

Short Communication

Mechanism study on Raney nickel-catalyzed amination of resorcinol



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ARTICLE INFO

Article history:

Received 31 July 2013

Received in revised form 2 December 2013

Accepted 18 December 2013

Available online 24 December 2013

Keywords:

Amination

Raney Ni

Resorcinol

Catalysis

ABSTRACT

Amination of resorcinol catalyzed by Raney nickel has been examined with good yield. Using the first principle density functional theory, some detailed mechanism of the amination of resorcinol on the Ni(111) surface is explored. The resorcinol is adsorbed on the Ni surface at the hollow site to form ketone by isomerization. The isomerization has a barrier of 122.1 kJ/mol. Ketone can couple with secondary amine mediated by resorcinol to afford hemiaminal. For the formation of hemiaminal, the steric effect of the alkyl group of secondary amine is obvious. Hemiaminal undergoes dehydration to get final product, which occurs by the preferred adsorption in the bridge site, cleavage of C–O bond initially, followed by subsequent cleavage of C–H bond.

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1. Introduction

3-(*N,N*-dialkylamino)phenol is the key intermediate that has a wide application in pharmaceuticals and dyes. 3-(*N,N*-dimethylamino)phenol is used to synthesize *neostigmine bromide*, which has a reversible cholinesterase inhibition and is a useful drug in the treatment of myasthenia gravis [1]. *Astrazon Blue BG* (Basic Blue 3) that synthesized by 3-(*N,N*-diethylamino)phenol, is one of the dyes most commonly used in nylon and acrylic textiles [2].

The alkylation of alkyl halides with 3-aminophenol is a classical procedure [3]. However, it needs a large number of acid-binding agents and the atom economy of this route is poor. With the rise of green chemistry, the atom efficiency has become important. In the synthesis of 3-(*N,N*-dimethylamino)phenol, there are only two methods with the high atom economy. One of them is the reduction amination of 3-aminophenol with aldehyde [4], which proceeds addition of 3-aminophenol with aldehyde, dehydration and reduction by metal-catalyzed hydrogenation [5] or reducing agent [6]. The other attractive protocol is the amination of resorcinol with secondary amines. It is reported that phosphorous acid [7] and metaphosphoric acid [8] can catalyze this reaction and the byproduct is only water. The amination of resorcinol is also a relatively green method, but the catalysts such as phosphorous acid and metaphosphoric acid could pollute environment and its yield has room for improvement.

In this paper, we explored Raney Ni-catalyzed amination of resorcinol with secondary amines and described a detailed investigation on mechanism studies on the Ni surface.

2. Experimental section

General procedure for the amination of resorcinol with secondary amine catalyzed by Raney Ni. Resorcinol (2.2 g, 20 mmol), secondary amine (30 mmol) and Raney Ni (110 mg) were added to water (50 ml) in a 100 ml autoclave. The autoclave was purged with hydrogen gas three times, then maintained 0.05 Mpa pressure. The mixture was heated to 200 °C rapidly. Then stirring was maintained for 3 h. The reaction mixture was cooled to room temperature, and then extracted with *N*-butyl acetate. The organic layer was dried (MgSO_4), filtered and concentrated to give the crude product. The pure product was got through flash column chromatography on silica gel (petroleum ether/acetylacetic ester (3/1, v/v)).

3. Computational details

DFT calculations were performed with the program package CASTEP in Materials Studio of Accelrys Inc. [9–11]. Plane wave basis functions with spin polarization and the Perdew, Burke, Erzenhof gradient corrected functional (GGA-PBE) were used [12–15]. The transition state search was performed with the linear and quadratic synchronous transit (LST/QST) complete search [16]. Ultrasoftpseudopotential (USP) was used to perform simulation of core electron. Energy cut-off of 400.0 eV was used to improve computational performance [17].

Ni(111) surface was modeled using three-layer periodic slab model with a (6 × 6) super cell including 10 Å vacuum slab, within which the adsorption and reaction occurs. The reciprocal space of the (6 × 6) super cell was sampled with the *k*-points set of (3 × 3 × 2). Larger *k*-points sets are needed if more accurate energy value wanted. Study in this work focused on the relative results of different systems, so the *k*-points set of (3 × 3 × 2) should be enough. Geometry optimization was performed for all the relevant adsorbates with Ni atoms

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Table 1
Amination of resorcinol with secondary amines.^a

$\text{R}_1 = \text{alkyl}$

Entry	R ₁	Catalyst (wt.%)	Time/h	Yield/% ^b
1	CH ₃	H ₃ PO ₄ (5)	3	76
2	CH ₃ CH ₂	H ₃ PO ₄ (5)	6	5
3	CH ₃ CH ₂	Raney Ni (5)	3	68
4	CH ₃ CH ₂	Raney Ni (2)	6	47
6	CH ₃ CH ₂	Raney Ni (10)	3	67
7	CH ₃	Raney Ni (5)	3	93

^a Temperature is 200 °C. Raney-catalyzed amination is under hydrogen gas atmosphere. General procedure of H₃PO₄-catalyzed amination see supporting information.

