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Biomimetic self-condensation of malonates mediated by nucleosides

Qi Ji^a, Howard J. Williams, Charles A. Roessner, and A. Ian Scott^b

Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, TX 77843, USA

Abstract

Nucleoside mediated Claisen condensation of malonates has been achieved under biomimetic weak acid conditions, pH 3 or 4, 0.15 M NaCl, and 0.125 M Mg²⁺. The result illustrates the catalyzing property of end-nucleosides of t-RNA in the RNA world.

It has been suggested that the most primitive organisms used RNA's rather than proteinaceous enzymes as catalysts for their metabolic pathways.^{1,2} Molecular mechanisms were proposed by Scott for carbon-carbon bond forming processes (Figure 1) in the RNA world leading to the lipids necessary for the membranes.³ However, to our knowledge, no self Claisen condensation of nucleoside malonates has been reported. In this work, self-condensation of nucleoside malonates has been explored.

Previous attempts to observe Claisen condensation using solutions of adenosine malonate or deoxyadenosine malonate under various conditions were unsuccessful.⁴ As the active amino group of adenosine might interfere with the condensation and accelerate the hydrolysis of adenosine malonate, nucleoside malonates with lower polarity (**5a** and **5b**, Figure 2) were used in the condensation experiments.

The nucleoside malonates were synthesized from the corresponding nucleosides as shown in Figure 2. Separation of the 2'- and 3'- isomers of the nucleoside malonates was not possible because they immediately re-isomerized in solvents. NMR spectra confirmed that the malonyl groups of nucleoside malonates were switching between the 2'- and 3'-OH of the nucleosides.

A series of condensation experiments was carried out in aqueous solution under acidic condition, as shown in Table 1 and Scheme 3. For some experiments, we added Poly-U or Poly-A to see if the polynucleotides had some template effect^{4,5} for the condensation. For most experiments, Mg²⁺ was used as catalyst. All the experiments were carried out in 0.15 M NaCl solution which is similar in concentration to sea water. After 30 h incubation at 37 °C, the reaction mixture was analyzed by TLC (CHCl₃:CH₃OH = 2:1) to separate the products.

^aPresent address: Section of Molecular Genetics and Microbiology, School of Biological Sciences, University of Texas at Austin, Austin, TX 78712, USA

^bDeceased April 18, 2007

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Supplementary material

Supplementary material includes synthetic procedures, characterization and spectral data for compounds **2a-6a**, **3b-6b**, and ¹³C spectra of mono-benzylmalonate from Aldrich (lower trace) and from an ether extract of a 30 h incubation (upper trace).

As seen from Table 1, in the presence of Mg^{2+} (entry 1, 2, 5 and 6), the nucleoside malonates were converted into the corresponding 1,3-acetonedicarboxylic acid esters in yields of around 90% (Scheme 3). No template effects were observed in our experiment. Magnesium cation, as catalyst,⁶ was essential for successful condensation (entries 3, 4, 7 and 8). Generally, Claisen condensations of malonate oxyesters happen only under basic and harsher conditions. As a control experiment, mono-benzylmalonate (Aldrich) was incubated under the same reaction conditions and was unchanged after 30 h as indicated by a ^{13}C spectrum of ether reaction mixture extract. Our successful condensation experiment under acidic and mild condition (aqueous solution, no enzyme, no imidazole and body temperature) may suggest that the malonate moiety can be highly activated by linking to nucleosides and therefore can easily undergo a biomimetic decarboxylative Claisen condensation.

Although some examples of biomimetic self Claisen condensation of malonate esters had been reported,⁷⁻¹⁴ all used thioesters or amides as substrates, with the exception of Scott^{13,14} in which malonate catechol esters or monobenzyl malonates were used as substrates. Our results are the first to show that malonate can be activated simply by binding to nucleoside, and will provide us further understand to the function of the end-nucleosides of t-RNA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Mechanisms proposed for polyketide biosynthesis in the RNA world

Figure 2.
Synthesis of nucleoside 2'- and 3'- malonates.

Figure 3.
Decarboxylative Claisen condensation of nucleoside 2'- and 3'- malonates.

Table 1

Conditions for condensation experiments.

Entry	Substrate	Template	Condition	Product	Yield
1	5a (50 mM)	Poly-U (50 mM U)	0.15M NaCl, 0.125 M MgCl ₂ , pH 4	6a	93%
2	5a (50 mM)	None	0.15M NaCl, 0.125 M MgCl ₂ , pH 4	6a	90%
3	5a (50 mM)	Poly-U (50 mM U)	0.15M NaCl, pH 4	None	
4	5a (50 mM)	None	0.15M NaCl, pH 4	None	
5	5b (50 mM)	Poly-A (25 mM A)	0.15M NaCl, 0.125 M MgCl ₂ , pH 3	6b	86%
6	5b (50 mM)	None	0.15M NaCl, 0.125 M MgCl ₂ , pH 3	6b	87%
7	5b (50 mM)	Poly-A (25 mM A)	0.15M NaCl, pH 3	None	
8	5b (50 mM)	None	0.15M NaCl, pH 3	None	