Prebiotic Chemistry of Formamide

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The RNA World Hypothesis

Formamide as Prebiotic Probe

“Simulations based on Density Functional Theory show that formamide is the most stable species with molecular formula “CHON”

Pauzat, F. et al. 6th EANA 2006

“This one-carbon molecule was detected in the gas phase of interstellar medium” Crovisier, J. Astrobiology: Future Perspectives, Kluwer Eds, 2004 Chapter 8, p. 179-203.


And in Jupiter’s satellite Europa

“and tentatively in the solid phase on grains around the young stellar object W33A “

Formamide . Physical and chemical properties

“Formamide has a high boiling point, without azeotropic effects, and a wide range of uses as a solvent. It has an efficient solubilizing effect on nucleobases, nucleosides, nucleotides, amino acids, proteins, sugars, metals, and salts”

A comparison of micelle formation of ionic surfactants in formamide, in N-methylformamide and in N, N-dimethylformamide.
M. Salim Akhter, Sadeq M. Alawi

Solvation dynamics of formamide and N, N-dimethylformamide in aerosol OT reverse micelles.
Shirota H, Segawa H.
Elemental Formamide Chemistry

Space conditions:
- HCN + H₂O +NH₃ + H₂O
- CH₄ + N₂
- PI
- ice
- UV
- Pyr
- ΔT or cat

Terrestrial conditions:
- NH₃ + HCOOH
- NH₃ + CO
- Δp

Radical conditions:
- HCN + H₂O
- He-Ne laser
- Radical conditions
- HCNO
- NH₄⁺ NCO⁻
- CO CO₂ N₂O
- He-Ne laser

Degradation:
- H₂N⁻
- H₂O
- HCN
- H₂O
- HNCO
- H₂
- NH₂
- COx
Formamide prebiotic chemistry: Pioneering studies.

The role of minerals on prebiotic processes. A general overview

- Minerals can accumulate the prebiotic precursors (concentration effect)
- Minerals can act as catalytic environments, reducing the activation energy for the formation of products
- Minerals can tune the selectivity of prebiotic syntheses
- Minerals may act as a template
- Minerals are benign in environments to preserve newly formed biomolecules from degradation
A Possible Prebiotic Synthesis of Purine, Adenine, Cytosine, and 4(3H)-Pyrimidinone From Formamide: Implications for the Origin of Life

Raffaele Saladino, a, * Claudia Crestini, b Giovanna Costanzo, c Rodolfo Negri d and Ernesto Di Mauro c, d

Catalyst CaCO₃, Kaolin, Zeolite, Alumina, Silica
Analyzing the reaction mechanism. $^{13}$C-/$^{15}$N-NMR Experiments “route of the pyrimidine ring”

$$\text{Heat} \quad \text{*NH}_2\text{COH} \quad \rightarrow \quad \text{HCN} + \text{H}_2\text{O}$$

$$\text{*NH}_2\text{COH} + \text{H}_2\text{O} \quad \leftrightarrow \quad \text{HCO}_2\text{NH}_4$$

$$2 \quad \text{H}_2\text{O}^+ \quad \leftrightarrow \quad \text{H}_2\text{N}^+ - \text{NH}_2 \quad \text{formamide dimer}$$

$$+ 2 \quad \text{HCN} \quad \leftrightarrow \quad \text{Bredereck Ang. Chemie 1959}$$

$$- \quad \text{H}_2\text{O} \quad \leftrightarrow \quad \text{NH}_3$$

$\text{University of Tuscia, Viterbo, Italy}$
Analyzing the reaction mechanism. $^{13}$C-$^{15}$N-NMR Experiments “route of the pyrimidine ring”

$$\text{formamide dimer}$$

Redox
Synthesis and Degradation of of Nucleobases and Nucleic Acids by Formamide in the Presence of Montmorillonites

Raffaele Saladino, a, * Claudia Crestini, b Umberto Ciambecchini, a Fabiana Ciciriello, c Giovanna Costanzo, c and Ernesto Di Mauro c, d