^b Isolated yield.

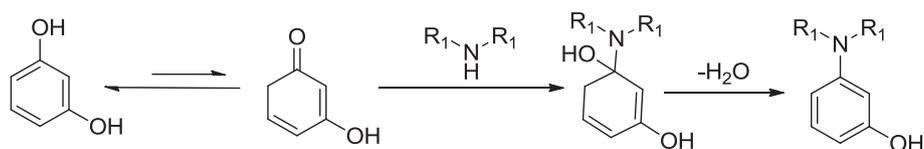


Fig. 1. The proposed mechanism of amination of resorcinol with secondary amines.

constrained except the uppermost layer. The convergence tolerances of energy and displacement were 2×10^{-5} eV/atom and 2×10^{-3} Å, respectively, and the SCF tolerance was 2×10^{-6} eV/atom.

Chemisorption energies were calculated using the equation

$$\Delta E_{\text{ads}} = E_{\text{adsorbate-Ni}} - E_{\text{adsorbate}} - E_{\text{Ni}}$$

where ΔE_{ads} represents the adsorption energy of the adsorbate on Ni(111) surface, $E_{\text{adsorbate}}$ is the energy of free adsorbate, E_{Ni} is the energy of clean slab and $E_{\text{adsorbate-Ni}}$ is the energy of adsorbate–Ni adsorption system.

For a reaction, which can be represented as: $A + B \rightarrow C + D$, the energy barrier was calculated as follows:

$$\Delta E_{\text{React}} = E_{\text{TS}} - E_{A+B-\text{Ni}}$$

where E_{TS} is the energy of the transition state and $E_{A+B-\text{Ni}}$ is the energy of $A + B - \text{Ni}$ adsorption system.

4. Results and discussion

Initially, we attempt H₃PO₄ to catalyze the amination of resorcinol with dimethylamine (DMA), which affords 76% yield (entry 1, Table 1). It is consistent with previous reported [7]. However, it failed to catalyze diethylamine (DEA) with 5% yield (entry 2, Table 1). Fortunately, we examine that the commercially Raney Ni can catalyze the reaction of resorcinol with DEA and attempt to optimize the reaction by varying other parameters systemically. As expected, lower catalyst loading (2 wt.%) incurs a significant decrease in chemical yield and prolonged reaction time (entry 4, Table 1). Thus, the appropriate catalyst loading is 5 wt.% (entries 3, 5, Table 1). With the presence of 5 wt.% Raney Ni at 200 °C in water, the product is got in 68% yield. Then the effects of DMA are examined with 93% yield (entry 6, Table 1).

The proposed pathway in Fig. 1 is preceded through three stages: the formation of ketone, the addition reaction of ketone with secondary amine and dehydration. It is slightly different from the *N*-alkylation of alcohol and amine that ketone is formed by the isomerization of resorcinol with Raney Ni as catalyst. We tried to find the suitable mechanism by the computational study.

The structure parameters of the Raney Ni were characterized by XRD, which was showed in Fig. 2.

The Raney Ni catalyst showed three diffraction peaks of Ni(111), Ni(200) and Ni(220). Ni(111) is the main diffraction peak of Raney Ni catalyst. Surface science studies have been performed on well-defined Ni(111) for the chemisorption and hydrogenation of benzene [18–23] and phenol [23,24]. The aromatic ring oriented parallel to the Ni(111) surface is adsorbed via the π orbitals [23]. Resorcinol is a benzene and phenol like molecule. At the same time, due to the fact that is a well understood system, Ni(111) represents a convenient model substrate. Thus herein Ni(111) model is applied for the investigation on the adsorption and reaction of resorcinol, in order to illuminate the mechanism.

4.1. Adsorption of resorcinol on Ni(111)

For resorcinol in gas phase, the calculations predicted bond lengths and angles are 1.397–1.404 Å (1.39 Å) for the distance between the carbon atoms, 1.391 Å (1.36 Å) for C1–O7, 1.389 Å (1.37 Å) for C3–O8, 123.53° (123°) for C6–C1–O7 and 117.193° (117.6°) for C4–C3–O8, respectively, which is consistent with the experimental results [25,26].

