CHIMIA 50 (1996) Nr. 12 (Dezember)

Chimia 50 (1996) 640–641

ISSN 0009–4293

Cyclic Peptides as Topological Templates in Biomimetic Chemistry

Pascal Dumy*

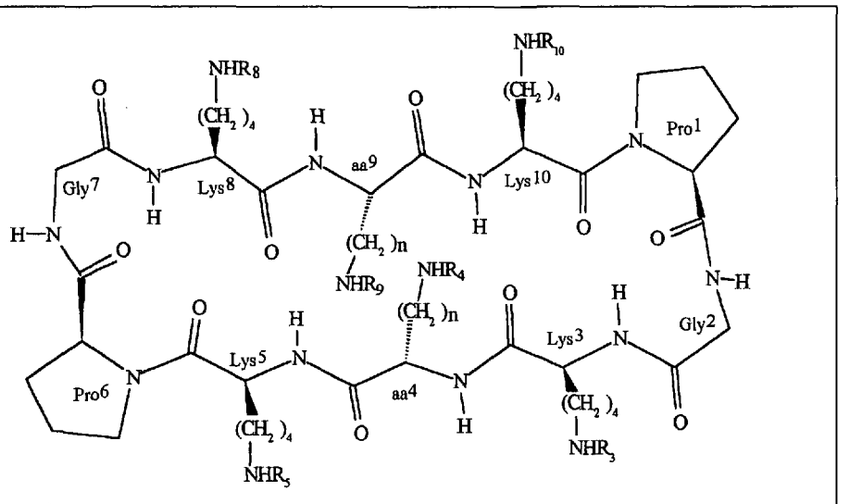
Abstract. Cyclic decapeptides containing up to four orthogonally protected lysine residues or selectively addressable faces represent a new class of Regioselectively Addressable Functionalized Templates (RAFT). We summarize here recent synthetic aspects and conformational properties of these constrained peptides along with potential applications for RAFT molecules in bioorganic chemistry and protein design.

Introduction

Selectively addressable topological templates represent a key feature in the *de novo* design of proteins using the TASP concept (Template Assembled Synthetic Proteins) [1]. In this approach, peptidic templates are used as structural motifs for directing covalently attached secondary structure units in predetermined folding topologies. We describe the design, synthesis and conformational analysis of cyclic templates which can be regioselectively modified to provide topological scaffolds for the construction of TASP molecules of high structural and functional complexity.

Design and Synthesis

We have recently described a concise route to topological templates which combines both solid-phase and solution-peptide synthesis to achieve greater flexibility and efficiency in the preparation of cyclopeptides [2]. As shown in the *Figure*, RAFT **1** offers complete differentiation of the four lysine residues, while **2** and **3** permit binary differentiation of these side chains on the same or on the opposite face of the cycle. Selective deprotection (R_5, R_3, R_8, and R_{10}) and acylation permit to regioselectively address and modify the four lysine side chains in turn, providing the proper order is respected. In addition, chemoselectivity can be used by combining groups with unique chemical reactivity instead of orthogonal protecting groups on the side chain of the peptide. The resulting RAFT serve as a scaffold to present, peptides, various functional organic molecules or combinations thereof in a well-defined spacial orientation [3]. As an example, lipophilic or hydrophilic properties can be tailored [4] by grafting one face of **3** with lipid or sugars unit, the other face being derivatized with an array of peptides. Consequently, numerous interesting possibilities for tailoring and modulating the physical and functional properties of the corresponding chimeric molecules can be achieved.



aa⁹=aa⁴=Ala **1** R_8=Dde; R_{10}=Boc; R_3=Aloc; R_5= Fmoc **2** R_8=R_3=Aloc; R_5=R_{10}=Boc

aa⁹=aa⁴=Lys **3** R_3=R_5=R_8=R_{10}=Boc; R_4=R_9=Aloc

Figure. *Combination of orthogonal protection and/or unique chemical reactivity (R_i) provide Regioselectively Addressable Functionalized Template* (RAFT) *molecules*

Conformational Properties

In parallel, we investigated the conformational properties of a series of RAFT molecules in solution [5]. For instance, analysis of the experimental data obtained for **1–3** confirm that these RAFT adopt well-defined solution structures based on an antiparallel β-sheet conformation, closed by two beta turns centred on the Pro-Gly dipeptides. Restrained molecular-dynamics calculations using NMR derived constraints support these findings. In particular, the four lysine side chains always remain on the same face of the cycle. Interestingly, position 4 or 9 appeared to be critical for the conformational rigidity of the system: substitution for glycine, for instance, resulted in a more flexible structure. Compilation of these results allowed us to deduce *a priori* a common secondary structural motif for the backbone of RAFT analogues, providing thus, valuable informations for the design and the fine-tuning of new complex RAFT molecules.

