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Synthesis and Solution Structures of Aminoacyl Compounds of Potential Prebiotic Significance

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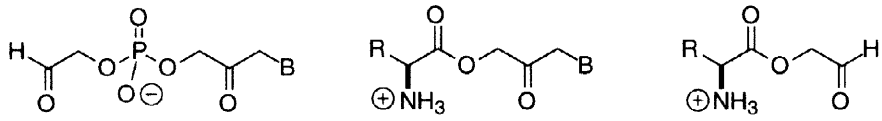
Abstract The chemical synthesis and solution structure determination of aminoacylated glycoaldehyde and base substituted dihydroxyacetone derivatives are described.

Keywords: aminoketones; nucleic acid analogues; ozonolysis.

Introduction

As part of an ongoing programme aimed at evaluating an aldol reaction based biogenesis of polymeric nucleic acids [1,2,3] we recently became interested in the potential for production of aminoacylated nucleic acids using similar chemistry [1]. Specifically we recognised the correspondence between the acyclic phosphodiester nucleic acid precursors **1** and the combinatorial array of aminoacylated base substituted dihydroxyacetone derivatives **2**, Fig. 1. In this paper we describe the synthesis and solution structure determination of a simple aminoacylated glycoaldehyde derivative **3** and two members of the array **2**.



1 **2** **3**

Fig. 1. Potentially prebiotic polymerisation monomers (B = A, C, G, U; R = amino acid side chain).

Results and Discussion

The aldehydic compound **3** was instated as the first synthetic objective. The aldehyde group of **3** was seen as arising from the ozonolytic cleavage of an olefin hence we first diacylated Z-but-2-ene-1,4-diol with *t*-Boc-L-valine, Fig. 2. The optimal coupling was found to require 3 equivalents of the protected amino acid and furnished the symmetrical diester **4** in moderate yield. Ozonolysis followed by reductive work-up furnished the N-protected aminoacyl glycoaldehyde **5** in excellent yield. Removal of the amino blocking group was accomplished with aqueous hydrochloric acid in 1,4-dioxane. Since it was envisaged that the product **3** might exist in a number of hydration/tautomeric states ranging from the iminium ion **3a** to the aldehydic hydrate **3e**, a series of experiments was carried out to elucidate the solution structure(s).

