ORGANIC LETTERS

2011
Vol. 13, No. 15
3798–3801

Interplay of Olefin Metathesis and Multiple Hydrogen Bonding Interactions: Covalently Cross-linked Zippers

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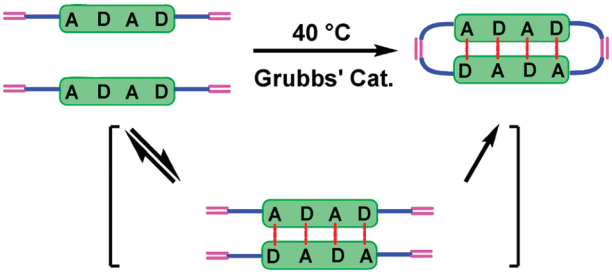
Received May 12, 2011

ABSTRACT



Hydrogen-bonded zippers bearing terminal alkene groups were treated with Grubbs' catalyst, leading to covalently cross-linked zippers without violating H-bonding sequence specificity. The yield of a cross-linked zipper depended on the stability of its H-bonded precursor, with a weakly associating pair giving reasonable yields only at high concentrations while strongly associating pairs showed nearly quantitative yields. The integration of thermodynamic (H-bonding) and kinetic (irreversible C=C bond formation) processes suggests the possibility of developing many different covalent association units for constructing molecular structures based on a self-assembling way.

One major objective of modern chemistry involves the development of strategies for controlling both the specificity and strength of the association of various structural components into higher-order assemblies or structures.[1] In nature, the assembly of molecular components mediated by highly specific, multiple noncovalent interactions leads to well-defined, thermodynamically stable aggregates. Inspired by natural examples, many artificial self-assembling structures have been successfully constructed.[2] For example, the pioneering studies by Jorgenson and Zimmerman on the association of nucleobases resulted in H-bonded pairs that mediate specific intermolecular interactions.[3] Subsequently, the groups of Zimmerman[4] and Meijer[5] reported highly stable H-bonded complexes based on

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10.1021/ol201282d
Published on Web 06/24/2011

aromatic heterocycles. These H-bonded complexes served as association units for forming various supramolecular structures.[6] Enlightened by duplex DNA, a series of information-storing molecular duplexes or zippers, consisting of oligoamide strands carrying complementary arrays (sequences) of H-bond donors and acceptors, were developed by us.[7] These H-bonded zippers are featured by tunable affinity, programmable sequence specificity, and ready synthetic availability and represent an alternative class of readily adjustable association units for the instructed assembly of molecular components. For example, our H-bonded zippers assisted the formation of β-sheets by bringing natural peptide strands into close proximity,[8] "glued" different polymer chains into supramolecular block copolymers,[9] and served as templates for directing reactions.[10]

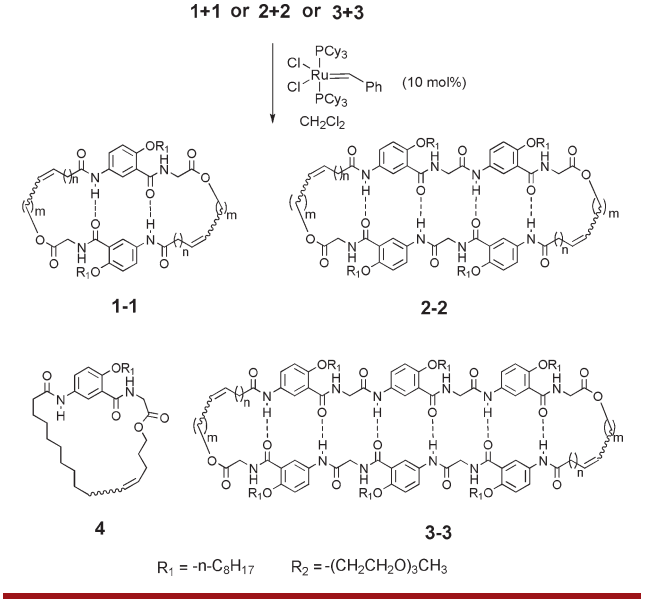
Despite their advantages, H-bonded complexes are limited by their thermal instability and dissociation in polar media. These drawbacks impede the application of H-bonded units in competitive media or at elevated temperatures. It was reasoned that introducing additional stabilizing forces, such as dynamic covalent interactions,[11] may address the inherent instabilty of H-bonded systems while maintaining the high specificity typical of multiple noncovalent forces. We have demonstrated that equipping our H-bonded zippers with disulfide bonds led to association units that are stable in aqueous media.[12] By combining both the sequence specificity of multiple H-bonds and the stability of covalent bonds, such units provided a new strategy for the construction of covalent structures in a self-assembling way. Olefin metathesis, as the other major type of dynamic covalent interactions, allows the formation of C=C bonds that are much more stable than disulfide bonds. As an attempt to establish the generality of integrating multiple H-bonding with dynamic covalent bonding interactions, we set to explore H-bonded zippers cross-linked via olefin metathesis.[9,13,14]

