source of ions in Europa's ocean may be different from those in Earth's oceans (*8*), but they should satisfy the conductivity requirement. A much thicker layer of water ice, even if it is heavily contaminated with frozen brine, cannot explain the data because the ions are relatively immobile compared with those in liquid water. Any plausible ocean flow (fluid currents relative to the ice shell) is unimportant because it will have a much lower velocity than the rotational motion of Europa's surface. A partially melted ice layer could match the required conductivity but is physically implausible because the melt would have to be interconnected over large distances, which would result in the melt percolating through and separating from the ice driven by the density difference of ice and water. Kivelson *et al.* (*1*) argue that Europa's tenous, external ionosphere also cannot provide the required conducting layer. The induced field declines as the inverse cube of the radius from the surface of the conducting layer, and any deep-seated conducting layer (such as a metallic core or a magma ocean in the rocky core) would therefore lead to a much lower field than is observed.

Some more exotic possibilities cannot be excluded (such as graphite or some other relatively high conductivity material, plausibly carbon-rich, intermingled within the ice but interconnected at the grain size scale), but a water layer is the most plausible explanation. A compelling demonstration of its existence or absence may be reached from gravity and altimetry data in the proposed Europa orbiter. The predicted diurnal tidal amplitude is over an order of magnitude larger for a Europa with a global ocean than for a Europa without one. More complex, intermediate scenarios can be envisaged (such as ice "grounding" on the underlying rocky topography in some places and not others). But the orbiter results will likely settle the fascinating question of whether Europa has an ocean. Defined broadly enough, oceans may not be that rare, but Europa's case may be special because the tidal heating may allow liquid water to get closer to the surface, possibly including occasional eruptions or flows. After Mars, it remains the most attractive extraterrestrial environment within our solar system in which to seek evidence of past or present life.

References and Notes

1. M. G. Kivelson *et al.*, *Science* **289**, 1340 (2000).
2. For a review of the Galilean satellites and Galileo results, see A. P. Showman and R. Malhotra, *Science* **286**, 77 (1999).
3. See sse.jpl.nasa.gov/missions/jup_missns/europa.html.
4. The history of theoretical work is long and complex; the pioneers were P. Cassen, R. T. Reynolds, and S. J. Peale [*Geophys. Res. Lett.* **6**, 731 (1979)] [corrected subsequently in *Geophys. Res. Lett.* **7**, 987 (1980)].
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7. Jupiter is a fluid planet and, unlike Earth, does not have a valid coordinate system fixed to actual objects. For example, we can talk about a satellite being "over" North America, but we have no corresponding meaningful language for Jupiter. The great red spot is not fixed. The location of Europa relative to Jupiter's field (called System III longitude) is central to the interpretation of the data.
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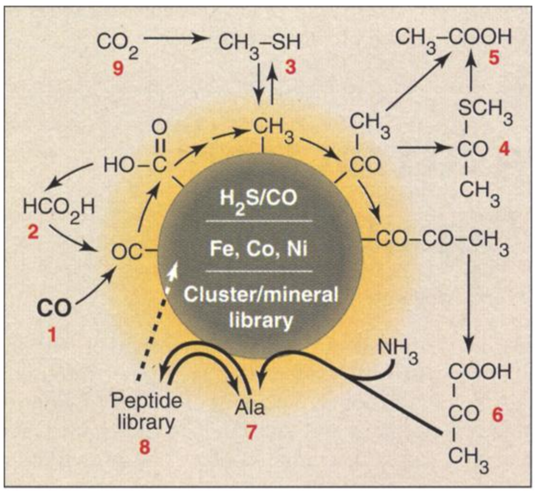
PERSPECTIVES: ORIGIN OF LIFE

Life as We Don't Know It

Günter Wächtershäuser

Theories of the origin of life on Earth fall into two general categories. Prebiotic broth theories postulate a protracted origin by the self-assembly of high–molecular weight structures, such as RNA, proteins, and vesicles, in a cold prebiotic broth of preaccumulated modules (*1*). More recently, theories based on a hydrothermal origin have gained ground. For example, the theory of a pressurized iron-sulfur world (*2*) suggests a fast origin by an autotrophic metabolism of low–molecular weight constituents, in an environment of iron sulfide and hot magmatic exhalations. Cody *et al.*'s (*3*) results on page 1337 of this issue provide key support for the latter theory and greatly strengthen the hope that it may one day be possible to understand and reconstruct the beginnings of life on Earth.