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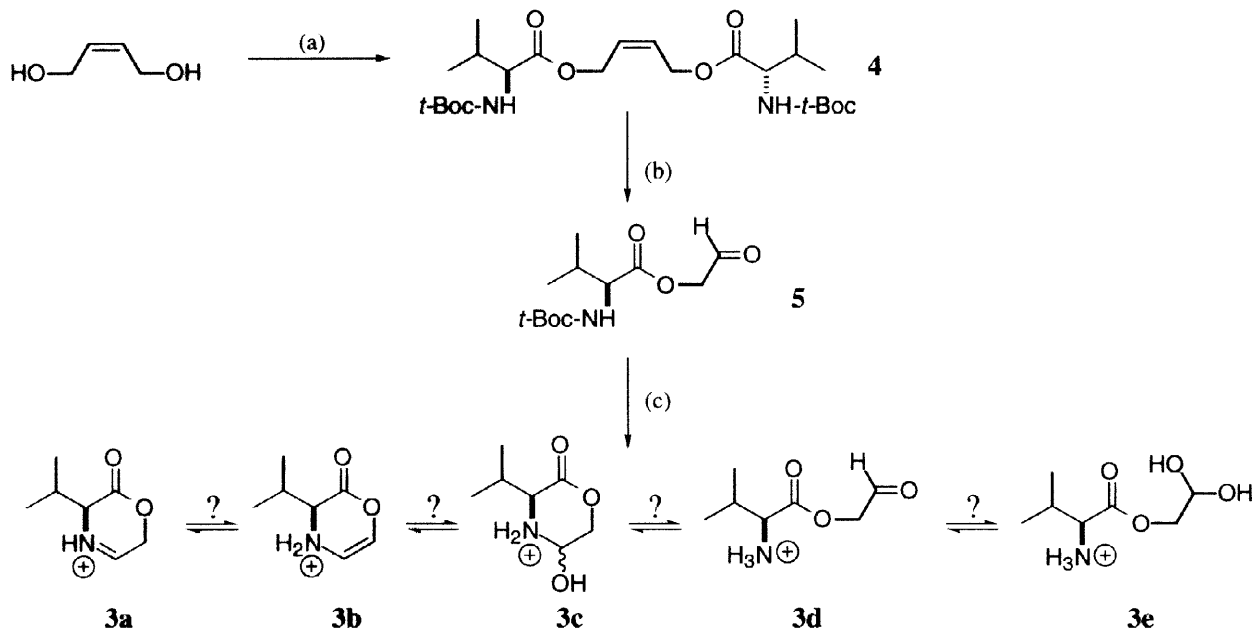
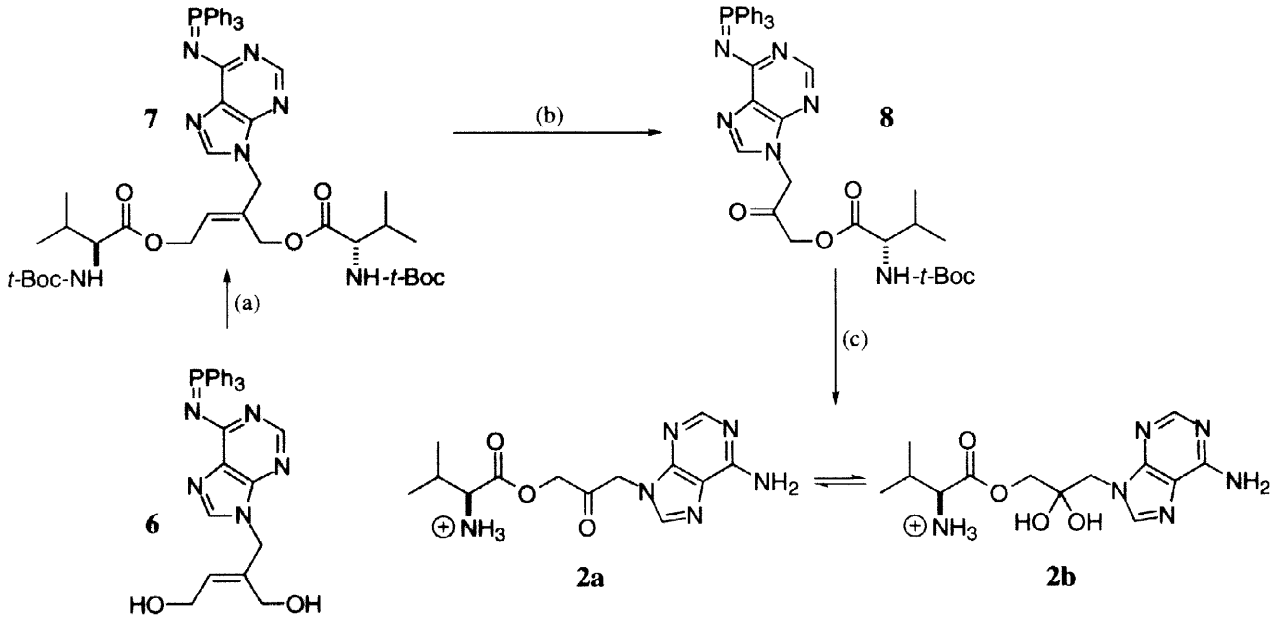


(a) $(Im)_2CO$, THF, *t*-Boc-L-valine, Et_3N, DMAP (45%); (b) i) O_3, CH_2Cl_2, ii) Me_2S (98%); (c) 1M HCl:1,4-dioxane (1:1) (quant.)

Fig. 2 Synthesis of valinyl-glycoaldehyde

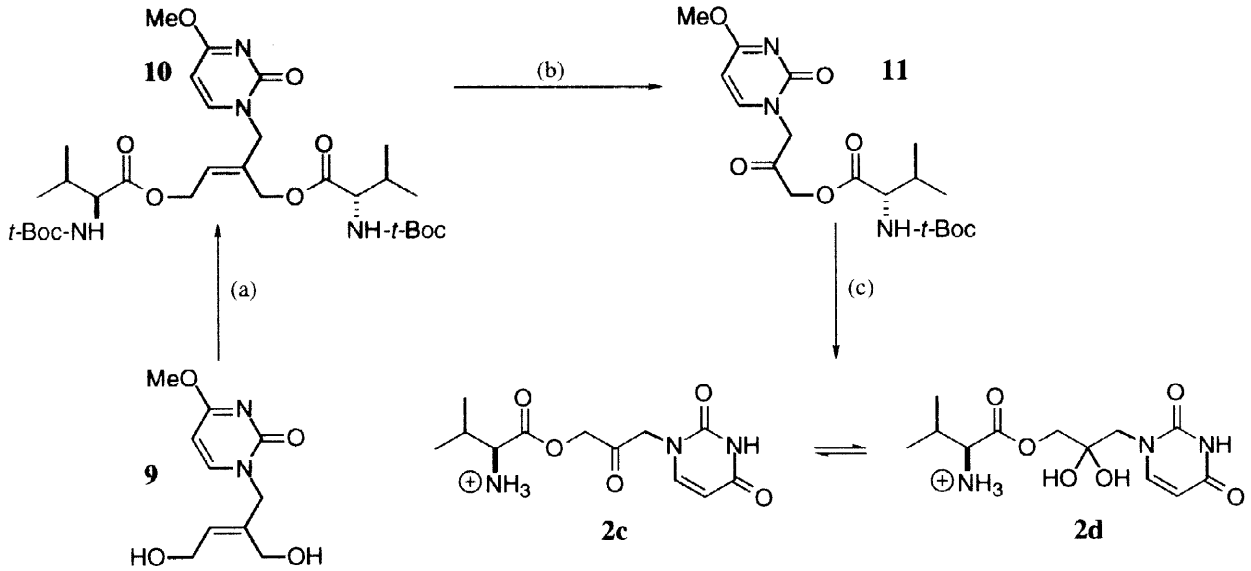
A solution of **3** in D_2O at pD 3 appeared to contain a single species; the methylene group gave rise to an ABM multiplet in the ^1H nmr spectrum and a signal at δ87 in the ^{13}C nmr spectrum indicated the presence of the hemiaminal **3c** or the hydrate **3e**. Lack of splitting of the peak at δ87 in the ^{13}C nmr spectrum of ^{15}N-labelled **3** and no correlation between the valinyl α-carbon and the CH proton of the glycoaldehyde unit in HMBC experiments strongly suggested that the hydrate **3e** was present. Electrospray ionisation mass spectrometry of **3** revealed peaks corresponding to MH^+ for all three hydration states, increasing cone-voltage biased the distribution of these species in favour of the dehydrated states [5].

