Heterocycl. Commun., Vol. 18(1), pp. 7–10, 2012 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/hc-2011-0054

Some heterocyclic compound formation under hydrothermal conditions: implications for prebiotic chemistry

Chao He, Bin Hu, Ziwei Liu, Yu Wang, Bohui Lv, Hongming Yuan, Ge Tian* and Shouhua Feng

State Key Laboratory of Inorganic Synthesis and Preparative Chemistry, College of Chemistry, Jilin University, Changchun 130012, China

* Corresponding author
e-mail: tiange@jlu.edu.cn

Abstract

The hydrothermal system is considered to be one of the most possible environments for the origin of life. Here we report a hydrothermal reaction from phenol and alanine to four important heterocyclic compounds, 2,3-dihydrobenzofuran (**1**), indoline (**2**), indole (**3**) and 2-methyl-1,2,3,4-tetrahydroquinoline (**4**). This reaction suggests a prebiotic route to synthesize the heterocyclic compounds which could be precursors for the chemical evolution of life.

Keywords: heterocyclic compound; hydrothermal synthesis; prebiotic chemistry.

Introduction

With potential relevance to the origin of life, the submarine hydrothermal vent has been the focus of much attention (Corliss et al., 1979; Martin et al., 2008). Under hydrothermal conditions the syntheses from inorganic molecules have already been carried out (Tian et al., 2007, 2010; Ji et al., 2008; He et al., 2010). Moreover, many bioorganic molecules have also been obtained, such as amino acids and their respective oligopeptides, phosphate esters, pyrimidine and purine bases (Hennet et al., 1992; Imai et al., 1999; Feng et al., 2008; Aubrey et al., 2009; Larowe and Regnier, 2009; Maheen et al., 2010). In our previous work, we synthesized phenol and alanine under similar conditions (Tian et al., 2007, 2010; Feng et al., 2008). In the present paper, we report our continuing effort to investigate the prebiotic implications of hydrothermal reactions. We found that four heterocyclic compounds (**1–4**) are synthesized from phenol and alanine, which enriches the hydrothermal organic synthesis chemistry, provides more raw materials for chemical evolution and could play a role in the origin and evolution of life.

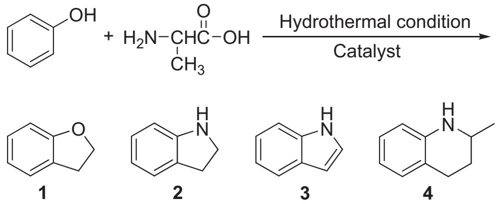
Indole is a precursor to the aromatic amino acid tryptophan (Keefe et al., 1995; Shimada et al., 2009). 2-Methyl-1,2,3,4-tetrahydroquinoline is present in the human brain. The prebiotic reaction of quinoline has been studied (Elsila et al., 2006) because quinoline and isoquinoline derivatives have been found in the carbonaceous chondrites meteorites (Sephton, 2005; Martins et al., 2008). The compounds **1–4** have been synthesized by a variety of traditional organic methods (Rindfusz, 1919; Boger and Coleman, 1984; Bouyssou et al., 1992; Fiirsmer and Ernst, 1995; Palucki et al., 1996; Pelkey and Gribble, 1997; Soderberg and Shriver, 1997; Larock et al., 1998; Barluenga et al., 1999; Zhu et al., 2000; Johnston et al., 2001; Sridharan et al., 2007). Our hydrothermal synthesis method provides an innovative way in synthesis chemistry and suggests intriguing clues for the origin of life. As shown in Scheme 1, the reaction starts with phenol and alanine, uses some minerals as a catalyst and finally yields compounds **1**–**4** under the hydrothermal condition.

Results and discussion

The reaction progress was tested by gas chromatography-mass spectrometry (GC-MS). It was rather evident that the compounds **1–4** were successfully synthesized when the mass spectra of the products were compared to that of standard substance. We investigated the effect of three parameters on the reaction, i.e., catalysts, temperature, and reaction time. In Table 1, the yields of the products are listed after 10 days of reaction under the influence of different catalysts and temperatures.