We describe herein H-bond-mediated covalent cross-linking of oligoamides **1**, **2**, and **3** that dimerize into two-, four-, and six-H-bonded zippers, as defined by their self-complementary H-bonding sequences.[15] With terminal alkene moieties attached to their ends, the H-bonded duplexes of these oligoamides are expected to undergo metathesis reactions in the presence of Grubbs' catalyst, leading to products **1-1**, **2-2**, and **3-3** cross-linked by C=C bonds (Scheme 1).

Oligoamide strands **1**−**3** were synthesized[16] and subjected to metathesis in CH_2Cl_2. As established by our previous studies, in solution, compounds like **1a**, **2a**, and **3** exist as H-bonded dimers with stabilities proportional to the numbers of their interstrand H-bonds.[15,16]

Thus, compounds **1a**−**1d** (2 mM) were first treated with Grubbs' catalyst in CH_2Cl_2 under reflux for 4 h, results from which should reveal the effect of the aliphatic [$-(CH_2)_m-$ and $-(CH_2)_n-$] spacers on the efficiencies of the corresponding reactions. The conversion of **1c** or **1d** was very inefficient ($<11\%$). In each case, a mixture containing the cross-linked **1c-1c** or **1d-1d**, the unreacted starting material, and another product from the metathesis of only one of the two terminal alkene groups was obtained. In contrast, compound **1b** exhibited a much higher conversion (40%), with **1b-1b** as the major product (36%). A drastic improvement of conversion (90%) was observed for **1a**, with **1a-1a** being formed in 41.5% yield (Table 1). However, the reaction of **1a** also led to a self-cyclized product **4** (49%).[16] Similar intramolecular cyclization was not observed for **1b**, **1c**, and **1d**. The shortened aliphatic spacers of these three compounds seemed to have compromised the yields of the cross-linked zippers. Thus the same aliphatic spacers of **1a** ($m = 3, n = 8$) were chosen to design **2a** and **3**. Compound **2b**, with shortened spacers, was also prepared for comparison.

Scheme 1. Metathesis of Oligoamide Strands **1**−**3**



Under the same conditions, compound **2a** (2 mM), which dimerizes via four H-bonds, was converted nearly

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(16) See Supporting Information for details.

quantitatively into **2a**−**2a**, with only a trace of the self-cyclized product being detected. In contrast, the metathesis of **2b** (2 mM) showed a significantly lowered conversion of 65%, resulting in a mixture consisting of the cross-linked product **2b**−**2b** and another open-chain product[16] derived from two molecules of **2b** that are cross-linked at one of their ends.[16] Results based on **2a** and **2b** again confirmed that the aliphatic spacers revealed by **1a** were appropriate for efficient cross-linking. High cross-linking efficiency was also observed for **3**. At 2 mM, cross-linked **3-3** formed as the only product (Table 1).

Thus, at the same concentration (2 mM), the efficiency for an oligoamide to form its cross-linked dimer is correlated to the stability of its H-bonded dimer. Compound **1a** formed the least stable H-bonded dimer and gave the lowest yield of the cross-linked **1a-1a**, while **3** formed the most stable H-bonded dimer and resulted in the highest yield of the cross-linked **3-3**. This suggests that the formation of a cross-linked zipper is determined by the abundance of its H-bonded precursor. A H-bonded zipper such as that of **3** represents the dominant species in solution, which forms **3-3** nearly quantitatively.

Table 1. Duplex-Assisted Olefin Cross Metathesis of Compounds **1**−**3**[a]

compd	concn (mM)	conv (%) (total yield %)	yield (%)	self-cyclized product yield (%)
1a	2.0	95 ± 1 (90 ± 1)	41 ± 2	49 ± 1
	0.5	94 ± 1 (90 ± 1)	14 ± 1	76 ± 2
	0.05	98 ± 1 (96 ± 1)	trace[b]	96 ± 1
1b	2.0	40 ± 1 (36 ± 1)	mix[b]	trace
1c	2.0	10 ± 1	mix[b]	nd[c]
1d	2.0	< 5	mix[b]	nd[c]
2a	2.0	100 (94 ± 1)	94 ± 1[b]	trace
	0.5	100 (95 ± 1)	91 ± 1[b]	4 ± 1
	0.05	100 (95 ± 1)	83 ± 1[b]	12 ± 1
2b	2.0	65 ± 2 (61 ± 2)	mix[b]	nd[c]
3	2.0	100 (97 ± 1)	97 ± 1	nd[c]
	0.5	100 (98 ± 1)	98 ± 1	nd[c]
	0.05	100 (97 ± 1)	97 ± 1	nd[c]
5 + **6**	2.0	100 (97 ± 1)	97 ± 1	trace
	0.5	100 (95 ± 1)	95 ± 1	trace