Conclusion

RAFT molecules represent conformationally stable scaffolds containing an array of selectively addressable sites. Proper combinations of orthogonal protection or unique chemical reactivity on that sites

**Correspondence*: Dr. P. Dumy
Institute of Organic Chemistry
University of Lausanne
BCH-Dorigny
CH-1015 Lausanne

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extend the possibility to orient and modulate the physico-chemical properties of covalently attached molecules and offer new perspectives in protein design and biomimetic chemistry [6]. In addition, RAFT with a variable number of selectively addressable sites may be useful for the preparation of libraries in drug development and functional screening.

Received: September 30, 1996

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Chimia 50 (1996) 641–643

ISSN 0009–4293

Organic Synthesis with α-Silylcarbonyl Compounds

Yannick Landais*

Abstract. Our interest in organosilicon compounds has led us to examine the chemistry of rarely used α-silylcarbonyl compounds. Possible applications of these synthons are not covered totally here, but a few examples along these lines should demonstrate the utility of these structurally simple substrates in organic synthesis. The preparation of the α-silyl esters and some examples of their stereocontrolled conversion into polysubstituted tetrahydrofurans is presented.

1. Introduction

This brief review is meant to supply the reader with a timely account of our studies to develop the synthetic utility of α-silylcarbonyl compounds. Major advances in this field have been the subject of a review by *Larson* [1] who pointed out that, until recently, these substrates have mainly been used as precursors of α,β-unsaturated esters and substituted ketones, *i.e.*, tranformations where the silicon group was regarded as a *super-proton* and thus eliminated in the last stage of the sequence. The discovery some thirteen years ago that the silicon group could also be used as a latent hydroxy group [2] has led us [3] and others [4] to reexamine the scope of the chemistry of these compounds. We describe here our own approach to the synthesis of α-silylcarbonyl substrates and their efficacy as building blocks in organic synthesis.

2. Synthesis of α-Silylcarbonyl Compounds

Our first contribution to this area was an approach to new α-(alkoxysilyl)acetates using Rh-carbenoid insertion into the Si–H bond of chlorosilanes [3]. These simple building blocks, possessing a unique chiral center, allowed the development of an asymmetric approach to produce α-silyl esters **1** with diastereoisomeric excesses ranging between 30 and 80% using menthol or, in the best cases, pantolactone as chiral auxiliaries (*Scheme 1*) [5]. Reduction of the ester function followed by oxidation of the C–Si bond with retention of configuration then led to optically enriched 1,2-diols. We soon realized that an extension of these preliminary results to the insertion of Rh-vinyl carbenoid species into the Si–H bond of a silane would provide a straightforward access to allylsilanes such as **2** (*Scheme 1*). Remarkably, it was found that the insertion occured *stereospecifically* with retention of the geometry of the double bond, hence giving an easy access to stereochemically defined (*E*)- and (*Z*)-allylsilanes [6]. As before, extension of this approach to chiral non-racemic series using pantolactone as chiral auxiliary led to selectivities of up to 70% d.e. It is noteworthy that recent studies in our group have shown that the insertion into O–H, N–H, and S–H bonds also provides the desired allylic alcohol, amine, and thioether, stereospecifically in excellent yields [7].

3. Acyclic 1,2-Stereocontrol

Our second task was to show that such allylsilanes could be versatile building blocks. We assumed that the allylic chiral center would efficiently control the stereochemistry of the new asymmetric centres during electrophilic reactions [8], and that the homoallylic OH group would direct the incoming electrophile preferentially onto one face of the π-system, thus ensuring a higher level of stereocontrol [9] (*Scheme 2*). This effectively proved to be the case with epoxidation and cyclopropanation, where high levels of diastereocontrol were observed. Interestingly, an inversion of the topicity, depending on the geometry of the double bond, was noticed during V- and Ti-catalyzed epoxidation. (*E*)- and (*Z*)-allylsilanes thus led to *syn*- and *anti*-epoxides, respectively [10]. The stereoselectivity of the epoxidations was rationalized using the '*chair-like*' transition states **A** and **B** (*Scheme 2*). The bulky silicon group occupies a pseudoequatorial position to minimize $A_{1,3}$ interactions [11]. With allylsilanes having a (*Z*)-substituent, the conformation **A**, where strong $Si \leftrightarrow R_Z$ interactions are absent, is preferred, explaining the high selectivity in favor of the *anti*-isomer obtained in such cases. In contrast, with (*E*)-allylsilanes, the major *syn*-isomer is formed through a '*chair-like*' transition state **B**, which is more

*Correspondance: Dr. Y. Landais
Institut de chimie organique
Université de Lausanne
Collège propédeutique
CH–1015 Lausanne-Dorigny