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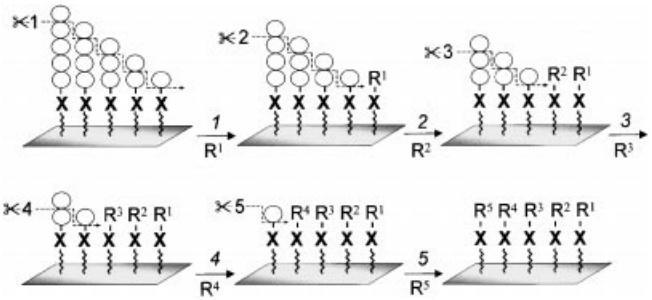

Figure 1. UCP exemplified by the deprotection and selective derivatization of five functional groups (R^{1-5}). The functional groups (**X**) are protected with a concatenated set of oligomeric protecting groups (○). The sequential removal of each protecting unit is achieved with a single reaction type. Selective derivatization of each newly unmasked functional group is performed after each deprotection step. This iterative process is repeated until all functional groups are deprotected and derivatized as desired.

Unichemo Protection: A Concept for Chemical Synthesis**

Les P. Miranda and Morten Meldal*

Chemical synthesis is a powerful method for creating complex molecules with tailored biological and physical properties for drug discovery, engineering, nanotechnology, and the investigation of biological processes. However, the applicability of chemical synthesis to peptides, oligosaccharides, and other organic molecules is limited and inherently complicated using the existing functional-group protecting strategies. The differential protection of functional groups of similar reactivity in chemical synthesis is a major challenge with conventional protecting-group strategies, namely orthogonal protection and modulated lability.[1–3] In particular, the development of effective protective schemes for polyfunctional molecules is not trivial.[4] The number and type of protecting groups influences the length, efficiency, and complexity of a given synthesis, and is often responsible for its success or failure.

Herein, a new concept, termed unichemo protection (UCP), illustrated in Figure 1, is introduced. This strategy only requires a single chemical process for all deprotection reactions. The UCP protecting groups are derived from a repetitive unit that permits their controlled and efficient stepwise removal. Functional site selectivity is achieved by varying the degree of oligomerization at each site, and, after each deprotection cycle, only the newly liberated functional site is available for derivatization.

In principle, the UCP strategy does not impose a restriction on the possible number of selectively protected sites in a molecule. This method should be particularly useful in areas including the combinatorial synthesis of highly substituted scaffolds, peptide synthesis, template-assisted synthetic proteins (TASP),[5, 6] automated oligosaccharide synthesis,[7] and the general goal of automated organic synthesis.

The effectiveness of the UCP chemistry was demonstrated by the controlled derivatization of a pentalysine-based amino-functionalized scaffold on the solid support. To facilitate this, a *N-sec*-butylglycyl-based protecting-group unit was devised for the protection of amino groups.[8] With conventional protection strategies, the controlled derivatization of five or more otherwise identical amino groups on the solid-support is a difficult challenge. Here, this problem was solved by using the UCP concept in the form of N^{ε}-oligo(*N-sec*-butylglycyl) protected lysine building blocks[9] for the assembly of scaffold **1** (see Figure 3).[10]

In its present form the UCP concept takes advantage of large reactivity differences between primary amino functional groups and the otherwise similar protecting groups. The use of oligomeric *N-sec*-butylglycyl protecting groups exploits the relatively high degree of steric hindrance around the secondary amino terminus to differentiate between deprotection and derivatization processes. High yields of oligomeric *N-sec*-butylglycyl protecting groups are readily obtained using strong activation during amide-bond formation on the solid support.[11] Importantly, the oligomers were completely inert to less activated carboxylic derivatives, such as readily prepared *para*-nitrophenyl (ONp) and succinimide (OSu) esters (Figure 2).[12, 13] The inert character of the UCP secondary amine protecting groups under acylation conditions thus allows for the chemoselective derivatization of newly liberated primary amino group with nitrophenyl esters. That is, chemical selectivity against the secondary amino terminus of the protecting groups is employed to distinguish between derivatization and removal steps.

