

Y-Zeolite-Catalyzed Cyclizations of Terpenols

Wei Yu,* Fengling Bian, Yuan Gao, Li Yang, Zhong-Li Liu*

National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, People's Republic of China
Fax: (+86)-931-862-5657, e-mail: yuwei@lzu.edu.cn

Received: April 13, 2005; Accepted: October 20, 2005

Abstract: Depending on the metal doped and the activation temperature, Y-zeolites can catalyze a diversity of reactions of geraniol (**1**), linalool (**2**) and nerol (**3**). Compound **1** can be transformed to α - and/or γ -cyclogeraniol (**4** and **5**) highly efficiently.

Keywords: catalysis; cyclization; cyclogeraniol; geraniol; zeolite

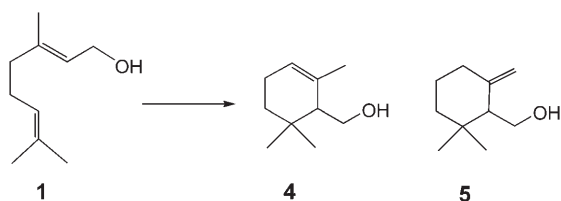
Besides their great success as industrial catalysts in petroleum chemistry and related fields, the use of zeolites in the laboratory for selective organic synthesis has grown continuously in recent years.^[1–5] The combination of Lewis acidity and/or Brønsted acidity and shape selectivity provides an opportunity to carry out a variety of selective reactions by use of zeolites, such as the reduction and isomerization of alkenes,^[6] the regioselective and diastereoselective ene reaction of singlet oxygen^[7] and the enantioselective epoxidation of alkenes.^[8] We report herein the selective cyclization reactions of geraniol (**1**), linalool (**2**) and nerol (**3**) in NaY and FeY zeolites. It was found that the cyclization products depended significantly on the metal doped and the activation conditions. A significant finding was that geraniol (**1**) could directly cyclize to α -cyclogeraniol (**4**) and γ -cyclogeraniol (**5**) (Scheme 1).^[9]

In a typical experiment, 20 mL of a hexane solution of the terpenol (1 mmol) was stirred at room temperature with 1.5 g of activated NaY. After the reaction was complete the zeolite was filtered, washed with hexane and then extracted with CH₂Cl₂. The solvent was removed and the reaction mixture was analyzed by GC, GC-

MS, and NMR and EI-MS if necessary. The results are summarized in Table 1.

The reaction of geraniol (**1**) in NaY gave α -cyclogeraniol (**4**) and/or γ -cyclogeraniol (**5**) as the major products. The ratio of these two products depended sensitively on the reaction temperature. When the reaction was conducted at 10 °C in NaY activated at 500 °C, **5** was the predominant product, while at 60 °C **4** was produced almost exclusively. Compound **5** was found to isomerize to **4** within NaY at elevated temperatures, showing that **4** was the thermodynamic product. These results are consistent with those obtained by Stratakis et al.^[9] The mass balance was about 50% with NaY activated at 500 °C and above 60% with NaY activated at 200 °C. A higher mass balance was reported at high substrate loading levels and with differently activated NaY.^[9] In the case of linalool (**2**) and nerol (**3**), *p*-cymene (**6**) was the major product, accompanied by a small amount of **4** and α -terpineol (**7**) (Fig. 1).

Cyclogeraniols are important intermediates in the synthesis of many natural products.^[10] It is believed



Scheme 1. NaY- and FeY-catalyzed cyclization of geraniol (**1**).