As shown in Table 1, the reaction takes place in the presence of hematite, montmorillonite or kaolin, and the reaction fails to occur in the presence of other minerals. Temperature plays a key role in the reaction, that is, the yields of the products increase as the temperature increases, especially from 200°C to 240°C. The most effective catalyst is hematite and the optimal temperature is 240°C. As shown in Figure 1, with the increase of the reaction time, the yields of the products increase first and do not change.

The mechanisms are suggested in Schemes 2–4. The reactions take place only when hematite, montmorillonite or kaolin is used as a catalyst. We speculate that Fe^{3+} or Al^{3+} in the hematite, montmorillonite or kaolin play an important role, as suggested in Schemes 2–4. The suggested mechanisms



Scheme 1 The hydrothermal reaction of phenol and alanine.

Table 1 Yields of the products **1–4** after 10 days of reaction in the presence of different catalysts and at different temperatures.

Catalyst	Product	Yield (%)[a]				
		80°C	120°C	160°C	200°C	240°C
Hematite (1 mmol, 0.160 g)	**1**	0.03	0.05	0.08	0.13	0.44
	2	0.02	0.03	0.05	0.11	0.37
	3	0	0.02	0.03	0.07	0.28
	4	0.05	0.08	0.10	0.15	0.56
Montmorillonite (0.500 g)	**1**	0.01	0.03	0.05	0.09	0.39
	2	0	0.02	0.03	0.07	0.33
	3	0	0	0.02	0.05	0.25
	4	0.03	0.07	0.12	0.17	0.53
Kaolin (0.500 g)	**1**	0	0.02	0.04	0.08	0.27
	2	0	0	0.02	0.04	0.21
	3	0	0	0.01	0.02	0.16
	4	0.02	0.05	0.07	0.11	0.41
Other[b]	**1–4**			Not detected		

[a] The average yield of three experiments. We did not carry out the experiment above 240°C for technical reasons.

[b] Other catalysts included titanium dioxide, zirconium oxychloride, samarium oxide, cerium oxide and yttrium oxide served respectively; the amount of each was 1 mmol.

are fully consistent with the experimental observation of trace amounts of 2-phenoxypropanoic acid and 2-(phenylamino) propanoic acid which are the proposed intermediate products. It has been reported that near the submarine hydrothermal vents there are many minerals (Gomes and Silva, 2007; Martin et al., 2008), such as hematite, montmorillonite and kaolin used as a catalyst in our reaction, which could play several important roles in the evolution of life. They can catalyze the synthesis of amino acids and nucleic acid bases, and adsorb biomonomers on their surfaces to provide a highly concentrated system for polymerization to biomacromolecules (Ponnamperuma et al., 1982; Hennet et al., 1992; Ferris, 2005; Hazen and Sverjensky, 2010). Our successful reactions suggest some important precursors for the chemical evolution of life.

Conclusion

We synthesized four heterocyclic compounds **1–4** from phenol and alanine under hydrothermal conditions. The catalyst, hematite, montmorillonite or kaolin, is essential for the reaction. The products are important natural products and synthetic precursors to many organic compounds related to life.

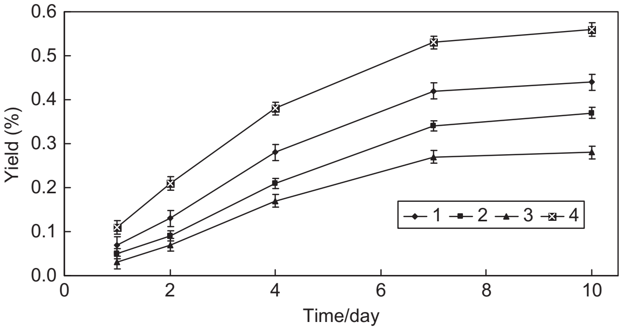
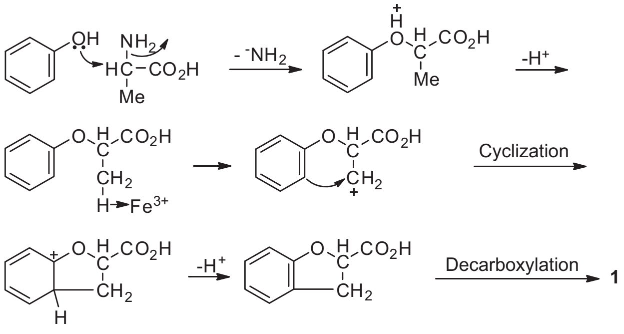


