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Extended peptoids: a new class of oligomers based on aromatic building blocks

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Abstract—Peptoids (N-substituted polyglycines) represent a class of bioinspired oligomers that have unique physical and structural properties. Here, we report the construction of 'extended peptoids' based on aromatic building blocks, in which the *N*-alkylaminoacetyl group of the peptoid backbone has been replaced by an *N*-alkylaminomethylbenzoyl spacer. Both *meta*- and *para*-bromomethylbenzoic acids were synthesized, providing access to a new class of peptoids. Further, inclusion of hydrophilic side chains confers water solubility to these compounds, showing that, like simple peptoids, extended peptoids add an extra dimension to synthetic poly-amide oligomers with potential application in a variety of biological contexts.

Peptoids[1] (N-substituted glycines) represent an interesting class of biomimetic oligomers that are structurally related to peptides but have different biological[2,3] and conformational[4–6] properties. The submonomer method of peptoid synthesis introduced by Zuckermann et al.[7] allows for considerable diversity to be incorporated into the construction of peptoid libraries due to the large number of commercially available primary amines. The submonomer method has been applied extensively in the creation of peptoid libraries,[8–12] and it has shown great versatility in incorporating a diverse set of amines[13,14] and hydrazines.[15] The peptoid scaffold has been further modified to create ureapeptoids[16,17] and incorporate a variety of chemoselective functionalities.[18] The bulk of these studies, however, have preserved the haloacetic acid component while focusing on variations in the nucleophilic displacement step. Here, we report the solid-phase synthesis of a new class of peptoid-inspired biomimetics in which the haloacetic acid groups are replaced by either *meta*- or *para*-halomethylbenzoic acids (Fig. 1b). These extended peptoids add further geometric diversity to oligomers based on the peptoid concept.

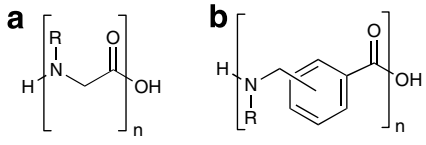

Figure 1. (a) General peptoid structure and (b) general extended peptoid structure.

The synthesis of *meta*-extended peptoids is shown in Scheme 1. *m*- and *p*-Bromomethylbenzoic acids were readily synthesized by bromination of the corresponding toluic acids.[19] All of the extended peptoids described here were synthesized on Wang resin (100–200 mesh, 1.1 mmol/g).[‡] The first bromomethylbenzoic acid submonomer was coupled to the resin with diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP) in dry DCM over 1 h at room temperature.

The addition of subsequent bromomethylbenzoic acid submonomers was performed without DMAP. Primary amines (5 equiv) were added in dry DMF and allowed to react at room temperature for 1 h. Elongation of the extended peptoid chain was performed by repeating the above steps over several cycles, followed by cleavage

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‡ Attempts to perform the synthesis on Rink amide resin resulted in significant impurities corresponding to nucleophilic attack by the Rink resin amine onto the bromomethyl group.

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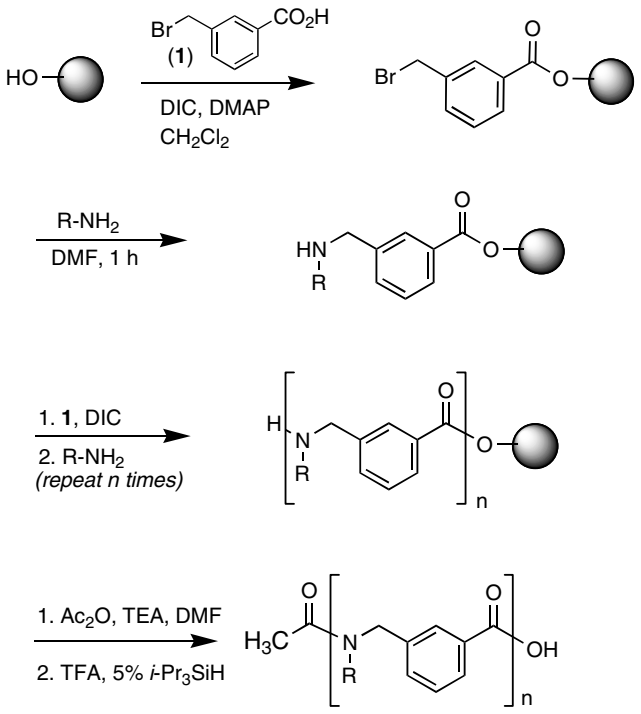
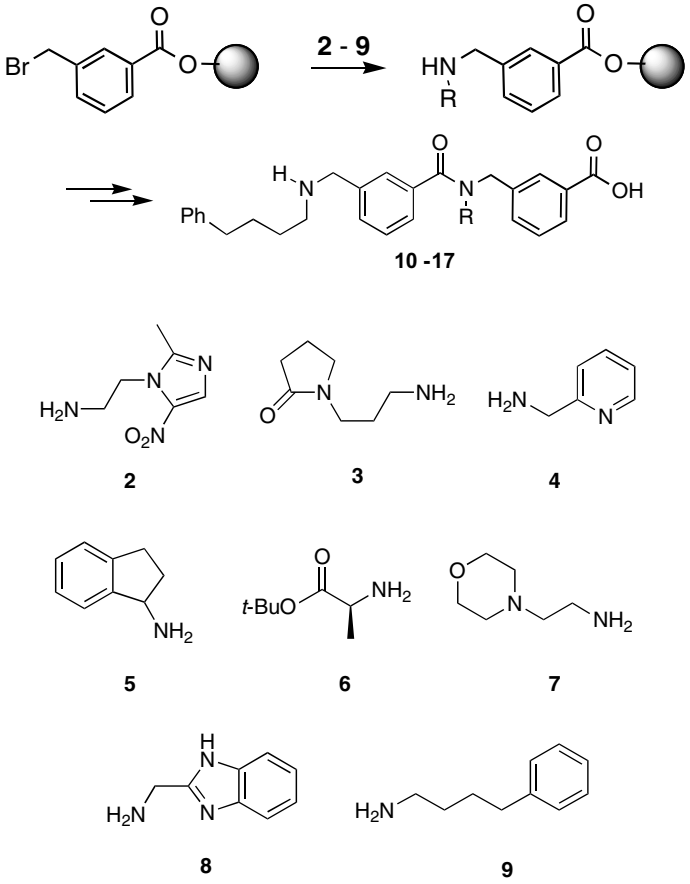


