloromethane) of the conjugates obtained at different times of the polymerization. Each conjugate sample was recovered after resin washing (THF), TFA cleavage (Scheme 2, last step), filtration, and precipitation (of the filtrate) in MeOH. Washing carefully the resin with THF before performing TFA cleavage allows the removal of side polystyrene chains, which could arise from thermal polymerization and thus ensures a quite good purity for the conjugate. The UV spectra evidenced the typical absorption peak of the tryptophan of the peptide (~280 nm) and those relative to the polystyrene, as expected for the conjugate. Furthermore, the ratio of the $OD_{conj\text{-}PS}$ at 262 nm to the $OD_{conj\text{-}trp}$ at 280 nm increased with the polymerization time, indicating an increase in the PS chain length during polymerization. These results strongly suggest the controlled character of the NMP.

GPC analysis in THF was performed on the corresponding samples (Table 1, Figure 5), except for the sample collected after 25 min of polymerization. This conjugate indeed presents a low molecular weight (as showed later) and was not soluble in THF (neither in DMF), probably

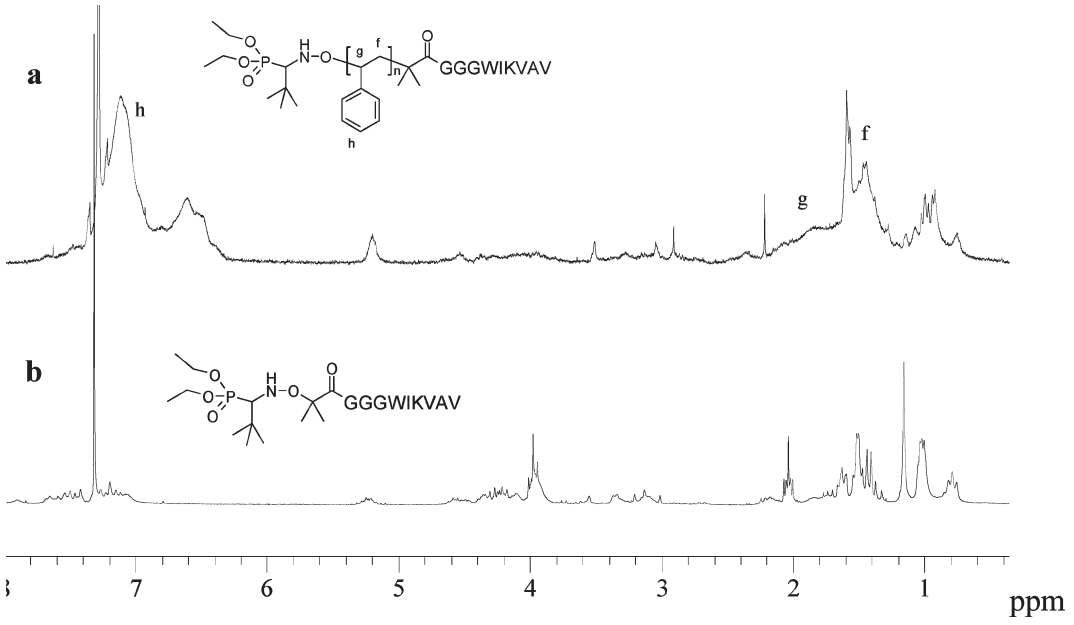


Figure 6. ^{1}H NMR ($CDCl_3$, 2 vol % TFA) spectra of the PS-peptide conjugate obtained at 25 min polymerization (bulk, 120 °C) after resin washing with THF, TFA cleavage, filtration, and precipitation in methanol (a) and peptide−SG1 precursor (after resin cleavage) as reference (b); peptide peak assignments were detailed in Figure 3.