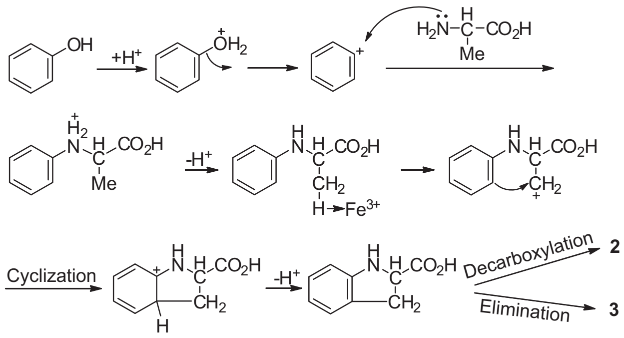
Figure 1 Yields of the products **1–4** at different reaction times for the experiment conducted in the presence of hematite at 240°C.

Experimental section

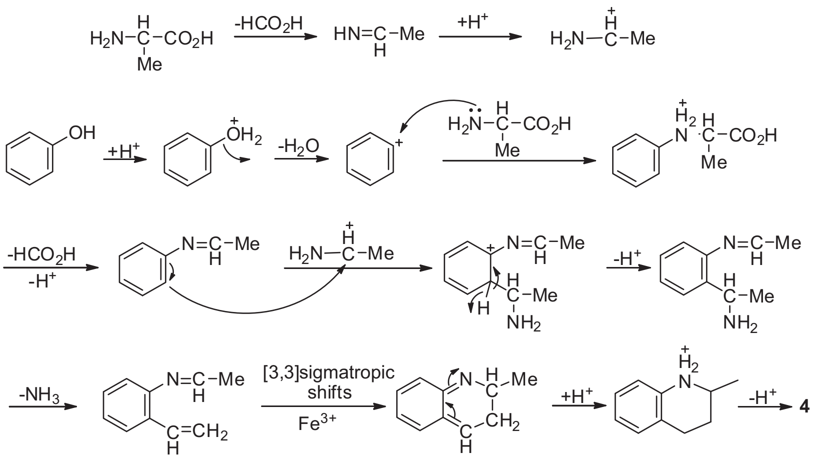
Phenol (5 mmol) and alanine (5 mmol) were dissolved by 27 mL of ultrapure water and the solution was loaded into a steel autoclave



Scheme 2 The proposed mechanism for the formation of **1**.



Scheme 3 The proposed mechanism for the formation of **2** and **3**.



Scheme 4 The proposed mechanism for the formation of **4**.

Table 2 Yields of the products **1–4** and the GC-MS results for a typical experiment conducted in the presence of hematite at 240°C.

Product	Yield (%)	GC retention time (min)	Molecular ion (*m/z*)	Fragment ion (*m/z*)
1	0.44	6.51	120	119, 92, 91, 89, 77, 65, 63, 51, 39
2	0.37	7.82	119	120, 118, 117, 91, 90, 89, 65, 63, 59, 51, 39
3	0.28	8.78	117	118, 116, 91, 90, 89, 63, 62, 59, 39
4	0.56	9.54	147	146, 133, 132, 130, 117, 115, 77, 52, 51, 39

(Fe-Cr-Ni alloy, GB1220-92) with a filling capacity of 90% and then treated with catalyst. The pH of the reaction mixture was approximately 5. Then the autoclave was sealed tightly and placed in an oven heated to 80–240°C for 1–10 days. Hematite, montmorillonite, kaolin, titanium dioxide, zirconium oxychloride, samarium oxide, cerium oxide and yttrium oxide were used as catalysts.

The reaction mixture was analyzed by GC-MS (DSQ, Thermo Fisher Scientific Int., Waltham, MA, USA) using the TR-5MS column (25 m length×0.25 mm ID, film thickness 0.12 μm). A sample (0.5 μL) was injected into the GC injector at a splitting ratio of 1:30 and analyzed using the full scan mode (29–300). The inlet, MS transfer line and ion source temperatures were set at 200°C, 250°C and 250°C, respectively. The carrier gas was He (99.999%) and carrier flow mode was constant flow (1.0 mL/min). Temperature program for the column: the initial temperature was held for 3 min at 80°C, then the temperature was increased at the rate of 15°C/min, and a final temperature of 200°C was held constant for 10 min.