Resorcinol can adsorb at different high-symmetry sites of the (111) surface. It is similar to the benzene adsorbed Ni(111) surface [21]. After the adsorption on the Ni surface, the hollow(0) site (Fig. 3) was found to be the preferred adsorption site, with calculated adsorption enthalpy of –88.8 kJ/mol (Supporting information). Adsorption at the hollow-hcp

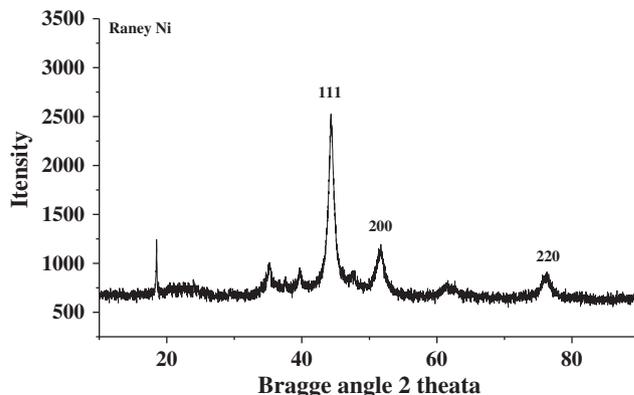


Fig. 2. X-ray diffraction patterns of Raney Ni catalyst.

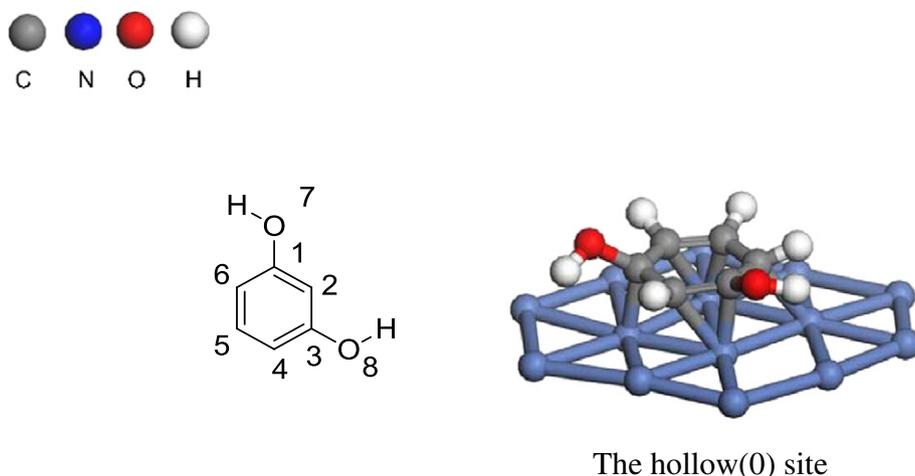


Fig. 3. Sites of resorcinol adsorbed on Ni(111) surface.

site was found to be more stable than at the hollow-fcc site. But their stability difference is so small that we will not distinguish between the fcc and hcp site. Adsorption of resorcinol at the top site is unfavorable. Resorcinol molecule adsorbed at the bridge(30) was found to be

transition state during the surface diffusion and relax to the hollow(0) site. Since the diffusion of resorcinol from the most stable hollow(0) site is activated, the difference in energy between the hollow(0) and the bridge(30) site is 29.2 kJ/mol.