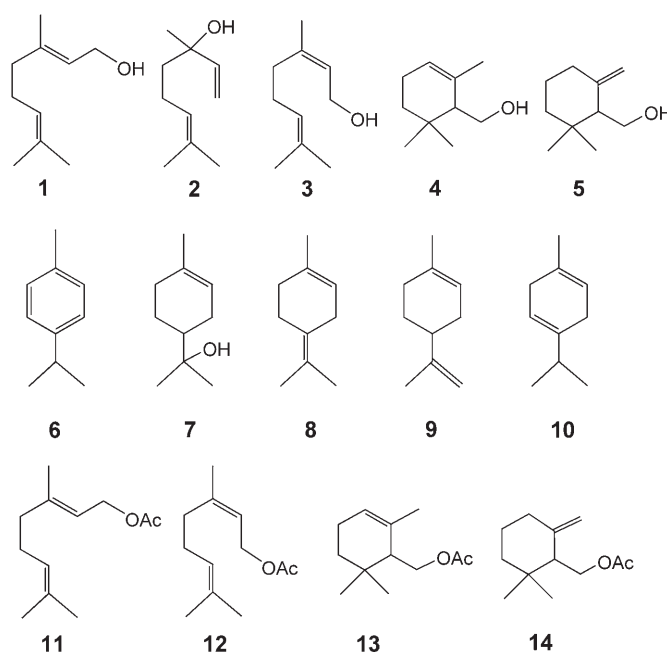


Figure 1.

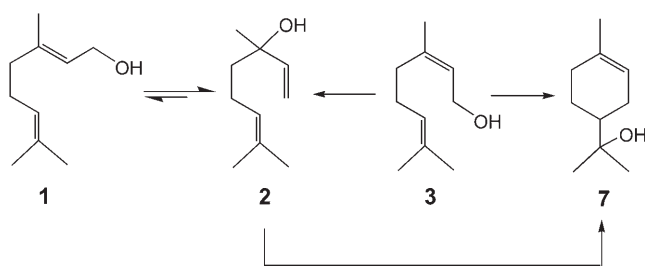
Table 1. NaY- and FeY-catalyzed reactions of geraniol (**1**), linalool (**2**) and nerol (**3**).^[a]

Substrate	MY	Activation temperature (time)	Reaction time	Products (yield %)
1	NaY	500 °C (5 h)	48 h (10 °C)	4 (2), 5 (89)
			1.5 h (25 °C)	4 (30), 5 (62)
			1 h (60 °C)	4 (84), 5 (trace)
	NaY	200 °C (5 h)	6 h	4 (19), 5 (70), 6 (3)
	NaY	100 °C (2 h)	12 h	No reaction
	FeY	100 °C (2 h)	2.5 h	4 (15), 5 (3), 6 (5), 7 (41), 8 (11), 9 (6), 10 (3)
2	FeY	200 °C (5 h)	0.5 h	4 (91), 5 (trace)
	NaY	500 °C (5 h)	1.5 h	6 (76), 7 (6), 4 (4)
	FeY	100 °C (2 h)	1 h	6 (11), 7 (47), 8 (21), 9 (8), 10 (5)
3	FeY	200 °C (5 h)	0.5 h	6 (85)
	NaY	500 °C (5 h)	1.5 h	4 (11), 6 (72), 7 (8)
	FeY	100 °C (2 h)	1 h	4 (3), 6 (9), 7 (52), 8 (13), 9 (7), 10 (4)
11	FeY	200 °C (5 h)	0.5 h	4 (8), 6 (79)
	NaY	500 °C (5 h)	1.5 h	13 (92), 14 (2)
	NaY	500 °C (5 h)	12 h (0 °C)	13 (23), 14 (72)
12	NaY	200 °C (5 h)	2 h	13 (31), 14 (65)
	FeY	200 °C (5 h)	1.5 h	13 (90), 14 (trace)
12	NaY	500 °C (5 h)	6 h	6 (13), 13 (14), 14 (61) ^[b]
	FeY	200 °C (5 h)	2 h	13 (78), 14 (14)

^[a] The reactions were run at room temperature except were otherwise specified. The products were identified by GC-MS and compared with the authentic samples except **4** and **5** which were identified by ¹H and ¹³C NMR and EI-MS. The yields were determined by GC at 100% conversion.