For deprotection cycles, efficient stepwise removal of terminal protecting group units is facilitated by a reliable two-step procedure originally developed by Edman for protein sequencing.[14] In the first step, phenylisothiocyanate (PITC) reacts quantitatively at pH 8 with the terminal unit of the oligomeric protecting group (Figure 2). In the second step, a quantitative cyclization and elimination reaction occurs at

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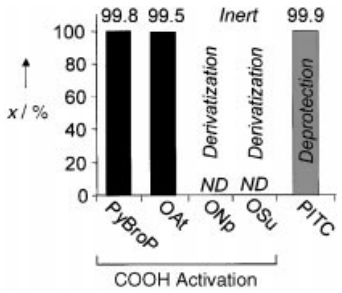

Figure 2. Selective modification of *N-sec*-butylglycyl protecting groups, $x = \%$ conversion of *N-sec*-butylglycyl groups. For the assembly of the oligomeric UCP groups, coupling reactions (PyBroP and HOAt active esters[9]) efficiently acylate the hindered secondary amine in DMF at room temperature in 1 h. Importantly, for the derivatization of liberated primary amines, the protecting group secondary amine is resistant to acylation by less activated ONp and OSu esters at room temperature, such as 0.1 M Boc-Ala-ONp in DMF. For deprotection, PITC reacts in high yield to form the key phenylthiocarbamyl intermediate. The PITC reaction was carried out twice at 55 °C.[15] Boc = *tert*-butoxycarbonyl.

acidic pH, to give the shortened protecting group by the expulsion of a phenylthiohydantoin derivative.

Accordingly, following assembly of scaffold **1** each of the five primary amino groups on the scaffold was successively liberated with PITC/TFA (TFA = trifluoroacetic acid) deprotection cycles (Figure 3).[15] Each newly exposed amino group was then acylated with a given carboxylic acid derivative. After five deprotection – derivatization cycles, cleavage from the solid support afforded **2**, in good purity and yield.[16] Molecular dynamics simulations indicate that low-energy conformers of *N-sec*-butylglycyl protecting-group oligomers are generally flexible, extended, and hydrophobic, which agrees well with experimental observations in terms of accessibility and solubility in organic solvents.

The advantage of UCP is its conceptual and practical simplicity. In contrast, orthogonal protection requires the identification, availability, and interplay of a range of sufficiently different orthogonal protecting groups and a multitude of unique chemical conditions for the removal of each individual protecting group in a selective and efficient manner.[17] This may create a problem particularly in the case of polyfunctional molecules because the cleavage of one protecting group strictly requires not only the stability of all the other protecting groups, but also of the masked molecule itself under a multitude of reaction conditions.[18–20] At the core of the problem is the limited availability of fully orthogonal protecting groups that work well together.

UCP effectively facilitates an orthogonal process that is not dependent on a range of finely tuned and differently compatible processes. Moreover, since UCP is based on uniform deprotection reactions, the requirement of reaction compatibility with other parts of a molecule only increases linearly with the degree of polyfunctionalization (Figure 4 and 5). That is, after the initial requirement of parent-molecule stability is satisfied, only the sequential requirements towards each newly introduced group is an issue. In contrast, a quadratic increase in complexity with respect to the number of protected functional groups, even in the simplest cases, accompanies existing orthogonal protection strategies.

In the implementation of the strategy described here, a highly efficient PITC/TFA cycloelimination process, which enabled the differential protection of five otherwise identical amino groups, was employed. Differential derivatization of five or more amino groups in a single molecule would be an extraordinary challenge for conventional protection strategies. With UCP chemistry, the number of a given functional group that can be successfully protected and sequentially assessed may exceed twenty. The UCP concept should be amenable to the protection of many other types of functional groups, such as hydroxyls, thiols, and carboxylates. A host of different UCP units may be devised from other sequential cleavage processes. However, several issues need to be considered for their development, these include: 1) the