[a] Grubbs' catalyst 10 mmol %; solvent: CH_2Cl_2; temperature: reflux. Conversions and yields of the cross-linked products were based on isolated products by chromatography or by PTLC or on the reaction mixture determined by ^{1}H NMR (400 MHz) analyses using DMF as an internal quantification standard. [b] Containing the cross-linked zipper, the product cross-linked at one of their ends and/or unreacted starting material. [c] Not detectable on TLC and by MALDI-TOF.

The metathesis of **1a**, **2a**, and **3** was further explored at different concentrations (Table 1). Upon diluting from 2.0 to 0.05 mM, the yield of **1a-1a** decreased from ~42% to nearly 0, with the self-cyclized **4** becoming increasingly predominant as the concentration decreased. On the other hand, boosting the concentration of **1a** to 40 mM led to **1a-1a** in 60% yield. Compared to **1a**, compound **2a**, which exists mainly as its H-bonded dimer ($K_{dimer} > 10^4$ M^{-1} in $CHCl_3$)[15] in a much broader concentrations range, gave **2a-2a** as the dominant product with only a small amount of the self-cyclized product appearing when the concentration was lowered to 0.05 mM. The H-bonded zipper formed by **3**, with its extremely high stability ($K_{dimer} \geq 10^9$ M^{-1} in $CHCl_3$),[7b] exists as the dominant form down to extremely low concentrations, which translates into the exclusive formation of **3-3** at all the concentrations tested.

These results suggest that the presence of the H-bonded dimer of **1a**, **2a**, or **3** precedes the formation of the cross-linked **1a-1a**, **2a-2a**, or **3-3**. The abundance of a H-bonded dimer relies on both the concentration of the oligoamide component and the stability of such a dimer. At low concentrations, the weakly H-bonding **1a** exists mostly as free molecules whose only option was to self-cyclize. Increasing the concentration of **1a** drives the equilibrium toward the H-bonded dimer, which led to **1a-1a** in increasing yields. The strongly dimerizing **2a** and **3**, on the other hand, exist mostly as their H-bonded dimers in a wide range of concentrations, which led to **2a-2a** and **3-3** in a seemingly concentration-independent fashion.

Thus, the above results indicate that the formation of the cross-linked **1a-1a**, **2a-2a**, and **3-3** relies on the presence of their H-bonded zipper precursors in solution. Such an observation may be rationalized by a mechanism consisting of two synergistically interacting steps: (1) the reversible, sequence-specific pairing of the oligoamide components, which leads to the correponding H-bonded dimers that then undergo (2) irreversible cross-linking due to the metathesis of the terminal olefin units that is brought into close proximity. The rate of the second step is expected to be very rapid, i.e., similar to that of a intramolecular

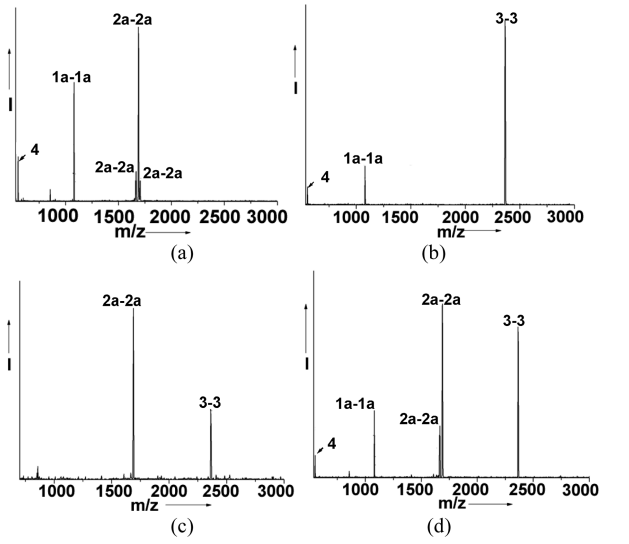


Figure 1. MALDI-TOF spectra of (a) the 1:1 mixture of **1a** and **2a**; (b) the 1:1 mixture of **1a** and **3**; (c) the 1:1 mixture of **2a** and **3**; (d) the 1:1 mixture of **1a**, **2a**, and **3** at 2.0 mM in CH_2Cl_2 (m/z values: 1079.7 [**1a-1a** + Na^+], 551.4 [**4** + Na^+]; 1704.5 [**2a-2a** + K^+], 1688.1 [**2a-2a** + Na^+], 1666.5 [**2a-2a** + H^+], 2364.4 [**3-3** + Na^+]) (2.0 mM).

