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The oxidation of the alpha-carbon of amines in hydrothermal condition: an alternative synthetic route of compounds containing amide bond

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ABSTRACT

Here we report experimental evidence for the simple synthesis of *N*,*N*-diethylhydroxylamine and an amide bond formation reaction from oxidation of the alpha-carbon of tertiary amines by the reaction of triethylamine and hydrogen peroxide in hydrothermal conditions. It is proved that 120 °C is a turning point: when the temperature is lower than that, the main product is *N*,*N*-diethylhydroxylamine as a result of a cope rearrangement reaction mechanism; on the contrary, the product is more complex and the main products are amides via a radical chain mechanism involving three steps: initiation, propagation, and oxidation, followed by decarbonylation and electrocyclization because the radical is easier to form under high temperature.

Water, a source of energy, and organic raw materials are assumed to be necessary for the origin and propagation of life.[1] On the basis of these assumptions, we can approach the origin-of-life problem by repeating the most plausible chemical processes leading from simple compounds to supramolecular complexes with biochemical properties, under the conditions found on primitive Earth.[2] Amide bonds, often called peptide bonds, covalently join the amino acids together to form a protein chain: for this reason, proteins are also known as polypeptides. Previous papers have already shown potential prebiotic pathways to peptide bond formation under the rough primordial conditions. Almost all of these methods are based on two steps: synthesis of amino acids (although only the simple amino acids, such as glycine, alanine,[3] and other alkyl amino acids,[4] could be made), and condensation of amino acids to form peptides.[5] However, in general the formation of oligopeptides from amino acids is a rather unfavorable reaction in water, thermodynamically and kinetically, as the reaction requires the removal of water from the reaction partners.[5a]

According to research by NASA astronomers using a 10-meter Keck II telescope, Jupiter's ice-encrusted moon Europa has hydrogen peroxide, a compound that could potentially provide energy for life. And the availability of oxidants like peroxide on Earth was a critical part of the rise of complex, multicellular life.[6] To prove this we chose hydrogen peroxide as the oxidant and hydrothermal conditions, similar conditions seen around the undersea hydrothermal vent which is considered as the most possible place for life's origin,[7] as the environment of the reaction. Moreover, we chose triethylamine as the reactant for two reasons. Firstly, from primary atmosphere (CO_2, N_2, etc.),[8] ethanol, acetic acid, and other organic compounds were synthesized by Fischer–Tropsch synthesis[9] or other synthetic methods[10] in hydrothermal systems. With these organics and N_2, triethylamine could be formed.[9] Secondly, the nitrogen atom in the tertiary amine has a weaker activity than that in primary or secondary amines, which could make the oxidation site on the carbon atom instead of on the nitrogen atom. Here, from the triethylamine and hydrogen peroxide, we synthesized some compounds containing the amide bond. In the experiment, the oxidant is green and we perform the reaction in hydrothermal conditions with no catalyst, which are also suitable on primitive Earth. And it is different from the traditional organic synthetic methods of compounds with an amide bond, which use more complex organic oxidants and lots of catalysts in toxic solvent.[11]

The gas chromatography–mass spectroscopy (GC–MS) spectrum indicated that there were no detectable organic compounds in the starting purified triethylamine. In a typical synthesis, 0.6 ml (4.3 mmol) purified triethylamine and 10 mL 30% (0.1 mol) hydrogen peroxide solution were mixed with water and then