Bu, Y.; Lin, M.C. Langmuir 1994
AICA: Amino Imidazole Carboxy Amide
fAICA: formyl Amino Imidazole Carboxy Amide
fpurine: N(9)-formyl purine
Analyzing the reaction pathway. The “route of the pyrimidine ring”
The first example of Chemiomimetic pathway

"certain biosynthetic pathways can be considered as chemiomimetic of early prebiotic chemistry"


In exant cell!
The origin of sugars and nucleosides
One-pot TiO2-Catalyzed Synthesis of Nucleic Bases and Acyclonucleosides From Formamide: Implications for the Origin of Life

Raffaele Saladino, a, * Claudia Crestini, b Umberto Ciambecchini, a Rodolfo Negri, c Giovanna Costanzo, c Ernesto Di Mauro c.
Thymine synthetic pathway

\[ *\text{NH}_2\text{COH} + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_2\text{NH}_4 \]

\[ *\text{NH}_2\text{COH} \xrightarrow{\text{TiO}_2} \text{HCOH} \]

R. H. Barker, 1975
Sugars synthetic pathway. The formose reaction. Butlerow, 1861.

Single headed arrows represent aldol Condensations. Double-headed arrows represent enolizations. Aldotrose can undergo a reverse aldol condensation.

\[
\begin{align*}
\text{aldotetrose} & \quad \xrightarrow{\text{H}^+} \quad \text{aldotrose} \\
\text{aldotrose} & \quad \xrightarrow{\text{H}^+} \quad \text{glyceraldehyde} \\
\end{align*}
\]
A novel formose reaction

NH₂

+ NH₂CHO →

NHCHO

N9-formylpurine

TiO₂

NHCHO

N9-formylpurine

Complex nucleoside derivatives
Role of clays in the prebiotic synthesis of sugar from Formamide

Raffaele Saladino,¹*, Neri Veronica, Claudia Crestini,²

Scheme: Formamide (HCONH₂) reacts with Mg(OH)₂ or Pb(NO₃)₂ (2%, w/w) at 160°C for 24 h to form a mixture of purines, pyrimidines, and carbodiimide.
H₂NCH₂ + H₂C → Mg(OH)₂ or Pb(NO₃)₂ or mixture (2%, w/w) → 160°C, 24h DHA, H₂O → deoxy-pentoses, pentoses, dihydroxyacetone

N.W. Gabel, C. Ponnampemuna, Nature 1967

KSF
Formamide prebiotic chemistry with extraterrestrial materials
Synthesis and Degradation of Nucleic Acid Components by Formamide and Cosmic Dust Analogues

Raffaele Saladino, a,∗ Claudia Crestini, b Veronica Neri, a John R. Brucato, d Luigi Colangeli, d Fabiana Ciciriello, c Giovanna Costanzo, c and Ernesto Di Mauro c, d

L2021B6
Cosmic dust analogue olivines (Mg,Fe)$_2$SiO$_4$ are synthesized by laser ablation technique (Nd-YAG 10$^8$ Wcm$^{-2}$). Oxide pellets of MgO, FeO$_2$, SiO$_2$ are used as laser target vaporized in 10 mbar atmosphere of O$_2$.

CDAs qualitative composition

Fe  Si  Mg

olivine
fayalite
forsterite

CDAs or olivines

DHU: 5,6-DiHydroUracil

HCONH2

160°C, 48h

DHU: 5,6-DiHydroUracil

pyrimidinone

cytosine

uracil

purine

urea
Moving towards the metabolism
REDUCTIVE CITRIC ACID CYCLE

In eubacteria and archea

- CO₂
- pyruvate → oxaloacetate → malate → fumarate → succinate → ketoglutarate
- citrate → cis-aconitate
- isocytrate → oxalosuccinate
- ATP
- GTP

