a concerted mechanism in which hydrogen incorporation takes place as the iodine atom leaves the methyl iodide molecule. It should be pointed out that this step is qualitatively different than that seen on clean surfaces and that even in the presence of surface hydrogen about 30% of the methyl iodide does react following the more conventional pathway where methane desorption is rate limiting.

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Efficient Method for the Preparation of Peptoids [Oligo(N-substituted glycines)] by Submonomer Solid-Phase Synthesis

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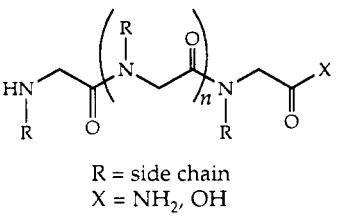
Oligomers of N-substituted glycines, or "peptoids", represent a new class of polymers (Figure 1) that are not found in nature, but are synthetically accessible and have been shown to possess significant biological activity and proteolytic stability.[1] We present here an efficient, automated solid-phase method for the synthesis of oligo(N-substituted glycines) (NSGs) which is general for a wide variety of side-chain substituents and allows the rapid synthesis of molecules of potential therapeutic interest.

The original method[1] for the synthesis of oligomeric NSGs is analogous to standard solid-phase methods for peptide synthesis. Specifically, the carboxylate of N^{α}-Fmoc-protected (and side-chain-protected) NSGs is activated and then coupled to the secondary amino group of the resin-bound peptoid chain. Removal of the Fmoc group is then followed by addition of the next monomer. Thus, oligomeric NSGs have been treated as condensation homopolymers of N-substituted glycine. A disadvantage of this approach, however, is the necessity of preparing suitable quantities of a diverse set of protected N-substituted glycine monomers.

In the method presented here, each N-substituted glycine monomer is assembled from two readily available "submonomers" in the course of extending the NSG polymer (Scheme I). Thus, oligomeric NSGs can also be considered to be alternating condensation copolymers of a haloacetic acid and a primary amine. As in the original method, the direction of polymer synthesis with the submonomers occurs in the carboxy to amino direction. The solid-phase assembly of each monomer, in the course of controlled polymer formation, eliminates the need for N^{α}-protected monomers, as only reactive side-chain functionalities need to be protected. The α-haloacetyl submonomer is common to all cycles of chain extension. Moreover, each RNH_2 submonomer is simpler in structure and many are commercially available; thus, oligo(NSG) synthesis is dramatically simplified.

The preparation of NSG oligomers by the submonomer method[2] in a solid-phase mode has been adapted to a robotic synthesizer.[3] Each cycle of monomer addition (Scheme I) consists of two steps, an acylation step and a nucleophilic displacement step—there is no N^{α}-deprotection step. The first step, acylation of a resin-bound secondary amine with a haloacetic acid,[4] uses a carbodiimide or other suitable carboxylate activation method. A haloacetyl halide could also be used. Acylation of a secondary amine can be difficult, especially when coupling a bulky amino acid. The new process is facilitated by the use of haloacetic acids which, in the presence of a carbodiimide, are potent acylating agents. The second step introduces the side chain by nucleophilic displacement of the halogen (as a resin-bound α-haloacetamide) with an excess of primary amine. The efficiency of the displacement is modulated by the choice of halide (e.g., I > Cl). Protection of carboxyl, thiol, amino, and other reactive side-chain functionalities is required to minimize undesired side reactions. However, the mild reactivity of some side-chain moieties toward displacement or acylation may allow their use without protection (e.g., indole, imidazole, and phenol).



R = side chain
X = NH_2, OH

Figure 1. Representative structure of an oligomeric N-substituted glycine. These polyamide structures differ from polypeptides in that the side chains are substituted on the nitrogen rather than the α-carbon.

Optimization of penta(NSG) synthesis was performed using combinations of chloro-, bromo-, and iodoacetic acids for the haloacetyl submonomer, with both aniline and cyclohexylamine for the RNH_2 submonomer. Bromoacetic acid and iodoacetic acid proved superior to chloroacetic acid in forming penta(*N*-phenylglycine) (79%, 83%, and <5% yields, respectively). All three haloacetyl compounds successfully gave the penta(*N*-cyclohexylglycine) oligomer in >75% yield. However, inclusion of 0.6 M *N*-hydroxybenzotriazole in the acylation reactions[6] yielded <5% of the penta(*N*-cyclohexylglycine) polymer. In further optimization studies, the molar concentration of amine was varied from 0.25 (4.0 equiv) to 2.5 M (40 equiv) for *n*-butylamine, cyclopropylamine, and diphenylethylamine using bromoacetic acid. Pentamers were obtained in >80% yield with *n*-butylamine and cyclopropylamine at concentrations ≥1.0 M and with diphenylethylamine at concentrations ≥2.5 M.

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‡ The Scripps Research Institute.