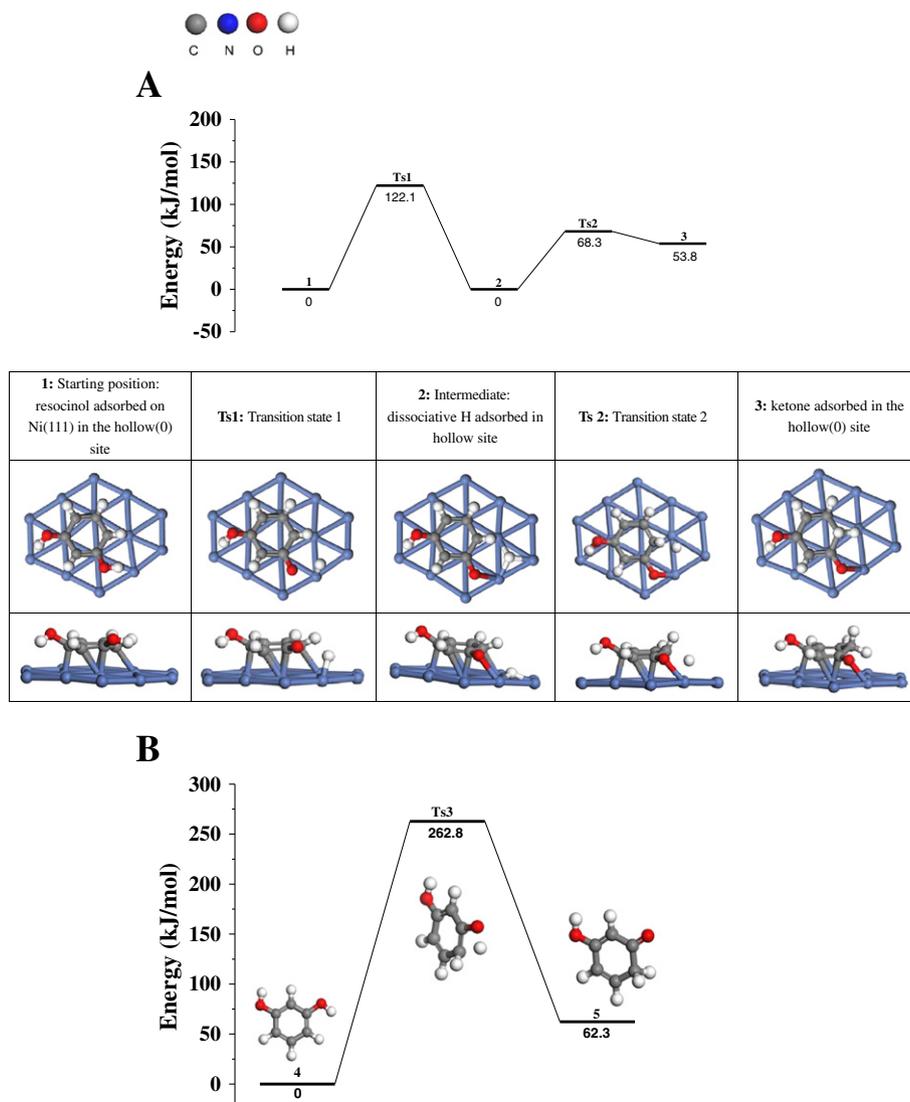


Fig. 4. Energy profile of the indirect (A) isomerization of resorcinol adsorbed on Ni(111) surface in the hollow(0) site and the direct (B) isomerization.