Pyruvic acid, CH_3-CO-COOH, is one of the most crucial constituents of extant intermediary metabolism. It occurs in numerous metabolic pathways, notably the reductive citric acid cycle and the pathways that produce amino acids and sugars. It has been suggested that pyruvic acid or its anion pyruvate formed primordially by double carbonylation (*4*). Cody *et al.* provide experimental support for this suggestion. They show that pyruvic acid forms from formic acid in the presence of nonylmercaptane and iron sulfide at 250°C and 200 MPa. Water is initially absent and forms only by the dehydration of the formic acid. This result poses fascinating thermodynamic and kinetic questions. Pyruvic acid is an extremely heat-sensitive compound that decomposes at its boiling point of 165°C. It appears paradoxical that at the very high temperature required for dehydration of formic acid, the relatively unstable pyruvic acid can form and exist at detectable concentrations. Moreover, it is astonishing that acetic acid is formed at a lower yield than pyruvic acid. The explanation may well lie in the very high pressure.



Reactions in the iron-sulfur world. Reaction conditions are given in the table on the next page. The dotted arrow represents ligand feedback.

The work is particularly exciting because experience with organic synthesis in the high-pressure/high-temperature regime is very limited. The experiments require a combination of 200 MPa (corresponding to a rock depth of about 7 km or a 20-km water column) and 250°C, in addition to high CO pressure in the absence of water. It remains to be established whether such conditions are geophysically possible.

The new finding, if it holds, fills a critical gap in the experimental picture of the iron-sulfur world (see the figure). All individual reaction steps for a conversion of carbon monoxide **1** to peptides **8** have now been demonstrated: formation of methyl thioacetate **4** (*4*), of pyruvate **6** (*1*), of alanine **9** by reductive amination of pyruvate **6** (*5*), and of peptides **8** by activation of amino acids with CO/H_2S (*6*). The challenge will now be to overcome the discrepancies in

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the reaction conditions and to establish the right conditions for autocatalysis (reproduction) and evolution. This may involve a primitive version of the citrate cycle in which (methyl) thioacetate and pyruvate participate (*3*, *6*, *7*) and/or ligand (notably peptide) feed back to the catalytic metal center (*3*, *6*).

The reaction scheme in the figure is in substantial agreement with extant metabolism in terms of overall metabolic patterns, reaction pathways, and catalysts. The newly demonstrated formation of pyruvic acid by double carbonylation, however, has no analog in extant metabolism. It may have disappeared because of metabolic takeover, first by a reverse pyruvate-formate-lyase reaction and later, after the advent of thiamine pyrophosphate, by carboxylation with pyruvate oxidoreductase.

Cody *et al.*'s results support the view that the primordial organisms were autotrophs feeding on carbon monoxide. But more importantly, the reactions shown in the figure can still occur today because the required conditions are in general still available on Earth, albeit at a lesser frequency. They may thus be a source for geoorganics today; these geoorganics may serve as food for extant heterotrophs, and primitive microbes feeding on CO might still be tracked down in hot pressurized spaces previously inaccessible to exploration.

The reaction conditions chosen by Cody *et al.* are a compromise between the requirements of geochemical modeling and the requirements of the experimental technique. CO gas cannot be used at these very high pressures without extreme danger. Decomposition of formic acid was therefore used as a source for CO. This requires a temperature of 250°C and the absence of water. But in the real world, the temperature may well have been lower, as may have been the pressure. On early Earth, outgassing (the release of gases by volcanic activity) must have been massive and omnipresent, with a wide spectrum of physical conditions, which only later became restricted to vents and volcanoes because of a thickening crust.