^[b] The conversion is 90%.

that naturally occurring cyclogeraniols are derived biosynthetically from the acid-induced cyclization of geranyl diphosphate, the usual substrate for monoterpene cyclases, followed by diphosphate hydrolysis, or directly by the enzymic cyclization of geraniol itself.^[11] On the other hand, Brønsted acid-catalyzed cyclization of **1**, **2**, **3** in solution generally produced α -terpineol and monoterpenes rather than cyclogeraniols.^[12] Therefore, the direct cyclization of geraniol to α - and γ -cyclogeraniols in the zeolite is interesting from both synthetic and mechanistic points of view. The transformation of geraniol to α -cyclogeraniol was achieved at low temperature using the super acid FSO₃OH,^[13] but the formation of γ -cyclogeraniol has never been reported. By comparison, NaY not only can effect the reaction under mild conditions, but can also simplify the procedure considerably. More important, both the α - and γ -cyclogeraniols can be obtained with high selectivity. Therefore, NaY is a superior catalyst.

**Scheme 2.**

Zeolites contain both Brønsted acid sites and Lewis acid sites. There are many Lewis acid sites within the NaY framework due to the presence of metal ions.^[3,14] However, NaY is generally considered to be weakly acidic since it contains only a small number of Brønsted acid sites.^[15a] As the catalyzing activity of zeolites is associated with their acidic character, the reactions of these terpenols were further explored in CaY, which has been proved to be a much stronger Brønsted acid catalyst when activated at 500 °C under air.^[15] In this case, however, only a small amount of mixed monoterpenes and *p*-cymene were exacted out in CH₂Cl₂ as products for all the three substrates, most of the substrates were probably cracked inside the zeolite framework.

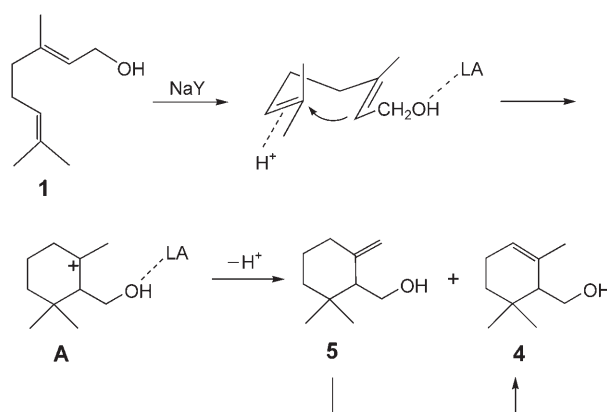
We found recently that FeCl₃·6 H₂O could serve as a Lewis acid to catalyze the isomerization and cyclization of **1**, **2** and **3** in acetonitrile giving α -terpineol (**7**) as the major product (Scheme 2),^[16] similar to the mineral acid-catalyzed reactions reported previously.^[12] Therefore, Fe³⁺-exchanged Y zeolites were prepared^[17] and used to catalyze the cyclization reactions of **1**, **2** and **3**. The results are also listed in Table 1. It can be seen that the reaction products depend significantly on the activation temperature of the zeolite. When FeY was activated at 100 °C for 2 h the major product for all the three terpenols was α -terpineol (**7**), consistent with the result of FeCl₃-catalyzed reactions.^[16] In addition, mixed monoterpenes including *p*-cymene (**6**), terpinolene (**8**), limonene (**9**) and α -terpinene (**10**), and a small amount of **4** in the case of geraniol and nerol, were also formed. With FeY activated at higher temperature (200 °C), **1** was trans-

formed to **4** exclusively, while **2** and **3** were transformed predominantly to *p*-cymene (**6**), similar to the NaY-catalyzed reactions mentioned above. Activating FeY at higher temperatures (between 200 and 500 °C) did not change the composition of the products appreciably.