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(2) Oligomer syntheses were performed on a robotic synthesizer.[3] The syntheses were conducted with Rink amide polystyrene resin[7] (50 μmol, substitution level 0.45 mmol/g) to avoid diketopiperazine formation. Acylation reactions were performed by addition of bromoacetic acid (600 μmol, 83 mg) in DMF (0.83 mL), followed by addition of *N,N'*-diisopropylcarbodiimide (660 μmol, 103 μL) in DMF (170 μL). Reaction mixtures were agitated at room temperature for 30 min. Each acylation was repeated once. Displacement reactions were performed by addition of primary amine (2.0 mmol) as 2.5 M solutions in dimethyl sulfoxide (1.0 mL), followed by agitation for 2 h at room temperature. Optimization of displacement reactions was performed by varying amine concentrations from 0.25 to 2.5 M. Side-chain protecting groups were removed, and the oligomer was released from the resin support by treatment of the oligomer–resin with 95% trifluoroacetic acid in water (10 mL) for 20 min at room temperature, followed by filtration, dilution, and lyophilization.

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(5) Analytical HPLC was performed on a Rainin HPX system with a C4 reversed-phase HPLC column (Vydac, 25 cm × 4.6 mm) and a gradient elution (solvent A: H_2O/0.1% TFA; solvent B: CH_3CN/0.1% TFA; 10–75% B in 35 min).

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Scheme I. Solid-Phase Assembly of an N-Substituted Glycine from Two Submonomers

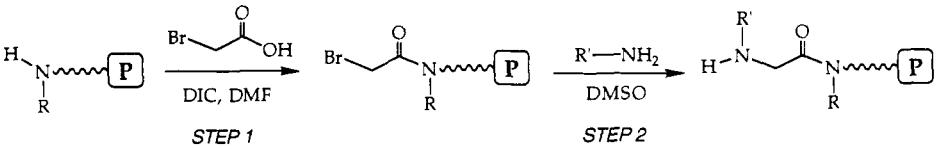
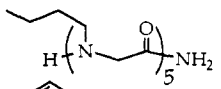
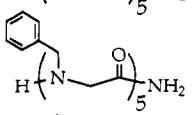
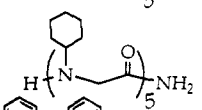
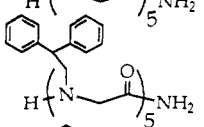
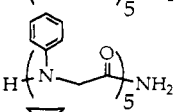
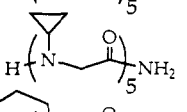
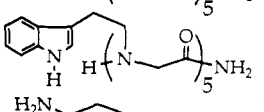
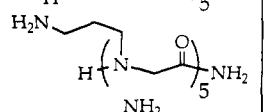
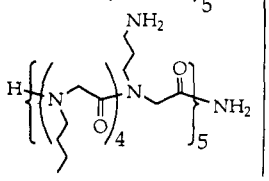


Table I. Oligo(N-Substituted Glycines) Prepared by the Submonomer Method

Oligomer	Crude product characteristics		
	purity (%) [a]	yield (%) [b]	mass (MH^+) [c]
	>85	90	583.5
	>85	74	753.2
	>85	79	713.4
	>85	70	1204.1
	>85	83	683.3
	>85	83	503.3
	>60	52	1018.4
	>85	63 [d]	588.4
	>65	86 [d]	2850.9

[a] Determined by HPLC. [b] Determined from dry weight. [c] Liquid-matrix secondary-ion mass spectrometry. [d] Made from Boc-NH-$(CH_2)_3NH_2$.

Using optimized synthetic conditions[2] eight penta(NSGs) were prepared by the submonomer method from a variety of amines, including poorly nucleophilic, sterically-hindered, and side-chain-protected amines. The purity, yields, and mass spectrometry data on the pentamers are shown in Table I. All compounds were successfully synthesized as established by mass spectrometry, with isolated crude yields between 52 and 90% and purities generally greater than 85% by HPLC.[5]

A 25-mer, $[(N\text{-butylglycine})_4(N\text{-(3-aminopropyl)glycine})]_5$, was synthesized by the submonomer method, thereby demonstrating the utility of this method for the preparation of longer oligomers. Mass spectroscopy confirmed the identity of this compound (MH^+ = 2850.9), which was obtained in 86% yield and 65% purity by HPLC.[5]

The efficient synthesis of a wide variety of oligomeric NSGs using robotic synthesis technology, as presented here, makes these polymers attractive candidates for the generation and rapid screening of diverse peptidomimetic libraries. The compatibility of this method with conventional peptide synthesis should allow the incorporation of novel structures into peptides. Furthermore, the solid-phase submonomer method should allow the efficient synthesis of a wide variety of novel N-substituted biopolymers.

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Bioorganometallic Chemistry. 1. Synthetic and Structural Studies in the Reactions of a Nucleobase and Several Nucleosides with a (η^5-Pentamethylcyclopentadienyl)rhodium Aqua Complex

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Interactions of metal complexes with DNA/RNA nucleobases, nucleosides, nucleotides, and oligonucleotides have been extensively studied in order to determine the mode of action of these metal complexes as a consequence of drug activity, as useful tools for molecular biology, and as regulators of gene expression.[1] The great majority of these bonding studies have been carried out with inorganic complexes,[2] while few have utilized organometallic compounds.[3]

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[†] Lawrence Berkeley Laboratory.
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