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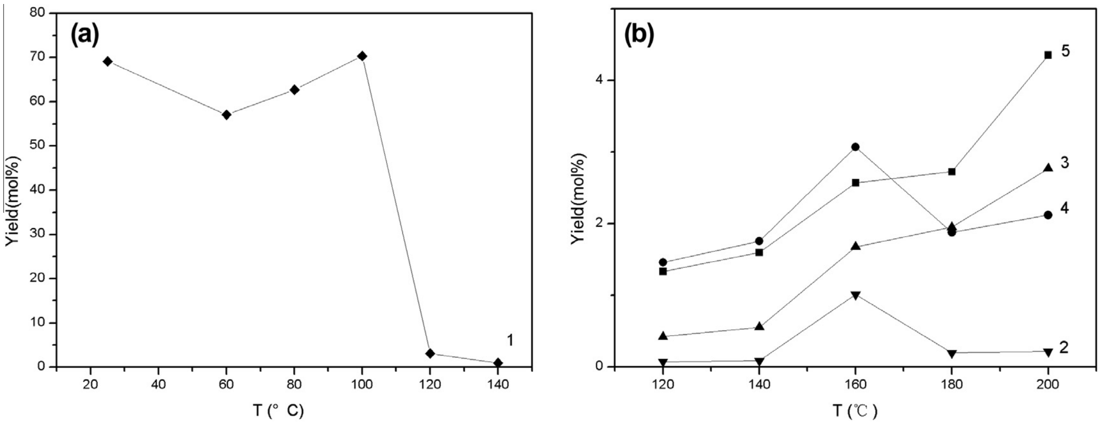
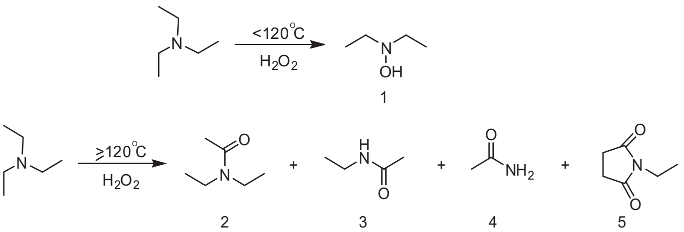
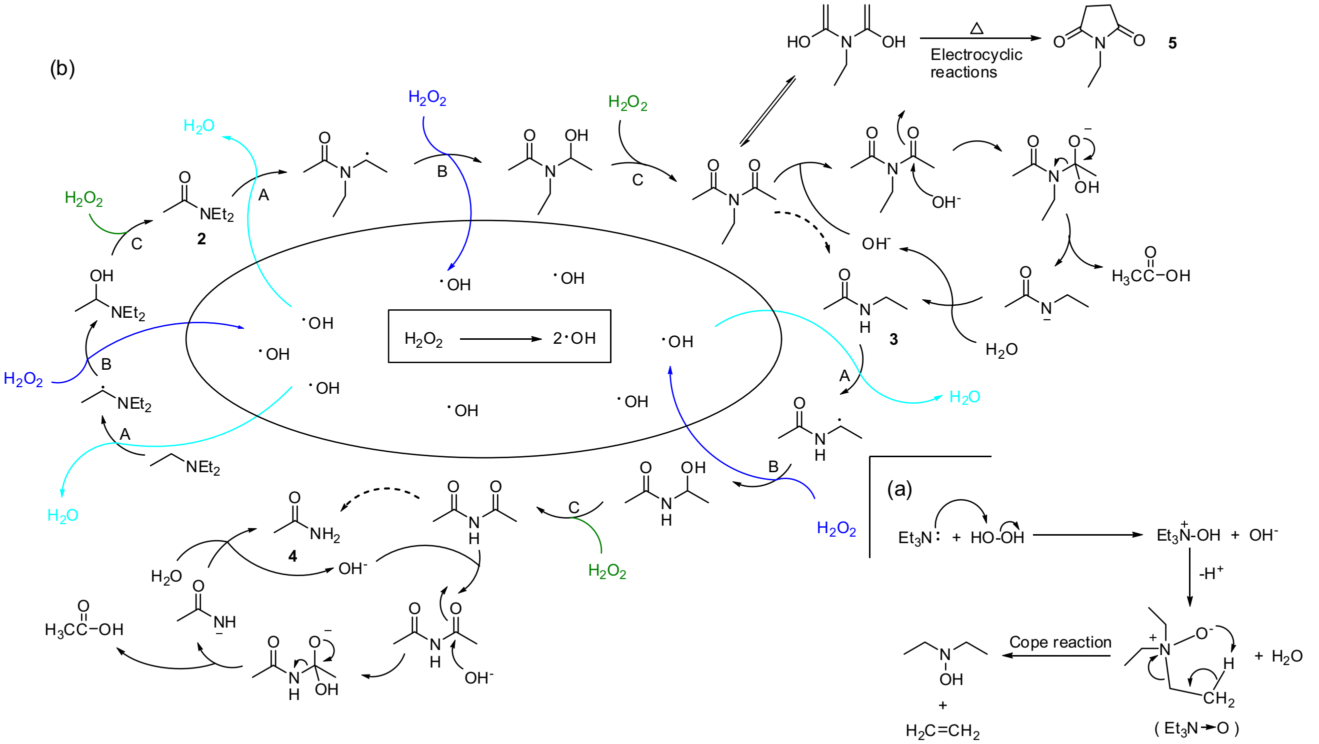