Scheme 1. General scheme for the solid-phase synthesis of *meta*-extended peptoids.

from the resin with trifluoroacetic acid (TFA) containing triisopropylsilane.

In order to establish the generality of the synthesis toward different primary amines, extended peptoid dimers were synthesized using amines **2**–**9**. Amine coupling and acylation efficiencies were assessed using model compounds with the test amine at the first monomer position and amine **9** in the second position (Scheme 2). Amines with a primary substituent coupled efficiently, whereas those with a secondary substituent (e.g., **5** and **6**) showed little to no reaction with the resin-bound bromomethyl benzoate ester (Table 1). Relatively electron deficient amines such as **2** and **8** also showed diminished coupling efficiencies at the amine addition step. This observation contrasts with reports in the literature on the efficient synthesis of similarly substituted peptoids. LC/MS analysis showed that the principal impurity among the poorly coupled amines was an end-capped deletion sequence, consistent with a failure at the nucleophilic displacement step. Despite these limitations, however, the high coupling efficiencies for amines **3**, **4**, **7**, and **9** show that a range of functionalities can be tolerated during the amine addition step and that extended peptoids can be generated from a diverse collection of building blocks.

To demonstrate the viability of synthesizing larger extended peptoids, pentamers using both *para*- and *meta*-bromotoluic acids and amines **7** and **9** were made. Product purities after each monomer addition were assessed by HPLC and yields were determined by weighing the final cleaved products. Excellent purities and moder-



Scheme 2. Monomer assessment studies using amines **2**–**9** on model extended peptoid backbone.

Table 1. Coupling efficiencies of amines **2**–**9**

Amine	Compound	% Purity[a]	% Crude yield[c]
2	**10**	9	54
3	**11**	87	>99
4	**12**	79	>99
5	**13**	0[b]	0[b]
6	**14**	0[b]	0[b]
7	**15**	>99	>99
8	**16**	46	55
9	**17**	>99	>99

[a] Determined by % area of light scattering signal in LC/MS analysis of crude product after cleavage from resin.
[b] No product was detected by mass.
[c] TFA removed by evaporation; crude product washed several times with Et_2O, resuspended in 1:1 H_2O ACN and lyophilized.

Table 2. Yields and purities of extended peptoid oligomers

	Spacer	Sequence[a]	% Purity[b]	% Purified yield[c]
18	*m*	Ac-7-7-7-7	94	37
19	*m*	Ac-9-9-9-9-9	99	12
20	*p*	Ac-7-7-7-7	95	20
21	*p*	Ac-9-9-9-9-9	99	12

[a] Ac = *N*-acyl.
[b] Determined by % area of light scattering signal in LC/MS analysis of crude product after cleavage from resin.
[c] Compounds purified by preparative HPLC and lyophilized.

ate isolated, purified yields were obtained (see Table 2). NMR spectra taken at room temperature for all four synthesized pentamers were highly complex, most likely due to the presence of multiple amide bond rotamers.

When NMR spectra were obtained at 100 °C in DMSO-d_6, the spectra for pentamers based on amine **9** were greatly simplified and amenable to straightforward interpretation; however, pentamers based on amine **7** degraded (in both DMSO-d_6 and D_2O) at the high temperatures required to coalesce the amide rotamers.[§] Pentamers incorporating amine **7** were found to be highly water soluble (80 mg/ml), suggesting that the backbone's intrinsic hydrophobicity can be overcome with appropriate hydrophilic side chains to generate water-soluble extended peptoids.

The discrepancy between the high purity of the crude product and moderate isolated yield is likely due to aminolysis of the peptide from the Wang linker. Future studies will be aimed at optimizing conditions on the Rink resin or attempting syntheses on the more sterically hindered 2-chlorotrityl resin. Microwave-based synthesis of these compounds was explored but showed no significant improvement for either impurities or yields (data not shown).

In principle, the extended peptoid concept could be further elaborated to include vinylogous, heterocyclic, and polycyclic spacer elements that contain reactive allylic and benzylic halides, further increasing the potential diversity of this class of compounds. These compounds represent a new type of oligomer based on a simple elaboration of standard peptoid chemistry, providing access to a large variety of new compounds with potentially interesting properties. Among these properties, the inherent hydrophobicity and rigidity of these extended peptoids, in particular, may be well suited as macromolecule ligands for proteomics and drug discovery applications.

[§] It should be noted that the aromatic resonances due to the side chain of **7** were not distinguishable from those of the extended peptoid backbone in the NMR spectrum.

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Supplementary data

Supplementary data (general experimental procedures; LC/MS traces for compounds **10**–**21** and NMR spectra for compounds **18**–**21**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.075.

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