These results demonstrate that the catalytic behavior of the zeolites depends remarkably on the metal doped and on the activation temperature. The FeY activated at 100 °C acted similarly to FeCl₃·6 H₂O, giving α -terpineol as the major product. By comparison, NaY heated at 100 °C for the same period of time has no catalytic effect. On the other hand, FeY activated at 200 °C behaved similarly to the activated NaY. In fact, FeY is more powerful than NaY in catalyzing the reaction. Although both NaY and FeY activated at 200 °C were effective for catalyzing the reaction of geraniol, the reaction proceeded much faster in FeY than in NaY. While the conversion was complete within 30 min with FeY as catalyst, the conversion was only little more than 1/3 with NaY over the same time span. Ammonia absorption-desorption chromatography measurements indicate that there are more acidic sites in FeY than in NaY.

In the case of nerol and linalool, the composition of the products was consistent with the mechanism of acid-catalyzed reactions in solution. Both linalool and nerol were transformed mainly to *p*-cymene in NaY and FeY (activated at 200 °C). Obviously, *p*-cymene was derived from the dehydrogenation of monoterpenes **8**, **9** and **10**, which resulted from the dehydration of α -terpineol (**7**) or dehydration-cyclization of linalool and nerol. A relevant example was reported recently that monoterpenes including **8**, **9** and **10** incorporated in methyl viologen (MV²⁺)-supported NaY undertook spontaneous electron transfer reactions to generate *p*-cymene (**6**) in high yields.^[18]

The formation of α - and γ -cyclogeraniol under the same conditions, in the case of geraniol, was apparently *via* a pathway which is generally not accessible under homogeneous Brønsted acidic and/or Lewis acidic conditions. Zeolites are in nature crystalline aluminosilicates with a highly ordered crystalline structure. Cavities of a definite size (for Y zeolite, the cavity is about 13 Å in diameter) are formed in the rigid, three-dimensional networks composed of SiO₄⁻ and AlO₄⁻ tetrahedra.^[1] Therefore, zeolites exert some kind of shape selectivity to the organic molecules inside the cavities. The unique supercage structure as well as the acidity of NaY provides a favorable environment for the direct transformation of geraniol to cyclogeraniols. It is believed that the superacidic cyclization of geraniol to form α -cyclogeraniol involves the carbocation intermediates as the result of protonation of the 6,7-double bond.^[13] It is possible that a similar process occurred in the NaY/FeY-geraniol system (Scheme 3). When these terpenols entered the cavities of NaY or FeY, both the hydroxy group and the carbon-carbon double bond could interact with the acid sites. We suppose that the hydroxy group should



Scheme 3.

have a stronger complexation with acid sites, most likely with Lewis acid sites since there are many more Lewis acid sites than Brønsted acid sites in NaY.^[14] This interaction would act somewhat like an “anchor” to fix the molecule, thus determining the effectiveness of the interaction between the remote double bond and the acid sites. In the case of geraniol, the structural feature of the molecule would effect the protonation of the 6,7-carbon carbon double bond, and the conformation of the molecule in the confined space of cages is favorable for cyclization to form the carbocation **A**. The subsequent deprotonation from **A** giving the exocyclic double bond seems to be kinetically favored, as with NaY at low temperature the γ isomer was formed predominantly, while at high temperature, or with FeY, the more stable α isomer was almost the only product.

In the case of nerol, however, this action leading to the formation of carbocation **A** was less effective, probably due to the *Z* configuration of the 2,3-double bond. Meanwhile the competitive route, the formation of α -terpineol and monoterpenes, was facile for nerol and linalool under acidic conditions.^[12] As a result, only a small amount of α -cyclogeraniol was generated.

It is interesting to note that both geraniol and nerol acetates (**11**, **12**) could be transformed efficiently to cyclogeraniol acetates under same conditions (Table 1). The mass balance was > 70% in these cases. Probably after acetylation, the orientation of the terminal double bond of nerol acetate inside the cavities was adjusted to be such that more effective interaction with the acid sites was achieved, enabling the transformation to cyclogeraniol acetates to occur. Besides, as the acetate is more stable than the hydroxy group towards acid, the competitive cyclization pathway toward *p*-cymene was hampered for nerol acetate.