reaction, because of the greatly enhanced molarity of the terminal olefins attached to a H-bonded zipper. The rapid, irreversible metathesis reaction serves to covalently capture the various molecular and H-bonded species that exist in equilibrium in solution.

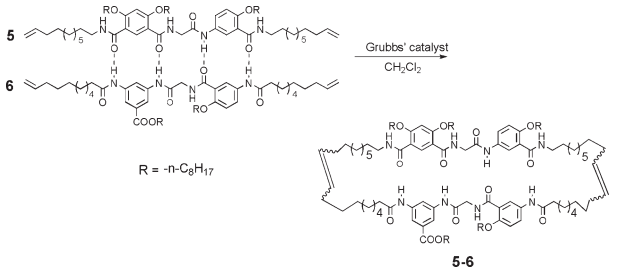
The irreversible, i.e., kinetically controlled, nature of the cross-linking step is reasonable given that the metathesis reaction of terminal olefin units generates ethylene as the other product that is highly volatile and thus is easily lost from the reaction system.[17] Despite the irreversibility of the cross-linking step, the above results demonstrate that H-bonded zippers with a large dimerization constant, when equipped with terminal alkene groups, could serve as specific covalent association units at very low concentrations. In contrast, the low stability of the H-bonded pair of **1a** means that acceptable yields of the cross-linked product could only be achieved at elevated concentrations.[16]

Despite their overlapping H-bonding sequences, compounds **1a**, **2a**, and **3** (2.0 mM in CH_2Cl_2) demonstrated an interesting self-sorting behavior in the formation of their cross-linked dimers (Figure 1). When subjecting these compounds to Grubbs' catalyst, only homodimers and the self-cyclized product of **1a** were detected. For example, a mixture of **1a** and **2a** led to products **1a**-**1a** and **2a**-**2a** and the self-cyclized **4**. The presence of **1a**, **2a**, and **3** in solution did not lead to any cross-coupled products. Such high selectivity was further evidenced by NMR experiments.[16]

The high efficiency observed for the metathesis of **2a** and **3** is not a phenomenon limited to those having self-complementary H-bonding sequences only. Oligoamides **5** and **6** pair sequence-specifically based on their complementary H-bonding sequences.[16] Upon treating with Grubbs' catalyst, **5** and **6** (2.0 mM in CH_2Cl_2) led to the cross-linked **5**−**6** almost exclusively, which demonstrates the strict sequence specificity of these covalent association units (Scheme 2).

In summary, the cross-linking of H-bonded pairs with four and six interstrand H-bonds demonstrated high efficiency and selectivity. The formation of a cross-linked zipper involves a mechanism consisting of a reversible association step followed by an irreversible covalent cross-linking step. In comparison to the formation of disulfide-linked zippers,[12] which is based on fully reversible noncovalent and covalent interactions and shows no concentration or stability dependence, forming the cross-linked zippers based on olefin metathesis depends on stability (i.e., **1a** vs **2a** vs **3**) and/or concentration (i.e., **1a**). Besides leading to covalent linkages of greatly enhanced strength, the mechanism revealed for the current system could add additional options for tuning covalent linking units. The self-sorting behavior shown by the self-complementary pairs and the similarly high efficiency in the cross-linking of the heterozipper consisting of **5** and **6** greatly enhance the diversity and specificity allowed by this class of H-bond-mediated covalent association units, which may be used in the construction of various covalent assemblies, robust materials, and supramolecular polymers.

Scheme 2. Cross Metathesis of Strands **5** (2.0 mM) in AADA and **6** (2.0 mM) in DDAD Sequence for Forming H-Bonded Heteroduplex in CH_2Cl_2



Acknowledgment. The authors acknowledge the National Natural Science Foundation of China (20874062), the National Science Foundation of the USA (CBET-1036171 and CBET-1066947). This work is also part of a Project sponsored by SRF for ROCS, SEM (20071108-18-16). We also thank the Analytical Center of Sichuan University for NMR analyses.

Supporting Information Available. Synthesis, analytical data, 2D NMR, HPLC, and MALDI-TOF spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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