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Synthesis and Solution Structures of Aminoacyl Compounds of Potential Prebiotic Significance

John D. Sutherland* and Stephen D. Cook

The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K..

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Abstract The chemical synthesis and solution structure determination of aminoacylated glycoaldehyde and base substituted dihydroxyacetone derivatives are described. © 1998 Elsevier Science Ltd. All rights reserved.

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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.



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).



(a) (Im)₂CO, THF, t-Boc-L-valine, Et₃N, DMAP (45%); (b) i) O₃, CH₂Cl₂, ii) Me₂S (98%); (c) 1M HCl:1,4-dioxane (1:1) (quant.)

Fig. 2 Synthesis of valinyl-glycoaldehyde

A solution of 3 in D₂O 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 $\delta 87$ in the ¹³C nmr spectrum indicated the presence of the hemiaminal 3c or the hydrate 3e. Lack of splitting of the peak at $\delta 87$ in the ¹³C nmr spectrum of ¹⁵N-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 value 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 D₂O at pD 4. The major species in aqueous solution was shown to be the ketone hydrate **2b** (¹³C nmr: δ 93; ¹H nmr: both CH₂ signals singlets). The minor species in aqueous solution was identified as the ketone **2a** (¹³C nmr: δ 199; ¹H nmr: one CH₂ 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 d₆-DMSO where increased stability allowed fuller characterisation which was assisted by the synthesis of labelled material starting from ¹⁵N-labelled L-valine (¹³C nmr: δ 197 (not split by ¹⁵N cf. valinyl- α -carbon, J 7.5Hz); ¹H nmr: both CH₂ signals AB systems, valinyl-NH₂ split by ¹⁵N, J 72Hz).



(a) *i*-BuOCOCl, THF, *t*-Boc-L-valine, Et₃N, DMAP (55%); (b) i) O₃, CH₂Cl₂, ii) Me₂S (45%); (c) 1M HCl:1,4-dioxane (1:1)

Fig. 3 Synthesis of valinyl-adenine derivative



(a) *i*-BuOCOCl, THF, *t*-Boc-L-valine, Et₃N, DMAP (60%); (b) i) O₃, CH₂Cl₂, ii) Me₂S (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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