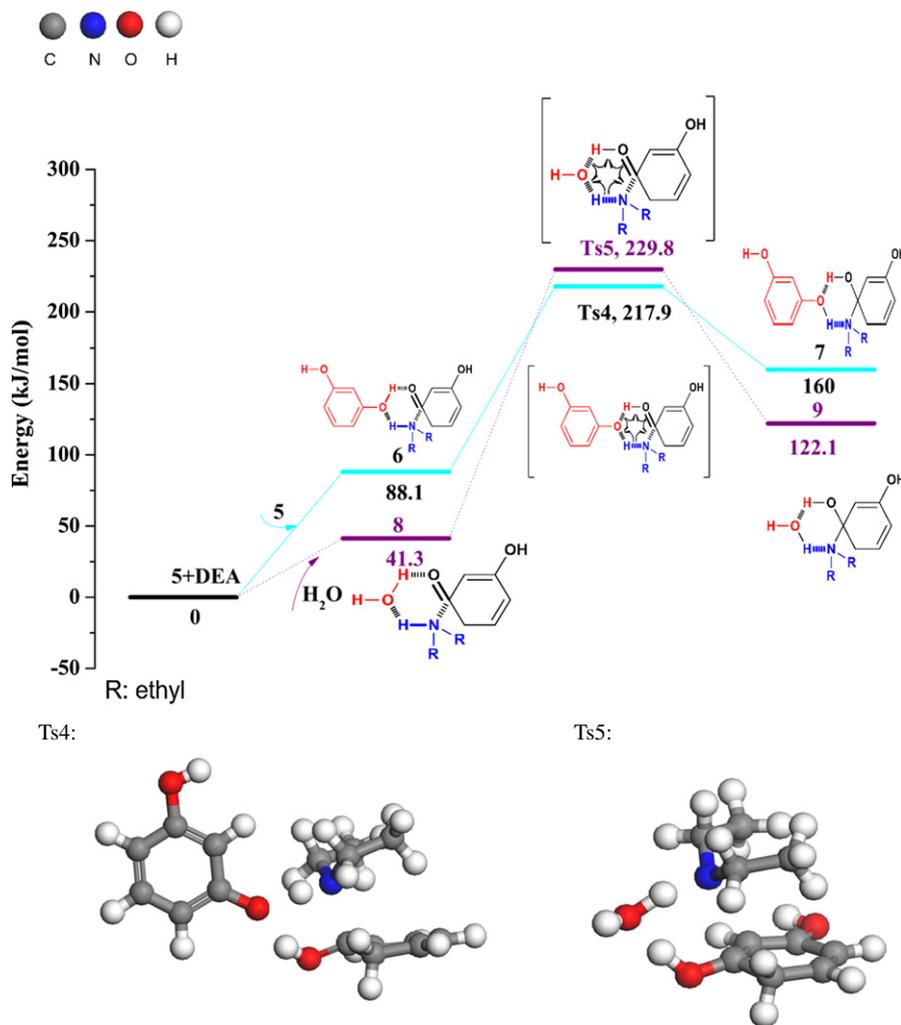


Fig. 5. Energy profile of resorcinol-DEA addition reaction mediated by resorcinol, in water.

In the hollow(0) site, the calculated bond lengths for the benzene ring carbon–carbon increase to 1.444–1.457 Å. The other calculated lengths and angles are 1.386 Å for C1–O7, 1.404 Å for C3–O8, 121.65° for C6–C1–O7, 114.9° for C4–C3–O8. For the three close to the top positions, the distances of C1–Ni, C3–Ni, C5–Ni are 1.979 Å, 1.949 Å, 1.985 Å respectively. For the three others, the distances are 2.178 Å for C2–Ni, 2.179 Å for C4–Ni, 2.186 Å for C6–Ni.

4.2. Isomerization of resorcinol

Generally, in the *N*-alkylation of alcohol and amine, alcohol dehydrogenation to form more reactive aldehyde or ketone, is considered the key intermediate activation step [27,28]. However, resorcinol is different from alcohol, which can undergo the isomerization to give ketone. As the hollow(0) site is the preferred site, we only study the isomerization of resorcinol adsorbed in hollow(0) site. In the following section, we will rationalize why the isomerization of resorcinol is preferred over Raney Ni-catalyzed.

Resorcinol has two hydroxyl groups O7–H and O8–H, which all can be isomerized to form ketone. However, when the hydroxyl group O8–H is undergoing isomerization, the C2–H bond is forming. Because C2 is located against the two hydroxyl, there are high steric hindrance in the bonding of C2–H, which is confirmed by computed (Supporting Information). Fig. 4 examines two isomerization pathways of resorcinol, including the indirect isomerization mediated via **Ts1** and **Ts2**, and the direct isomerization via **Ts3**.

The indirect isomerization involves two pathways initiated by cleavage of O7–H bond. In the initial step, the O7–H bond is ruptured and Ni–H bond forms after overcoming the energy barrier of 122.1 kJ/mol (**Ts1**). It is similar to phenol adsorbed in Pt(111)[29] and Ru(111)[30] that the O–H bond is cleaved below 300 K and 350 K, forming adsorbed phenoxy. Then via bonding between the C1–O7 atoms and two neighboring Ni atoms on the surface, the first reaction intermediate (**2**) is formed. The hydrogen atom is located in neighboring hollow site, which is favored for the adsorption of H on a clean Ni(111) surface [21]. The following reaction step is the hydrogenation of the intermediate **2**. In the transition state (**Ts2**), the C–Ni bond is already broken and a C–H bond is being formed. When H atom approaches resorcinol, resorcinol is slightly rotated. It stretches the distance between C6–Ni to 2.48 Å, which weakens the C6–Ni bond and eventually leads to the C6–Ni bond broken. **Ts2** has a lower energy barrier of 68.3 kJ/mol. After the hydrogenation with a low energy barrier of 14.5 kJ/mol, the ketone **3** adsorbed in the hollow(0) site is formed.

The direct isomerization is very different from the indirect one. First resorcinol molecule **4** and the ketone molecule **5** are optimized, and then the **Ts3** structure is found and optimized. The energy profile and the optimized structures are shown in Fig. 4B. The direct isomerization is also initiated by cleavage of O7–H bond. With bonding between C6 atom and H atom, the carbonyl π bond is being formed. **Ts3** has a very high energy barrier of 262.8 kJ/mol.