Having characterised the behaviour of **3** we set about the synthesis of the more complicated aminoacyl compounds **2**, Figs. 3 & 4. The synthetic strategy again employed oxidative olefin cleavage as a means of generating the reactive carbonyl function. In the adenine series, Fig. 3, the iminophosphorane **6** [2, 6] served as a convenient starting material. Double acylation was best achieved using *iso*-butyl-chloroformate to generate a mixed anhydride which reacted with protected valine to generate **7**. Ozonolytic cleavage with reductive work-up of the olefin of **7** provided a mixture of **8** and **5** which were separated by chromatography. Simultaneous deblocking of the aromatic and aliphatic amino groups of **8** was accomplished using dilute acid. After neutralisation the product was observed to exist in two hydration/tautomeric states in the ratio 2:1 in D_2O at pD 4. The major species in aqueous solution was shown to be the ketone hydrate **2b** (^{13}C nmr: δ93; ^1H nmr: both CH_2 signals singlets). The minor species in aqueous solution was identified as the ketone **2a** (^{13}C nmr: δ199; ^1H nmr: one CH_2 AB system). Electrospray ionisation mass spectrometry revealed peaks corresponding to MH^+ for all three possible hydration states. The ketone proved to be the sole species in d_6-DMSO where increased stability allowed fuller characterisation which was assisted by the synthesis of labelled material starting from ^{15}N-labelled L-valine (^{13}C nmr: δ197 (not split by ^{15}N *cf.* valinyl-α-carbon, *J* 7.5Hz); ^1H nmr: both CH_2 signals AB systems, valinyl-NH_2 split by ^{15}N, *J* 72Hz).



(a) *i*-BuOCOCl, THF, *t*-Boc-L-valine, Et_3N, DMAP (55%); (b) i) O_3, CH_2Cl_2, ii) Me_2S (45%); (c) 1M HCl:1,4-dioxane (1:1)

Fig. 3 Synthesis of valinyl-adenine derivative



(a) *i*-BuOCOCl, THF, *t*-Boc-L-valine, Et_3N, DMAP (60%); (b) i) O_3, CH_2Cl_2, ii) Me_2S (57%); (c) 1M HCl:1,4-dioxane (1:1) (quant.)

Fig. 4 Synthesis of valinyl-uracil derivative

In the uracil series the lactim methyl ether **9** [2,6] was transformed by a similar double acylation reaction into **10**. Selective ozonolysis of the trisubstituted olefin of **10** was accomplished by calibrating an ozone-enriched stream of oxygen using destruction of the chromophore of Solvent Red 19 and then passing one equivalent of ozone through a solution of **10** in CH_2Cl_2. Double deprotection of the resultant ketone **11** by treatment with dilute acid furnished the valinyl-uracil derivative in quantitative yield. Similar spectroscopic techniques to those employed before revealed that this material exists as a 1:1 mixture of ketone **2c** and hydrated ketone **2d** in aqueous solution at pH 3.

Conclusion

In conclusion the synthesis of three potentially prebiotic aminoacylated materials has been achieved. A combination of spectroscopic techniques has demonstrated the solution structures adopted by these materials. The hydration behaviour of **2** is significant in that it parallels that of the monomers **1** for which predisposed phosphoketonic enolate formation has been shown. It is thus possible that the compounds **2** will function as chain initiators in the aldol based polymerisation of monomers **1**. Studies on the enolisation behaviour of **2** and **3** and results of polymerisation experiments will be reported in due course.

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