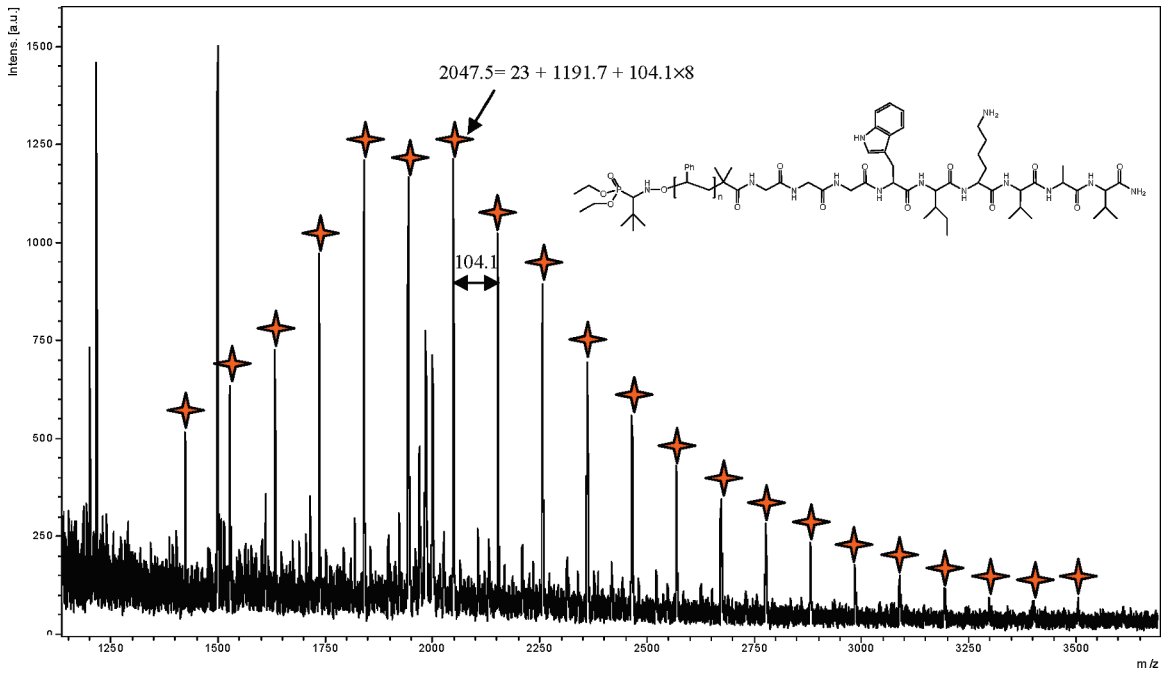


Figure 7. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry analysis of the polystyrene−peptide conjugate obtained at 25 min polymerization (bulk, 120 °C), after resin washing with THF, TFA cleavage, filtration, and precipitation in methanol. The observed peaks correspond to polymer species charged with residual sodium ion (23 g·mol^{-1}).

because of the strong contribution of the peptide in the whole conjugate (peptide is not soluble in THF and DMF). The M_n values obtained from GPC (Table 1) supported the UV analysis regarding increasing molecular weights with polymerization time. The polydispersity index (PDI) values were rather low (1.2 to 1.3), indicating a relatively good control of the PS chain growth. The use of double detection by both UV at 280 nm and refractive index in GPC (Figure 5, sample corresponding to 75 min polymerization) further evidenced the presence of the expected bioconjugate, even if a slight shouldering was observed at higher elution times.

^{1}H NMR analysis was performed on the purified PS-peptide conjugate obtained after 25 min of polymerization. As shown in Figure 6, the characteristic proton signals of both polystyrene and the peptide appeared. The molecular weight of the PS block could be calculated by integration calculation using the CH_3 peaks of the peptide (δ 0.6 to 1) and the phenyl protons of the polystyrene (δ 6.2 to 6.8) and was found to be ~2000 g·mol^{-1}, leading to a total molecular weight for the conjugate of 3200 g·mol^{-1}. Such NMR determination of the molecular weight was however not suitable for higher PS chain lengths, due to the weak intensity of the peptide signals. Finally, the structure of the polystyrene-peptide conjugate after 25 min polymerization was unambiguously confirmed by MALDI-TOF mass spectrometry, as shown in Figure 7. A narrow distribution of sodiated molecules $[M + Na]^+$ was obtained, with molecular weight such as $m_M = 1191.7 + 104.1 \times n$ ($2 < n < 21$), corresponding to the expected conjugate after TFA cleavage (i.e., loss of *t*-Bu group of the SG1 fragment). These results were consistent with the ESI results previously obtained for the SG1-based peptide initiator after TFA cleavage (Figure 2). It is to point out that the loss of the *t*-Bu group on the SG1 chain end of the final conjugate is not a drawback at all because it occurs only during final TFA cleavage from resin and does not affect the NMP process. This could even be beneficial for the final conjugate because this modified chain end is shown to be more stable (less thermolabile) than the net SG1 alkoxyamine moiety, as indicated here by the production of intact ionic species in MALDI, whereas the homolytic cleavage of the C−ON bond was systematically observed for SG1-terminated polymers.[22] The M_n calculated from the MALDI data was 2120 g·mol^{-1}, roughly corroborating that obtained from ^{1}H NMR analysis, and the M_w was found to be 2220 g·mol^{-1}, indicating a very low PDI (1.05, Table 1).

Conclusions

In this work, an SG1-functionalized peptide (SG1-GGG-WIKVAV) was prepared by simple reaction of the carboxylic acid function of the MAMA-SG1 with the glycine peptide terminal amine as the last step of the SPPS. The latter was characterized by ESI-MS and NMR (after TFA cleavage) and further used as an initiator for NMP of styrene to obtain the PS−peptide conjugates in a controlled manner. These results show the versatility of our approach based on the use of MAMA-SG1 and NMP to achieve valuable resin-bound SG1-based peptide alkoxyamines for preparation of peptide−vinyl polymer conjugates. Further studies are ongoing for applying this strategy to the preparation of conjugates based on biocompatible polymers and bioactive peptides for biomaterial applications.

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