Comparing the two isomerization pathways in Fig. 4, it is found that the indirect pathway is more favorable than the direct one. The

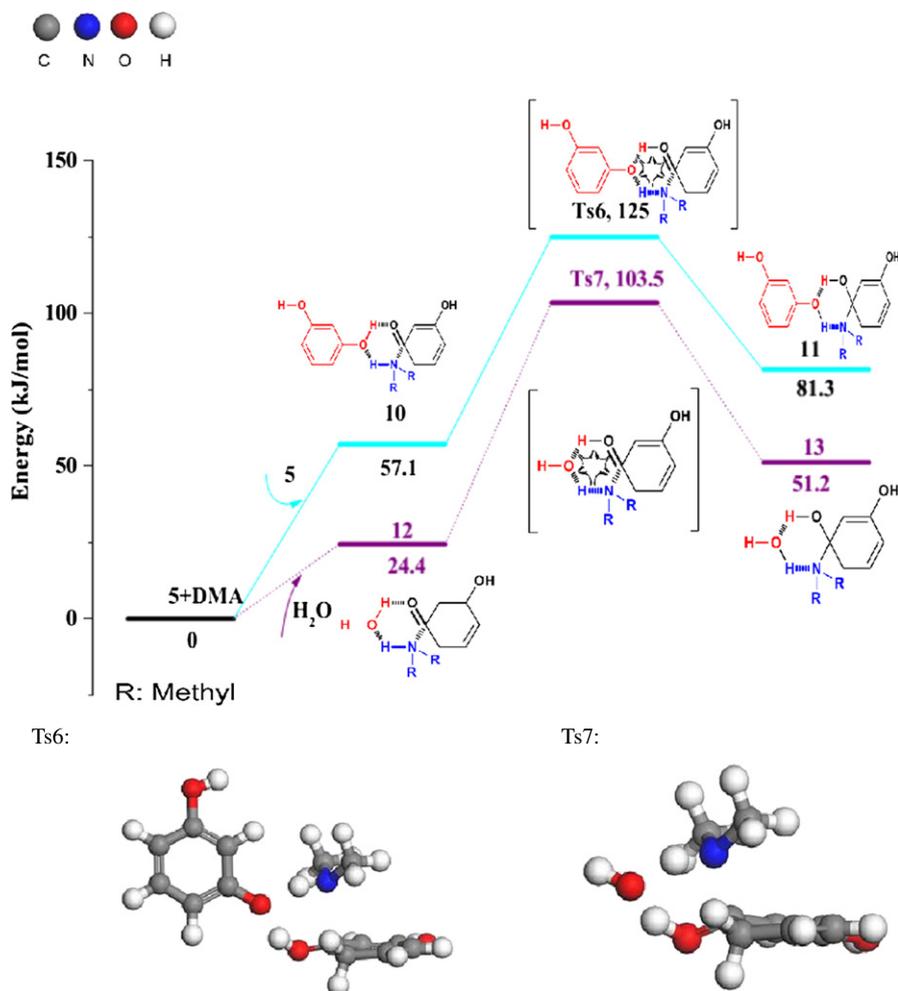


Fig. 6. Energy profile of resorcinol-DMA addition reaction mediated by resorcinol, in water.

transition state (**Ts3**) in the direct pathway is much higher than the two (**Ts1**, **Ts2**) transition states in the indirect pathway. Therefore, the isomerization of resorcinol is preferred over Raney Ni-catalyzed.

4.3. Addition of ketone with secondary amine

The ketone **5** from the isomerization of resorcinol can couple with secondary amine to give hemiaminal which can be further dehydrated to generate amide. In the addition of ketone with secondary amine, the hydrogen atom is transferred to carbonyl group from the amino group, and then the C–N bond was formed. The direct coupling of ketone with secondary amine is difficult and inaccessible because of the high steric hindrance. Therefore indirect coupling is studied that the hydrogen transfer can be mediated by resorcinol or water.

In view of the steric hindrance, we first study the addition of resorcinol with DEA. The energetic and geometric results of the indirect ketone and DEA coupling mediated by resorcinol or water are shown in Fig. 5. Firstly the resorcinol-mediated pathway is discussed. The transition state (**Ts4**) describes the mechanism for the resorcinol-mediated addition. Resorcinol donates the hydrogen atom of hydroxy group to ketone **5** and gets the amino hydrogen atom of DEA simultaneously, which promotes the formation of C–N bond, with an energy barrier of 129.8 kJ/mol. The mediator resorcinol exhibits a catalytic effect. Similar to resorcinol, water, as solvent, can mediate the ketone-DEA addition. Therefore, water as a mediator of the addition is studied. The transition state (**Ts5**) of the water-mediated addition has energy barrier of 188.5 kJ/mol, which is higher than **Ts4**. To further investigate the effect of alkyl group steric hindrance, the indirect ketone and DMA is studied.

