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A theoretical and experimental study on mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization

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ABSTRACT

The mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization was studied by means of the density functional theory (DFT) method. A new possible reaction pathway is proposed. The calculations further indicate that the proposed pathway is preferable. In addition, quantum mechanical calculations were employed to study temperature, pressure, and the solvent effect on the proposed mechanism which could be used to predict the ratio of two anomers expected from the proposed pathway. Furthermore, the experimental results are in good accordance with the computation outcomes.

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1. Introduction

N-(4-hydroxycyclohexyl)-acetamide, which was obtained by the catalytic hydrogenation of 4-acetamide-phenol, is commonly constituted by two diastereomers (*cis*- and *trans*-isomers) [1–6]. Because only the *trans*-isomer is an important medical intermediate, which could be used to synthesize many kinds of medicine, such as ambroxol hydrochloride [1–6], it is vital to separate the *trans*-isomer from the two diastereomers. The conventional separation methods are column chromatography [1] and crystallization [7], but those methods are inevitably associated with one or more disadvantages, such as a small amount of diastereomers separated, excessive solvent consumption and poor yield, which tend to confine the space that conventional methods are applied to in industrial processes.

Recently, Yang et al. found that *N*-(4-hydroxycyclohexyl)-acetamide could realized *cis-trans* epimerization only using Raney-Ni as catalyst under an atmosphere of hydrogen, so that the disadvantages mentioned above can

be avoided and the *trans*-isomer is acquired [8]. So, it is of significance to explore the mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization, which is helpful to obtain more *trans*-isomer by controlling the reaction conditions. As the intermediates are unstable and difficult to be detected in the experiments, theoretical studies seem to be more important to prove the rationality of the mechanism in the aid of discreet calculations.

The aim of this paper is to conduct theoretical studies on the mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization with the density functional theory (DFT) method. To determine the conformational stability of the intermediates and products, we have carried out molecular geometry optimization calculations for all conformations using the 6-31G^{*} basis set with the B3LYP method. In addition, temperature, pressure, and the solvent effect on all conformations were studied. Furthermore the computation outcomes were compared with the results obtained in the experiments.

2. Calculations

All calculations were performed with the Gaussian 98 program package [9]. The geometries of all the stationary

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points at different temperatures and pressures were fully optimized at the B3LYP/6-31G* level of the theory. The B3LYP functional is composed of Becke's three-parameter hybrid exchange functional (B3), as implemented in GAUSSIAN 98, and the correlation functional of Lee, Yang, and Parr (LYP). The solvation energies for the products and intermediates at different temperatures and pressures were computed using solvation model PCM with the permittivities of 78.39, 36.64, 24.55, 20.7, 8.93 and 2.02, for H₂O, CH₃CN, CH₃CH₂OH, CH₃COCH₃, CH₂Cl₂, and C₆H₁₂, respectively.

3. Experimental

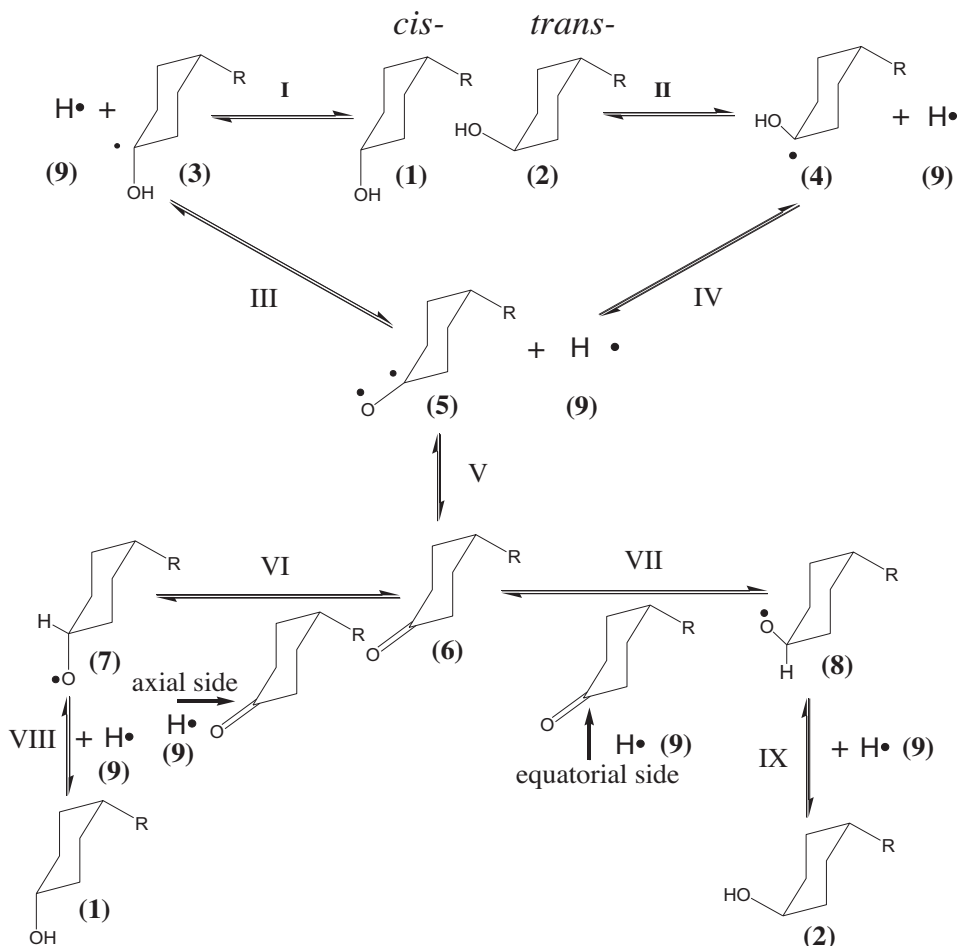
To 40 g *N*-(4-hydroxycyclohexyl)-acetamide (*cis*:*trans* = 80:20), 100 mL of water and a freshly prepared Raney-Ni were added. The reaction mixture was refluxed under an atmosphere of hydrogen for several hours. The products (*cis*:*trans* = 30:70) were obtained after the reaction was completed. The products were recrystallized by methanol/acetone mixture to give *cis*:*trans* = 15:85, and the recovered mother liquid was reused in seven cycles to give *cis*:*trans* = 4:96.