The products were identified by comparison of the GC-MS results of the sample with that of the standards. The yields of the products were determined by external standard methods. More specifically, the standard solutions of different concentrations were tested and standard curves were drawn. The concentrations of the products were determined by comparison to the standard curves and then the yields of the products relative to the reactants were calculated. For a typical experiment (in the presence of hematite at 240°C), the yields of the products and the GC-MS results are given in Table 2.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 20901026 and 90922034).

References

Aubrey, A. D.; Cleaves, H. J.; Bada, J. L. The role of submarine hydrothermal systems in the synthesis of amino acids. *Orig. Life Evol. Biosph.* **2009**, *39*, 91–108.

Barluenga, J.; Fananas, F. J.; Sanz, R.; Fernandez, Y. Synthesis of 4-functionalized indoles via benzyne cyclization of N-(2-1ithioallyl)-2-fluoroanilines. *Tetrahedron Lett.* **1999**, *40*, 1049–1052.

Boger, D. L.; Coleman, R. S. Intramolecular Diels-Alder reactions of 1,2-diazines: general indoline synthesis. Studies on the preparation of the central and right-hand segments of CC-1065. *J. Org. Chem.* **1984**, *49*, 2240–2245.

Bouyssou, P.; Le Goff, C.; Chenault, J. Synthesis of 7- and 5,7-substituted-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolines: convenient precursors of quinolone antibacterial agents. *J. Heterocycl. Chem.* **1992**, *29*, 895–898.

Corliss, J. B.; Dymond, J.; Gordon, L. I.; Edmond, J. M.; von Herzen, R. P.; Ballard. R. D.; Green, K.; Williams, D.; Bainbridge, A.; Crane, K. et al. Submarine thermal springs on the Galapagos rift. *Science* **1979**, *203*, 1073–1083.

Elsila, J. E.; Hammond, M. R.; Bernstein, M. P.; Sandford, S. A.; Zare, R. N. UV photolysis of quinoline in interstellar ice analogs. *Meteorit. Planet. Sci.* **2006**, *41*, 785–796.

Feng, S.; Tian, G.; He, C.; Yuan, H.; Mu, Y.; Wang, Y.; Wang, L. Hydrothermal biochemistry: from formaldehyde to oligopeptides. *J. Mater. Sci.* **2008**, *43*, 2418–2425.

Ferris, J. P. Mineral catalysis and prebiotic synthesis: montmorillonite-catalyzed formation of RNA. *Elements* **2005**, *1*, 145–149.

Fiirsmer, A.; Ernst, A. Syntheses of camalexin, indolopyridocoline and flavopereirine. *Tetrahedron* **1995**, *51*, 773–786.

Gomes, C. S. F.; Silva, J. B. P. Minerals and clay minerals in medical geology. *Appl. Clay Sci.* **2007**, *36*, 4–21.

Hazen, R. M.; Sverjensky, D. A. Mineral surfaces, geochemical complexities, and the origins of life. *Cold Spring Harb. Perspect. Biol.* **2010**, *2*, a002162.

He, C.; Tian, G.; Liu, Z.; Feng, S. A mild hydrothermal route to fix carbon dioxide to simple carboxylic acids. *Organic Lett.* **2010**, *12*, 649–651.

Hennet, R. J. C.; Holm, N. G.; Engel, E. M. Abiotic synthesis of amino acids under hydrothermal conditions and the origin of life: a perpetual phenomenon. *Naturwissenschaften* **1992**, *79*, 361–365.

Imai, E.; Honda, H.; Hatori, K.; Brack, A.; Matsuno, K. Elongation of oligopeptides in a simulated submarine hydrothermal system. *Science* **1999**, *283*, 831–833.

Ji, F.; Zhou, H.; Yang, Q. The abiotic formation of hydrocarbons from dissolved CO_2 under hydrothermal conditions with cobalt-bearing magnetite. *Orig. Life Evol. Biosph.* **2008**, *38*, 117–125.

Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran. E. N. Nonconventional carbon additions to azomethines. aryl amination/indoline synthesis by direct aryl radical addition to azomethine nitrogen. *Org. Lett.* **2001**, *3*, 1009–1011.

Keefe, A.; Lazcano, A.; Miller, S. L. Evolution of the biosynthesis of the branched-chain amino acids. *Orig. Life Evol. Biosph.* **1995**, *25*, 99–110.

Larock, R. C.; Yum, E. K.; Refvik, M. D. Synthesis of 2,3-disubstituted indoles via palladium-catalyzed annulation of internal alkynes. *J. Org. Chem.* **1998**, *63*, 7652–7662.

Larowe, D. E.; Regnier, P. Thermodynamic potential for the abiotic synthesis of adenine, cytosine, guanine, thymine, uracil, ribose, and deoxyribose in hydrothermal systems. *Orig. Life Evol. Biosph.* **2009**, *39*, 91–108.

Maheen, G.; Tian, G.; Wang, Y.; He, C.; Shi, Z.; Yuan, H.; Feng, S. Resolving the enigma of prebiotic C-O-P bond formation: prebiotic hydrothermal synthesis of important biological phosphate esters. *Heteroatom Chem.* **2010**, *21*, 161–167.

Martin, W.; Baross, J.; Kelley, D.; Russell, M. J. Hydrothermal vents and the origin of life. *Nature Rev.* **2008**, *6*, 805–814.

Martins, Z.; Botta, O.; Fogel, M. L.; Sephton, M. A.; Glavin, D. P.; Watson, J. S.; Dworkin, J. P.; Schwartz, A. W.; Ehrenfreund, P. Extraterrestrial nucleobases in the Murchison meteorite. *Earth Planet. Sci. Lett.* **2008**, *270*, 130–136.

Palucki, M.; Wolfe, J. P.; Periasamy, M. Synthesis of oxygen heterocycles via a palladium-catalyzed C-O bond-forming reaction. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.

Pelkey, E. T.; Gribble, G. W. Synthesis of 2-nitroindoles via the sundberg indole synthesis. *Tetrahedron Lett.* **1997**, *38*, 5603–5606.

Ponnamperuma, C.; Shimoyama, A.; Friebele, E. Clay and the origin of life. *Orig. Life Evol. Biosph.* **1982**, *12*, 9–40.

Rindfusz, R. E. Synthesis of chromanes and coumaranes. *J. Am. Chem. Soc.* **1919**, *41*, 669–670.

Sephton, M. A. Organic matter in carbonaceous meteorites: past, present and future research. *Phil. Trans. R. Soc. A* **2005**, *363*, 2729–2742.

Shimada, A.; Ozaki, H.; Saito, T.; Noriko, F. Tryptophanase-catalyzed L-tryptophan synthesis from D-serine in the presence of diammonium hydrogen phosphate. *Int. J. Mol. Sci.* **2009**, *10*, 2578–2590.

Soderberg, B. C.; Shriver, J. A. Palladium-catalyzed synthesis of indoles by reductive N-heteroannulation of 2-nitrostyrenes. *J. Org. Chem.* **1997**, *62*, 5838–5845.

Sridharan, V.; Avendano, C.; Menendez, J. C. CAN-catalyzed three-component reaction between anilines and alkyl vinyl ethers: stereoselective synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines and studies on their aromatization. *Tetrahedron* **2007**, *63*, 673–681.

Tian, G.; Yuan, H.; Mu, Y.; He, C.; Feng, S. Hydrothermal reactions from sodium hydrogen carbonate to phenol. *Organic Lett.* **2007**, *9*, 2019–2021.

Tian, G.; He, C.; Chen, Y.; Yuan, H.; Liu, Z.; Shi, Z.; Feng, S. Hydrothermal reactions from carbon dioxide to phenol. *Chemsuschem* **2010**, *3*, 323–324.

Zhu, J.; Benjamin, A. P.; Zhao, S. X.; Skonezny, P. M. Copper(I)-catalyzed intramolecular cyclization reaction of 2-(2-chlorophenyl)ethanol to give 2,3-dihydrobenzofuran. *Tetrahedron Lett.* **2000**, *41*, 4011–4014.

Received October 30, 2011; accepted November 30, 2011;
previously published online January 18, 2012