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Synthesis and reactivity of enediynyl amino acids and peptides: a novel concept in lowering the activation energy of Bergman cyclisation by H-bonding and electrostatic interactions†

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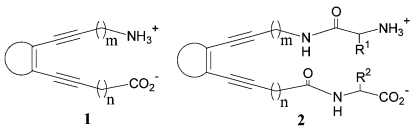
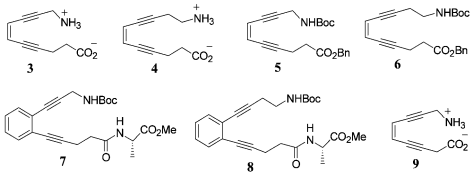
Novel enediynyl amino acids and peptides 3 and 5–8 were synthesized and their thermal reactivity towards Bergman cyclization studied and compared with the earlier reported amino acid 4, which demonstrated, for the first time, the effect of H-bonding and electrostatic interactions in lowering the activation energy of Bergman cyclization.

During our studies[1] on enediyne model systems, we became interested in the synthesis of ω-amino enediyne carboxylic acid **1**. The reason for our curiosity was two fold: 1) we wished to explore the influence of electrostatic and hydrogen bond forming interactions between the carboxylic acid and the amino group on the cycloaromatization process and 2) we were interested in the possible elaboration of these amino acids into β-turn mimetics as depicted in structure **2**.



1 **2**

Recently[2] we have reported the synthesis and conformational preferences of novel enediynyl tripeptides, which exist predominantly in the intramolecularly H-bonded form, to be used as a scaffold for β-turn mimetics. In this communication, we report the effect of weak interactions, especially H-bonding and electrostatic interactions, on the kinetics of Bergman cyclization by studying the thermal reactivity of the enediynyl amino acid in free (**3** and **4**) and protected forms (**5** and **6**) and also of the dipeptides (**7** and **8**). Specifically, our intention was to investigate the possibility of encouraging Bergman Cyclization (BC) by pulling the reactive centers together with electrostatic interactions. Incidentally, except for amino acid **4**, all other compounds are new and are reported here for the first time.



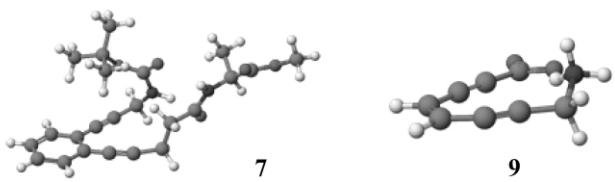
3 **4** **5** **6** **7** **8** **9**

Among the various parameters that control the kinetics of BC, the distance between the acetylenic carbon atoms undergoing covalent connection, commonly referred to as the c,d-distance,[3] has become extremely useful in spite of some limitations.[4] As compared to the cyclic ones, acyclic enediynes have a comparatively high c,d-distance, which is much greater than the critical distance range required for spontaneous cyclization as proposed by Nicolaou and others.[3] However, it is not unreasonable to think that acyclic enediynyl amino acids may form a cyclic network *via* intramolecular H-bond or electrostatic interactions between the terminal zwitterions thereby lowering the c,d-distance and hence the activation barrier for cycloaromatization. Metal ion coordination, in general, has been shown to lower the activation barrier for BC in acyclic enediynes[5–8] through metal–ligand interactions.

To know the effect of the electrostatic and H-bonding interactions on the c,d-distance, we carried out molecular mechanics calculations in the gas phase on the amino acid **9** using the program Hyperchem Pro6 (Hypercube Inc., Scientific Software). The energy minimized conformations were refined by performing an optimized geometry calculation using augmented MM force field parameters. Interestingly, although **9** is an acyclic enediyne, the c,d-distance surprisingly came out to be quite low, 3.298 Å, which is within the critical range for spontaneous cyclization. We have also carried out similar calculations on the peptides **7** and **8** (Fig. 1). The c,d-distance for peptide **7** (3.902 Å) came out to be lower than that for peptide **8** (4.067 Å).

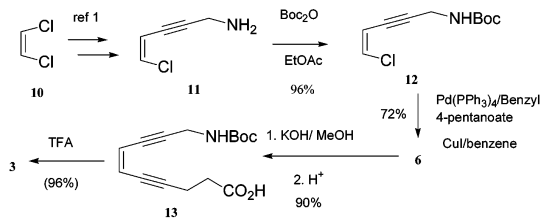
Although electrostatic or H-bond interactions will be different in the solution phase, initial calculations predicted some degree of reactivity difference in these compounds. Unfortunately, we could not synthesize the amino acid **9** as the Sonogashira coupling[9] involving propargylic esters created problems. The higher homologous acid, 3-butynoic acid, could not be used because of the problem of easy tautomerization to the allenic acid. This prompted us to synthesize the amino acids and the peptides from the commercially available 4-pentynoic acid.

The synthesis of the amino acid **3** started with the Pd(0)-catalysed coupling of *cis*-dichloroethylene and propargyl alcohol. The mono coupled product was then converted[1] to amine **11**, which was immediately t-Boc protected. A second round of Pd(0)-mediated coupling with 4-pentynoic acid benzyl ester gave the fully protected enediynyl amino acid **5**, which was isolated pure by column chromatography. The benzyl ester was then removed by stirring in an alkaline methanol solution. Final deprotection was done with TFA. The synthesis is shown in Scheme 1.



7 **9**

Fig. 1 MM2 minimized structures of enediynes **7** and **9**.