As shown in Fig. 6, the resorcinol-mediated addition is again more favorable than the water-mediated addition, with **Ts6** being 11.2 kJ/mol lower than **Ts7**. When Fig. 6 is compared with Fig. 5, **Ts6** and **Ts7** are 61.9 and 109.4 kJ/mol lower than **Ts4** and **Ts5**, respectively. Thus, the alkyl group steric effect of secondary amine is obvious. It leads to the higher yield of DMA than DEA.

It is illustrated that the catalytic effect of resorcinol is better than water. Although the resorcinol has higher steric hindrance, the hydroxyl group of resorcinol is more polar than water's. Thus, resorcinol is more effective than water in facilitating the addition. However, the energy barrier of hemiaminal formation is still so high that high temperature is necessary for amination of resorcinol with secondary amines, which can provide enough energy to cross the barrier.

4.4. Dehydration of hemiaminal

Dehydration of hemiaminal can afford the final product. Two dehydration pathways of hemiaminal are investigated including the indirect dehydration mediated (in Fig. 7) and the direct dehydration (in Fig. 8).

Firstly it is found that hemiaminal adsorbed in the bridge(30) site (**14**) is the preferred adsorption site. So indirect dehydration of hemiaminal will be investigated on the bridge(30) mode. The calculated structures and energy profile of the reactants, intermediates and transition states for proposed reaction pathways on indirect dehydration are shown in Fig. 7. The initial step is the cleavage of C1–O7 bond, with barriers of 30.7 kJ/mol for N,N-diethyl hemiaminal and 31 kJ/mol for N,N-dimethyl hemiaminal respectively. Then, the reaction intermediate (**15** and **18**) is formed. The hydroxyl group is located in