NUCLEIC ACID BASES
AMINO ACIDS
SUGARS AND LIPIDS
On a Hypothetical Generational Relationship between HCN and Constituents of the Reductive Citric Acid Cycle

by Albert Eschenmoser

Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, Hönggerberg HCI H309, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich (e-mail: eschenmoser@org.chem.ethz.ch)

and

The Skaggs Institute for Chemical Biology at The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

For Leslie E. Orgel, the critical conceptualist
Metabolism part 1. Thermal conditions
Borate and Prebiotic Chemistry: A possible relationship with formamide

(Cleaves and Miller, *OLEB* 2002
Data evaluated for the *Ocean* scenario)
The effect of borate minerals on the synthesis of nucleic acid bases, amino acids and biogenic carboxylic acids from formamide

Raffaele Saladino, Maurizio Barontini, Cristina Cossetti, Ernesto Di Mauro, Claudia Crestini
The urea/carbodiimide condensation cycle

\[ \text{HCN} \quad \text{Strecker condensation} \quad \begin{array}{c} \text{HCN} \\ \text{NH}_3 \end{array} \rightarrow \begin{array}{c} \text{HO} \\ \text{NH}_2 \end{array} \quad \text{Gly} \]

\[ \begin{array}{c} \text{HCN} \\ \text{NH}_3 \end{array} \rightarrow \begin{array}{c} \text{HO} \\ \text{NH}_2 \end{array} \quad \text{Gly} \]

\[ \text{H}_2\text{N-C} \quad \text{- H}_2\text{O} \quad \text{N-fGly} \]

\[ \text{H}_2\text{N-C} \quad \text{- NH}_3 \quad \text{N-fGly} \]

\[ \text{HCN} \quad \text{minerals} \quad \text{T} = 160^\circ\text{C} \]
The role of the formamide/zirconia system in the synthesis of nucleobases and biogenic carboxylic acids

Raffaele Saladino, Neri Veronica, Claudia Crestini, Costanzo Giovanna, Michele Graciotti, Ernesto Di Mauro

Baddeleyte ZrO$_2$
Zircon ZrSiO$_4$
Lithium zirconate Li$_2$ZrO$_3$
Lead zirconate PbZrO$_3$
Barium zirconate BaZrO$_3$
Zirconium oxinitrate ZrO(NO$_3$)$_2$
Catalytic effects of Murchison material: prebiotic synthesis and degradation of RNA precursors

Raffaele Saladino,* Claudia Crestini, Cristina Cossetti, Ernesto Di Mauro, David Deamer

\[\begin{align*}
1 & : \text{HO} & 2 & : \text{HN=C=O} & 3 & : \text{HN=CO} & 4 & : \text{HO} \\
5 & : \text{O} & 6 & : \text{HN} & 7 & : \text{H}_2\text{N} & 8 & : \text{NH}_2
\end{align*}\]

\[\begin{align*}
9 & : \text{Me} & 10 & : \text{HO} & 11 & : \text{OHCH} & 12 & : \text{HO} \\
13 & : \text{HO} & 14 & : \text{HO}
\end{align*}\]

HCONH \_2 \xrightarrow{\text{murchinson dust}} \text{140°C, 2 days}
FIST-REDUCTIVE CITRIC ACID CYCLE

- Pyruvate → Oxaloacetate
- Oxaloacetate → Malate
- Malate → Fumarate
- Fumarate → Succinate
- Succinate → Ketoglutarate

Reactions involving ATP and GTP:

- Pyruvate + GTP → Oxaloacetate + ATP
- Fumarate + GTP → Succinate + ATP
- Oxaloacetate + GTP → Malate + ATP
- Succinate + GTP → Ketoglutarate + ATP

Carbon dioxide (CO₂) is produced at multiple stages of the cycle.
Metabolism part 2. Photochemical conditions
UV

3.2 eV

\text{NH}_2\text{CHO} + \text{OH} \quad \text{H} \quad \text{NH}_2\text{C}OH\text{OH} \quad \text{Initiates coupling reactions}
\quad \text{Initiates oxidation reactions} \quad \text{Products (C,H,N,O)}
Photochemical synthesis of citric acid cycle intermediates based on titanium dioxide

Raffaele Saladino, a,*, John Robert Brucato, Antonio de Sio, b
Giorgia Botta, Emanuele Pace, Lisa Gambicorti

TiO$_2$ Anatase

Monochromatic Irradiation 3.2 eV

Anatase commercial
Anatase ground
Tab 2.1: Integral of the photons and energy dose of the different irradiation runs at 387.5 nm.