FeY activated at 100 °C for 2 h was much less effective for the formation of cyclogeraniols from geraniol. The reason for this might be that after heating FeY at 100 °C for 2 h, there were still some H₂O molecules remaining inside the zeolite, and only few Brønsted acid sites were generated within the framework. Therefore,

geraniol reacted mostly in a similar way to the $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ -catalyzed reaction. It was found that if FeY was kept at 100°C for a longer time, the yield of α -cyclogeraniol could be remarkably improved.

In conclusion, this work demonstrates that NaY and FeY exhibit a diversity of catalytic activities for the isomerization, dehydration, dehydrogenation and cyclization reactions of terpenols **1–3**. The catalytic behavior depends significantly on the metal doped and the activation temperature and enables the selective production of different products. A significant finding is that α - and γ -cyclogeraniols can be produced directly from geraniol in the zeolites, demonstrating interesting product selectivity and the potential of using zeolites in organic synthesis.

Experimental Section

Zeolite NaY was obtained from Nankai University Factory. The FeY was prepared by stirring a suspension of NaY zeolite (10 g) in an aqueous solution (100 mL, pH=3) of $\text{Fe}(\text{NO}_3)_3$ (4.6 mmol/L) at room temperature for 7 h.^[17] CaY was prepared as follows:^[15b] 10 g NaY were added to 200 mL of 10% $\text{Ca}(\text{NO}_3)_2$ solution, and the slurry was stirred at 80°C overnight. The slurry was filtered and the filtrate was washed thoroughly with distilled water. The above exchange procedure was repeated four times. The filtrate obtained was dried at room temperature in air. The MY zeolite was activated in an oven at the specified temperature in air for the indicated time. Then it was transferred into a desiccator to cool down. Usually MY was allowed to stand in the desiccator overnight before use. The zeolites could be stored in the desiccator for several days without losing their catalyzing ability.

General Procedure for the Reaction

To a hexane solution (20 mL) of the terpenol (1 mmol) were added 1.5 g of activated MY zeolite. The slurry was stirred at room temperature for the indicated time. After the reaction was complete the slurry was filtered, and the filtrate was stirred in 20 mL of CH_2Cl_2 at room temperature for 1 h. Then the slurry was filtered again. This extracting process was repeated at least three times. The combined CH_2Cl_2 extracts were concentrated under reduced pressure, and reaction mixture was analyzed by TLC, GC, GC-MS. The cyclogeraniols were separated by flash chromatography over silica gel.

Spectra Data

2,6,6-Trimethylcyclohex-2-enylmethanol (α -cyclogeraniol) (**4**): ^1H NMR (400 MHz, CDCl_3): δ =0.88 (s, 3H), 1.01 (s, 3H), 1.17 (dt, J =12.0, 4 Hz, 1H), 1.40 (br, OH), 1.60 (m, 3H), 1.72 (s, 3H), 1.98 (m, 1H), 3.72 (m, 2H), 5.58 (br, 1H); ^{13}C NMR (400 MHz, CDCl_3): δ =22.8 (CH_3), 22.9 (CH_2), 27.7 ($2 \times \text{CH}_3$), 31.7 (C), 32.4 (CH_2), 52.0 (CH), 61.4 (CH_2), 124.4 (CH), 131.8 (C); EI-MS: m/z (%) = 154 (4), 136 (10), 123 (65), 93 (38), 81 (100).