CONDITIONS FOR REACTIONS IN THE FIGURE

Reaction	Catalyst	Temp.	Pressure	Ref.
(1) → (2)	(Fe,Ni)S	100°C	0.2 MPa	(*4*)
(1) → (3)	(Fe,Ni)S	100°C	0.2 MPa	(*4*)
(9) → (3)	FeS	100°C	0.2 MPa	(*8*)
(1) → (5)	(Fe,Ni)S	100°C	0.2 MPa	(*4*)
(3) → (4)	(Fe,Ni)S	100°C	0.2 MPa	(*4*)
(2) → (6)	FeS	250°C	200 MPa	(*1*)
(6) → (7)	FeS	100°C	0.2 MPa	(*5*)
(7) → (8)	(Fe,Ni)S	100°C	0.2 MPa	(*6*)

It is occasionally suggested that experiments within the iron-sulfur world theory demonstrate merely yet another source of organics for the prebiotic broth. This is a misconception. The new finding drives this point home. Pyruvate is too unstable to ever be considered as a slowly accumulating component in a prebiotic broth. The prebiotic broth theory and the iron-sulfur world theory are incompatible. The prebiotic broth experiments are parallel experiments that are producing a greater and greater medley of potential broth ingredients. Therefore, the maxim of the prebiotic broth theory is "order out of chaos." In contrast, the iron-sulfur world experiments are serial, aimed at long reaction cascades and catalytic feedback (metabolism) from the start. The maxim of the iron-sulfur world theory should therefore be "order out of order out of order."

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PERSPECTIVES: NEUROBIOLOGY

Turning Attraction into Repulsion

Elena Pasquale

Neural circuits must be assembled with great precision in order to transmit and process information correctly. To form connections within a circuit during development, neurons extend processes under the influence of attractive and repellent molecular cues that help them to navigate the embryonic environment. Among these axon guidance molecules are ephrin ligands, membrane-anchored proteins that bind tightly to receptor tyrosine kinases of the Eph family (*1–3*). When the extending process (growth cone) of a neuron that has Eph receptors on its surface encounters ephrin ligands on the surface of another cell, the two cells adhere to each other through a "molecular Velcro" composed of Eph receptors and ephrins (see the figure). Yet, after the initial contact, the growth cone overcomes these adhesive forces and breaks away from the ephrin-coated cell surface. How can this happen? The report by Hattori *et al.* on page 1360 of this issue (*4*) proposes a solution for how the initial attraction/adhesion can be turned into repulsion. They demonstrate that the molecular Velcro is cut by a metalloprotease enzyme, which is activated after a time delay to cleave ephrin. Through this mechanism, the mechanical adhesion between ephrin and Eph on different cell surfaces is broken, resulting in the two cells moving apart.

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Ephrins interact directly with the 14 known Eph receptors, but there is some specificity: ephrin-A ligands preferentially bind to EphA receptors and ephrin-B ligands to EphB receptors. The five ephrin-A ligands are anchored to the cell surface through a glycosyl phosphatidylinositol (GPI) moiety, whereas the three ephrin-B ligands are anchored through a transmembrane segment. Expression patterns of Eph receptors and ephrin ligands determine which ligands interact with which receptors in particular tissues. This in turn dictates the precise spatial arrangement of signal activation, given that receptor- and ligand-bearing cells must be next to each other for the ephrin/Eph association to take place (juxtacrine signaling). The ephrin/Eph receptor interaction is unusual in other respects. Signals are propagated not only downstream of the Eph receptor but also downstream of the ephrin ligand (*1*, *2*) (see the figure). Through this bidirectional mode of signaling, two neighboring cells with distinct identities can reciprocally influence each other. Thus, for example, ephrin-