<table>
<thead>
<tr>
<th>Mineral Powder</th>
<th>Photon Dose</th>
<th>Energy dose (mW*s=J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. : Anatase BG</td>
<td>5.32 (^{15}) Photons</td>
<td>2.7</td>
</tr>
<tr>
<td>Exp. : Anatase FG</td>
<td>5.32 (^{15}) Photons</td>
<td>2.7</td>
</tr>
<tr>
<td>Exp. : Rutile</td>
<td>3.56 (^{15}) Photons</td>
<td>1.8</td>
</tr>
<tr>
<td>Exp. : Mix Rutile + Anatase</td>
<td>2.90 (^{15}) Photons</td>
<td>1.5</td>
</tr>
<tr>
<td>Exp. : Formamide</td>
<td>2.94 (^{15}) Photons</td>
<td>1.5</td>
</tr>
</tbody>
</table>

BG = Big grains >500 nm
FG = Fine grains <100 nm
R. Saladino, J.R. Brucato, A. de Sio, E. Pace
The process shown in the diagram involves the reaction of formamide (H₂NCHO) with TiO₂ Anatase under synchrotron hv conditions, leading to the formation of various compounds, including pyridine (C₅H₄N), pyrimidine (C₄H₄N₂), and other derivatives.
FIST-REDUCTIVE CITRIC ACID CYCLE

SUGARS AND LIPIDS
NUCLEIC ACID BASES
AMINO ACIDS

ATP
GTP

CO₂

pyruvate → oxaloacetate → malate → fumarate → succinate → ketoglutarate

citrate → acetate → cis-aconitate → isocitrate → oxaloacetate

University of Tuscia, Viterbo, Italy
<table>
<thead>
<tr>
<th>Mineral Type</th>
<th>Year</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal oxides (impact-induced minerals)</td>
<td>2001</td>
<td>CaO, MnO₂, SiO, MgO, Al₂O₃, SiO₂, FeO, CuO, CaCO₃</td>
</tr>
<tr>
<td>Carbonates</td>
<td>2003</td>
<td>TiO₂</td>
</tr>
<tr>
<td>Volcanism-related minerals</td>
<td>2004</td>
<td>Zeolites (Al, Ca, Na silicates), kaolin, montmorillonites (μcrystalline phyllosilicates) (Na, Ca) (Al, Mg)₆ (Si₄O₁₀)₃ (OH)₆ · nH₂O</td>
</tr>
<tr>
<td>Clays</td>
<td>2005</td>
<td>Forsterite</td>
</tr>
<tr>
<td>Circumstellar/cometary dusts</td>
<td>2006</td>
<td>Olivine</td>
</tr>
<tr>
<td>Phosphates</td>
<td>2007</td>
<td>Fayalite</td>
</tr>
<tr>
<td>Fe/S/Cu</td>
<td>2008</td>
<td>Forsterite</td>
</tr>
<tr>
<td>Zirconium</td>
<td>2010</td>
<td>Pirite, pirrotine, covellite, etc</td>
</tr>
<tr>
<td>Boron</td>
<td>2011</td>
<td>ZrO₂, ZrSiO₄, CeZrO₄, PbZrO₃, etc</td>
</tr>
<tr>
<td>Murchison</td>
<td>2011</td>
<td>Hydroboracite, ulexite, rodizite, ambersite, etc</td>
</tr>
</tbody>
</table>
Minerals catalysed prebiotic synthesis of nucleic acid components from formamide. Degree of confidence