2-Methylene-6,6-dimethylcyclohexylmethanol (γ -cyclogeraniol) (**5**): ^1H NMR (400 MHz, CDCl_3): δ =0.67 (s, 3H), 0.95

(s, 3H), 1.27 (dt, J =13.6, 4.4 Hz, 1H), 1.42 (dt, J =13.6, 4.4 Hz, 1H), 1.59 (m, 2H), 2.04 (dd, J =4.0, 10.8, 1H), 2.12 (t, J =6.8 Hz, 2H), 3.62 (t, J =10.8 Hz, 1H), 3.72 (dd, J =4.0, 10.8 Hz, 1H), 4.76 (d, J =2 Hz, 1H), 4.96 (d, J =2 Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3): δ =23.1 (CH_2), 26.6 (CH_3), 28.5 (CH_3), 31.7 (CH_2), 33.8 (C), 36.2 (CH_2), 56.4 (CH), 59.5 (CH_2), 111.8 (CH_2), 147.4 (C); EI-MS: m/z (%) = 154 (2), 136 (12), 121 (31), 93 (67), 81 (54), 69 (100).

Acknowledgements

We thank the National Natural Science Foundation (grant No. 20372030) and Foundation for University Key Teachers by Ministry of Education of China for financial support.

References

- [1] W. Hilderich, M. Hesse, F. Naumann, *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 226.
- [2] I. W. C. E. Arends, R. A. Sheldon, M. Wallau, U. Schuchardt, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1144.
- [3] S. E. Sen, S. M. Smith, K. A. Sullivan, *Tetrahedron* **1999**, 55, 12657.
- [4] D. E. De Vos, M. Dams, B. F. Sels, P. A. Jacobs, *Chem. Rev.* **2002**, 102, 3615.
- [5] A. Corma, *J. Catal.* **2003**, 216, 298.
- [6] a) K. Pitchumani, A. Joy, N. Prevost, V. Ramamurthy, *Chem. Commun.* **1997**, 127; b) M. Kojima, H. Takeya, Y. Kuriyama, S. Oishi, *Chem. Lett.* **1997**, 997.
- [7] M. Stratakis, G. Kosmas, *Tetrahedron Lett.* **2001**, 42, 6007.
- [8] M. J. Sabater, A. Corma, A. Domenech, V. Fornés, H. Garca, *Chem. Commun.* **1997**, 1285.
- [9] During the processing of our submission, a very similar work appeared in this journal; see: G. Tsangarakis, M. Stratakis, *Adv. Synth. Catal.* **2005**, 347, 1280.
- [10] a) R. M. Coates, A. Q. Jin, *J. Org. Chem.* **1997**, 62, 7475; b) A. Abad, C. Agulló, A. C. Cuñat, R. H. Perni, *Tetrahedron: Asymmetry* **2000**, 11, 1607; c) M. Bovolenta, F. Castronovo, A. Vadalá, G. Zanon, G. Vidari, *J. Org. Chem.* **2004**, 69, 8959.
- [11] R. Croteau, *Chem. Rev.* **1987**, 87, 929.
- [12] a) C. A. Bunton, D. L. Hachey, J. Leresche, *J. Org. Chem.* **1972**, 37, 4036; b) W. Rittersdorf, F. Cramer, *Tetrahedron* **1967**, 23, 3023.
- [13] P. F. Vlad, *Pure Appl. Chem.* **1993**, 65, 929.
- [14] H. W. G. van Herwijnen, U. H. Brinker, *Tetrahedron* **2002**, 58, 4963.
- [15] a) V. Ramamurthy, P. Lakshminarasimhan, C. P. Grey, L. J. Johnston, *Chem. Commun.* **1998**, 2411; b) H.-M. Kao, C. R. Grey, K. Pitchumani, P. H. Lakshminarasimhan, V. Ramamurthy, *J. Phys. Chem. A* **1998**, 102, 5627.
- [16] W. Yu, M. Wen, L. Yang, Z.-L. Liu, *Chin. Chem. Lett.* **2002**, 13, 493.
- [17] M. Alvaro, B. Ferrer, H. Garcia, A. Sanjuán, *Tetrahedron* **1999**, 55, 11895.
- [18] M. Stratakis, M. Stavroulakis, *Tetrahedron Lett.* **2001**, 42, 6409.