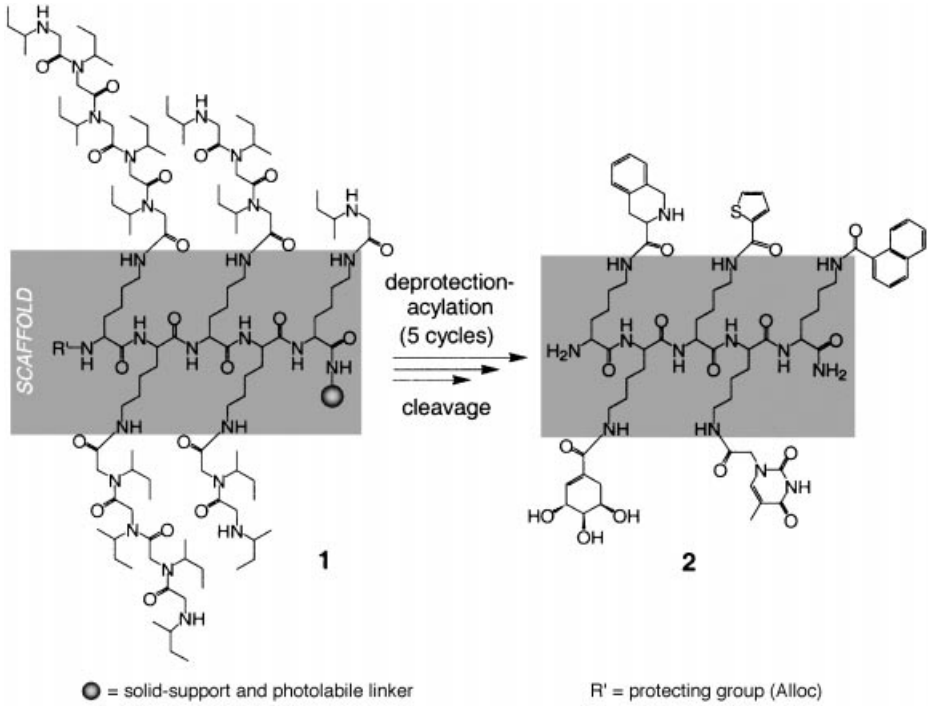

Figure 3. Derivatization of a polyamino scaffold **1** with UCP. The amino group were acylated in the order: β-naphthoic acid, thymine-1-acetic acid, thiophene-2-carboxylic acid, shikimic acid, and Boc-(L)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. The acids (1.05 equiv) were coupled with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU; 1.05 equiv, 0.05 M), *N*,*N*-diisopropylethlamine (DIEA; 4 equiv) in DMF (25 min). TBTU was initially used, ONp esters may be preferred for routine or combinatorial derivatization because they can be used in large excess while still maintaining selectivity. The target compound **2** was cleaved from the solid support in methanol with UV irradiation (3 h) and then purified by reversed-phase high-pressure liquid chromatography (HPLC).[16]

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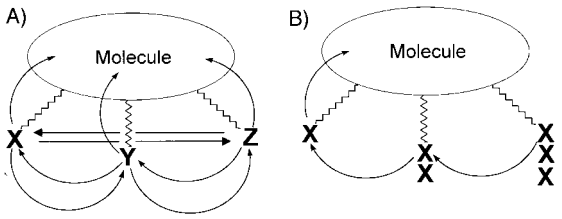

Figure 4. A) 3 orthogonal protection groups gives 9 requirements: 3 for compatible removal of X, Y, and Z with respect to molecule; 2 for compatible X removal with respect to Y and Z; 2 for compatible removal of Y with respect to Z and new X derivative; 2 for compatible removal of Z with respect to new X and Y derivatives. B) 3 UCP protecting groups gives 3 requirements: 1 for compatible removal X units with respect to molecule; 1 for compatible removal of 2nd X unit with respect to new X derivative; 1 for compatible removal of 3rd X with respect to new XX derivatives. Note that the removal of 3rd X with respect to new derivative is redundant with the 2nd X removal.

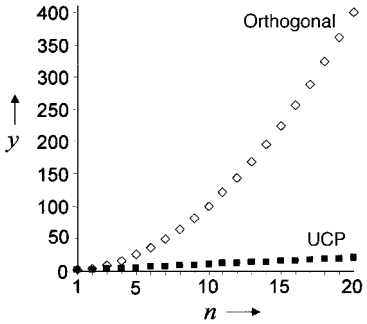

Figure 5. Minimal number of compatibility requirements for the synthesis of polyfunctional molecules with UCP and existing orthogonal protection strategies, y = number of compatibility requirements, n = number of functional groups. In this simple model, orthogonal protection strategies increase quadratically ($y = n^2$) in complexity per functional group (n), whereas UCP strategies only increases linearly ($y = n$).

ease and cost of assembling the protecting group; 2) the practicality, and particularly, the efficiency of the step-wise degradation method; 3) the inertness of the protecting group towards the expected synthesis conditions and reagents for a given application. In this regard, a three-step UCP process in which the UCP protection group is fully protected during derivatization would be advantageous.

UCP complements existing orthogonal protection strategies, and both approaches together will enable the synthesis of more elaborate and novel molecular structures. The experiments reported here show that it is possible to synthesize and derivatize polyfunctional molecules in a simple and effective fashion, without the need for complicated protection chemistry. One outcome of the simplification of both design and chemical requirements is the relative ease of using combinatorial techniques and automating the entire synthesis.

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