Scheme 1

† Electronic supplementary information (ESI) available: optimised geometry of peptide **8**, DSC curves of enediynes **3–6** and δ *vs. T* curves for peptides **7** and **8**. See http://www.rsc.org/suppdata/cc/b3/b308976m/

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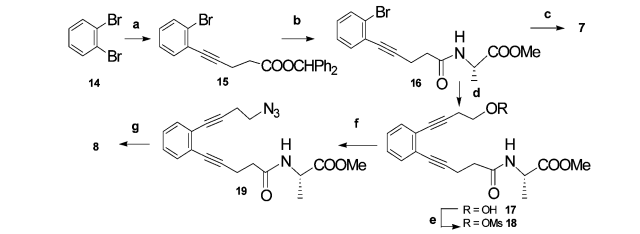
The preparation of the higher homologous amino acid **4** has already been reported.[2] The enediyne-based dipeptides **7** and **8** were synthesized from 1,2-dibromobenzene. After the first Pd(0)-mediated coupling with 4-pentynoic acid benzhydryl ester, the resulting bromo eneyne **15** was deprotected with TFA and then coupled with L-alanine methyl ester. Another round of coupling with N-t-Boc propargyl amine afforded the target peptide **7**. For the synthesis of the other peptide **8**, the second coupling was done with homopropargyl alcohol. The enediyne alcohol **17** was then converted to the target peptide **8** *via* the azide **19** as shown in Scheme 2.

The onset temperatures for BC for these enediynyl amino acids and the peptides were determined using Differential Scanning Calorimetric (DSC)[10] measurements which were recorded in the neat state without any solvent. For the fully protected amino acids **5** and **6**, which were viscous oils, the onset temperature for BC came out to be ~111 and 133 °C respectively. However when the same was recorded for the free amino acids (semi-solids), both the onset temperatures were lowered. For the amino acid **3**, the onset temperature for BC came out to be ~92 °C (a decrease of ~19 °C). For the higher homologous amino acid **4**, the exothermic rise started at ~99 °C showing a lowering of the onset temperature of ~34 °C. For the two peptides, the difference in onset temperature for BC is even more striking. While the peptide containing the propargyl arm **7** showed an exothermic rise starting from ~121 °C, the higher homologue **8** did not cyclize until being heated up to ~207 °C. As representative examples, the DSC curves of peptides **7** and **8** (both viscous oils) are shown in Fig. 2.

We ascribe this large difference in reactivity towards BC to the presence of stronger intramolecular H-bonding involving the carbamate NH and the amide carbonyl. This has been supported by the energy minimized geometry as well as by variable temperature NMR[11] experiments. The carbamate NH showed very low temperature dependence in d_6-DMSO (insert of Fig. 3) and is within the Kessler limit[12] of -3 ppb K^{-1} thus proving a high degree of intramolecular H-bonding in peptide **7**. Solution phase kinetics in DMSO in the presence of 1,4-CHD at 150 °C was also carried out, the rate of disappearance of the enediynyl peptides were monitored by HPLC using an internal standard (naphthalene).[13] This also revealed higher reactivity of peptide **7** ($k_{obs} = 12 \times 10^{-2}\ h^{-1}$) as compared to peptide **8** ($k_{obs} = 2.08 \times 10^{-2}\ h^{-1}$) (Fig. 3). That the BC is the major process occurring under these thermal conditions was evident from the appearance of new aromatic peaks in the ^{1}H-NMR which corresponded to the cyclized product. However, the cyclized product yields were low (15–25%) although most of the starting material was consumed. The low yield is attributed to the formation of polynaphthalene type compounds *via* BC followed by polymerization.[14] In general, cyclizations all have good mass balance.



Scheme 2 *Reagents and conditions*: **a** $Pd(PPh_3)_4$, benzhydryl 4-pentynoate, $CuBr_2$, NEt_3, 76%; **b** L-alanine methyl ester, EDCl, DMF, 82%; **c** N-Boc propargyl amine, $Pd(PPh_3)_4$, Cu_2Br_2, NEt_3, 70%; **d** 3-butyn-1-ol, $Pd(PPh_3)_4$, Cu_2Br_2, NEt_3, 70%; **e** NEt_3, MsCl, CH_2Cl_2, 89%; **f** NaN_3, DMF, 85%; **g** PPh_3, H_2O, THF then Boc_2O, EtOAc, 80%.

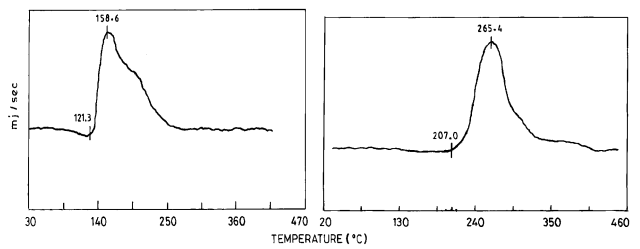


Fig. 2 DSC of peptides **7** (left) and **8** (right).

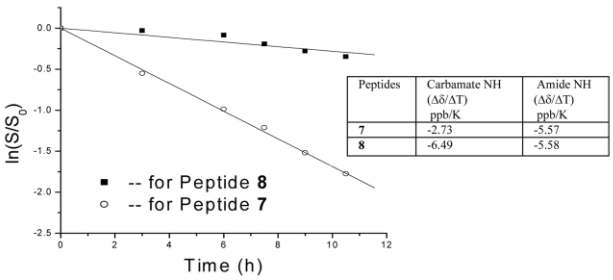


Fig. 3 BC kinetics in DMSO. **Insert**: Temperature dependence of NH chemical shifts.

In conclusion, we have been able to demonstrate the importance of H-bonding/electrostatic interactions in lowering the activation energy of BC. Current studies are aimed towards incorporating DNA-bases into the two arms of enediynes and exploring their reactivity.

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