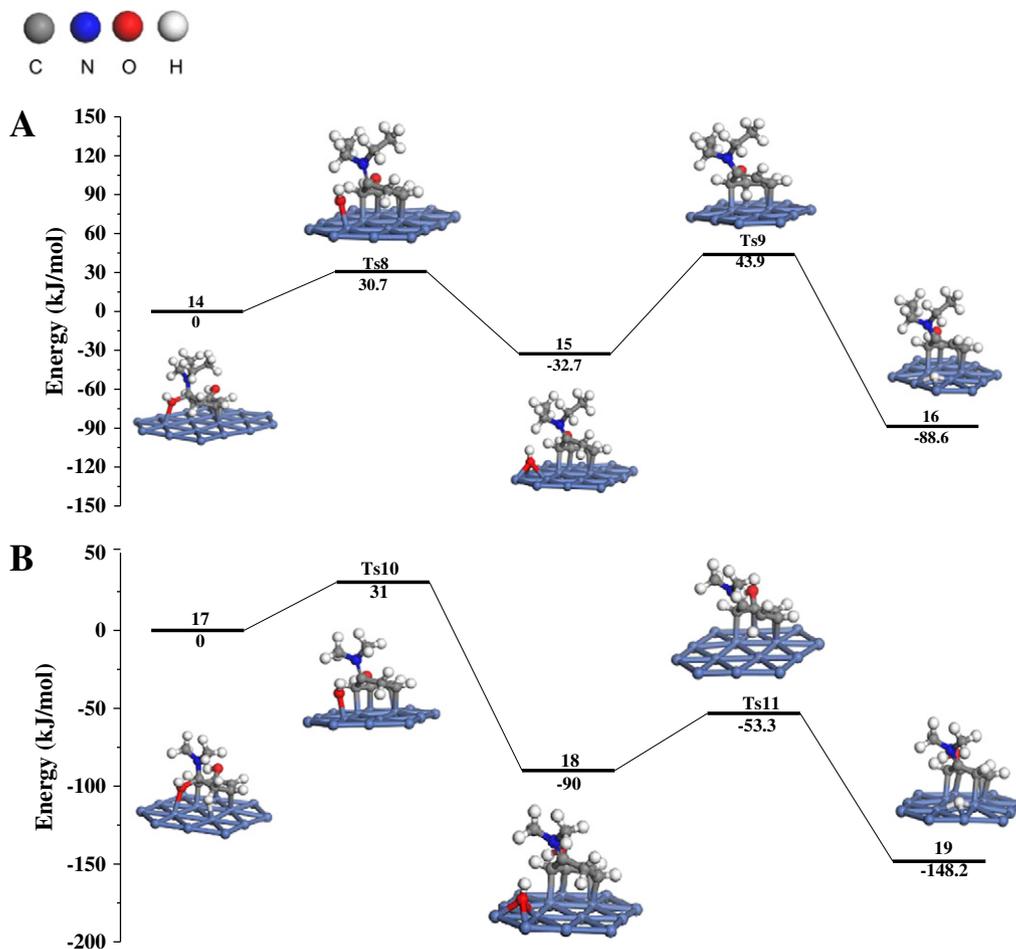


Fig. 7. Energy profiles of the indirect dehydration of *N,N*-diethyl (A) and *N,N*-dimethyl (B) hemiaminal.

the hollow site, which is the most stable adsorption. In the transition state (**Ts9** and **Ts11**), the formation of C=N indicates that the cleavage of C1–O7 bond change the hybridization of C1 from sp^3 to sp^2 . The following step is the cleavage of C6–H bond with higher barriers of 76.6 kJ/mol and 36.7 kJ/mol respectively. Then, the final product adsorbed on the Ni surface is got and the hydrogen atom is located in the hollow site, which is the favored adsorption of hydrogen atom on a Ni(111) surface.

In direct hydration of hemiaminal, hemiaminals and the final products are optimized, and then the structures of **Ts12** and **Ts13** are found and optimized (in Fig. 8). In the transition state (**Ts12** and **Ts13**), we found that the direct hydration of hemiaminal is also initiated by cleavage of O7–H bond with high barriers of 119.2 kJ/mol and 134.4 kJ/mol respectively. The hydroxyl group localizes the electron density of hydrogen atom, which stretches the C6–H distance. It eventually leads to the C6–H bond broken.

The possible pathway of hemiaminal dehydration has been found. The indirect dehydration pathway is more favorable, the preferred adsorbed in the bridge(30) site, cleavage of C1–O7 bond initially, followed by subsequent cleavage of C6–H bond.

5. Conclusion

In summary, we have described the amination of resorcinol with secondary amine catalyzed by Raney Ni with good yield. The reaction pathways proceeded through four stages: adsorption of resorcinol, isomerization to form ketone, addition of secondary amine to form hemiaminal and hemiaminal dehydration, are investigated by using periodic density functional theory (DFT).

The resorcinol is preferred adsorbed at the hollow(0) site, with calculated adsorption enthalpy of -88.8 kJ/mol. The isomerization of resorcinol by Raney Ni-catalyzed is more favorable than its isomerization. The barrier of resorcinol-mediated coupling is lower than water-mediated, which is preferred to form hemiaminal. The alkyl group steric effect of secondary amine influences obviously the reaction yield. Hemiaminal dehydration occurred by the preferred adsorbed in the

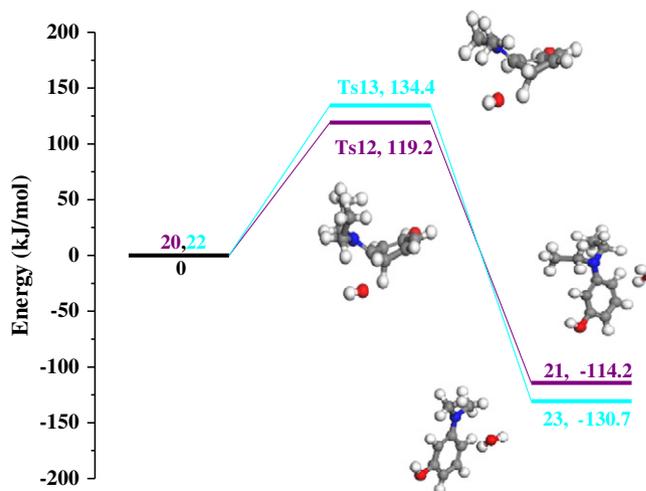


Fig. 8. Energy profile of the direct dehydration of *N,N*-dimethyl and *N,N*-diethyl hemiaminal.

bridge site is more favorable than its dehydration. It is initiated by cleavage of the C–O bond, followed by subsequent cleavage of the C–H bond.

Acknowledgment

The authors are grateful for the financial support from the Research Fund for the Doctoral Program of Higher Education of China (201201011110062) and the Low Carbon Fatty Amine Engineering Research Center of Zhejiang Province (2012E10033). Shang Zhicai group is thanked for helping us with calculations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.catcom.2013.12.021>.

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