Figure 1. Yields of products at different temperatures. (a) the yield of *N*,*N*-diethylhydroxylamine(1); (b) the yields of *N*,*N*-diethylacetamide(2), *N*-ethylacetamide(3), acetylamine(4) and 1-ethylpyrrolidine-2,5-dione(5). Triethylamine: 4.3 mmol. 30% Hydrogen peroxide: 10 mL. Reaction time: 120 h.

added into each steel alloy (Fe–Cr–Ni alloy, GB-1220-92) autoclave with a filling capacity of 90% (approx. 1.4 MPa). The autoclaves were then sealed tightly and placed in the oven with the temperature ranging from 20 to 200 °C at the interval of every 20 °C. After 5 days, the solution in the autoclaves was taken out and analyzed. The final pH of the reaction mixture was 9.7. Gas chromatography–mass spectroscopy (GC–MS) was employed to identify the products. It is proved that 120 °C is a turning point: when the temperature is lower than that, the main product is *N*,*N*-diethylhydroxylamine(1); on the contrary, the product is more complex and the main products are amides: *N*,*N*-diethylacetamide(2), *N*-ethylacetamide(3), acetylamine(4), and 1-ethylpyrrolidine-2,5-dione(5), when the mass spectra of the products were compared to those of standard substances (Figs. S1–S5). The reaction can be represented as follows:



The tendency of yield dependence of the temperatures is shown in Figure 1. The yield of product 1 is from 57 mol % (60 °C) to 70 mol % (100 °C); product 2 and 3 reached the max-yield at 160 °C; the yields of the product 4 and 5 increased continuously with



Scheme 1. (a) Proposed Cope reaction mechanism for the synthesis of *N*,*N*-diethylhydroxylamine; (b) Proposed radical chain mechanism for the formation of compounds containing the amide bond.

temperature. We proposed different possible reaction mechanisms for reaction 1 and 2 in Scheme 1. The synthesis of *N*,*N*-diethylhydroxylamine (reaction 1) undergoes a cope rearrangement reaction below 120 °C (Scheme 1a). And when above 120 °C, because radical is easier to form under high temperature, the reaction 2 is believed to proceed through a radical chain mechanism involving three simple steps: initiation reactions (a hydroxyl radical from homolysis of hydrogen peroxide bond to triethylamine/amides to form a triethylamine/amide radical, denoted as A), propagation reactions (the radical was propagated to hydrogen peroxide to form 1-(diethylamino) ethanol/*N*-ethyl-*N*-(1-hydroxyethyl) acetamide/*N*-(1-hydroxyethyl) acetamide and a hydroxyl radical, denoted as B), and oxidation reactions (hydrogen peroxide oxidized the hydroxyl to carbonyl, denoted as C), followed by decarbonylation and electrocyclic reactions (Scheme 1b). The fact that we caught acetic acid in the reaction confirms the suggested mechanisms.

Through the experiments, we obtained two series of products. *N*,*N*-Diethylhydroxylamine (1), the main product (below 120 °C), is one of important compounds in polymer science as an inhibitor and antioxidant. It could also be used as middle reductant for quinines. The conversion process follows the main principles of green chemistry, e.g., one-step process with no energy consumption, no catalyst, and no organic solvents. The main products at higher temperature (above 120 °C) are amides and pyridine derivatives. The α-C of the amines is translated into carbonyl group to form amides, which means that the origin of the oligopeptides has another possibility: at first, the compounds with amide bond are formed from the oxidation of C–N chains, and then amination and carboxylation are achieved to form a peptide. The other product, 1-ethylpyrrolidine-2,5-dione(5), is similar to phthalimide, the latter is an important reactant to synthesize the amino acid in organic chemistry. Furthermore, we raise a hypothesis that peptides (or proteins) come from amination of α-C and carboxylation after the oxidation of C–N chains. In this way, we can easily obtain reactants to synthesize the amino acid and more complicated peptides without the first step of synthesis in the complex amino acids.

As discussed above, in our synthesis, *N*,*N*-diethylhydroxylamine is prepared at room temperature, with a considerable yield, which is useful in industry in terms of green synthesis and low cost. Moreover, we develop an amide bond formation reaction from oxidation of the C–N chains by the reaction of triethylamine and hydrogen peroxide in hydrothermal condition, which is different from the previous synthesis of peptide bond from amino acid condensation. And all the organic compounds used in the experiment have been approved as existing in the hydrothermal system of primitive Earth, which enhances the possibility of our hypothesis. We will work on it to find out more evidence to prove it, such as the carbonylation of ethanediamine and the amination of products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.005.

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