Table 1
The selection of solvent.

| Solvent | Composition in equilibrium product (%) | | | <i>trans</i> /(<i>trans</i> + <i>cis</i>) × 100 % |
|-------------|--|--------------|--------|---|
| | <i>cis</i> | <i>trans</i> | Ketone | |
| Ethanol | 60.0 | 37.4 | 2.6 | 38.40 |
| 95% ethanol | 61.3 | 38.5 | Trace | 38.58 |
| Water | 29.5 | 70.4 | Trace | 70.47 |

4. Results and discussion

The experiment was initially tested in 100% ethanol; the yield of the *trans*-isomer was only 37.4%. When the solution is 95% ethanol (contains 5% water) and 100% water, the yield was 38.5% and 70.4%, respectively (Table 1). It indicates that the yield of the *trans*-isomer increases with increasing the polarity of the solvent. As it can be seen from Table 2, when the H₂ pressure is 0.1 MPa, the yield is 70.47%, which is same when the H₂ pressure is 0.4 MPa. It indicates that the H₂ pressure has no effect on the yield of the *trans*-isomer in the experiments.



Scheme 1. Mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis*-*trans* epimerization R = -NHCOCH₃.

Table 2
The effect of H₂ pressure.

| H ₂ pressure (MPa) | Composition in equilibrium product (%) | | | <i>trans</i> /(<i>trans</i> + <i>cis</i>) × 100% |
|-------------------------------|--|--------------|--------|--|
| | <i>cis</i> | <i>trans</i> | Ketone | |
| 0.1 | 29.5 | 70.4 | Trace | 70.47 |
| 0.4 | 29.5 | 70.4 | Trace | 70.47 |

According to the experimental results, the mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization was proposed (Scheme 1). For *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization, we can reasonably speculate that the *cis*-, *trans*-free radical intermediates and 4-acetamide-cyclohexanone are produced in the process. The *cis*- (**1**) and *trans*-isomers (**2**) can change, respectively, into free radical intermediates (**3**) and (**4**), (**3**) and (**4**) both can change into free radical intermediate (**5**), (**5**) changes into 4-acetamide-cyclohexanone (**6**), then the reaction has two routes to choose. Since the margin of energies of these two routes is only 1.88 kJ/mol, (**6**) can spontaneously change to either (**7**) or (**8**). Then, (**7**) or (**8**) can change, respectively, to (**1**) or (**2**). The whole pathway is cyclic and reversible. In Fig. 1, the ΔH_{298} of the I, II, III, IV, V, VI, VII, VIII, IX step in the reaction is given, respectively. In the whole process, the formation of (**3**) and (**4**) are the key steps.

As it can be seen from Fig. 1, it is easier to change from (**1**) to (**3**) than (**2**) to (**4**), according to the free energy of reaction (ΔG_{298}). So, (**1**), with the priority to *trans*-isomers (**2**), is more likely to change to (**6**). When (**1**) and (**2**) change to (**6**), (**6**) can choose to change either to (**7**) or (**8**). Taking into account the concept of catalyst hindrance, it is easier

Table 3
The absolute value of solvation energy (kJ/mol) of the reactants, intermediates and products in six distinct solvents.

| Entry | H ₂ O | CH ₃ CN | CH ₃ CH ₂ OH | CH ₃ COCH ₃ | CH ₂ Cl ₂ | C ₆ H ₁₂ |
|-------|------------------|--------------------|------------------------------------|-----------------------------------|---------------------------------|--------------------------------|
| 1 (1) | 69.29 | 59.45 | 57.49 | 56.82 | 48.24 | 19.41 |
| 2 (2) | 65.61 | 57.66 | 55.77 | 53.09 | 47.24 | 18.03 |
| 3 (3) | 63.18 | 57.99 | 56.19 | 53.72 | 47.45 | 18.07 |
| 4 (4) | 66.61 | 59.41 | 57.53 | 56.36 | 48.74 | 18.37 |
| 5 (5) | 62.63 | 56.27 | 54.48 | 53.26 | 46.11 | 17.70 |
| 6 (6) | 62.01 | 53.60 | 51.92 | 50.25 | 44.22 | 17.57 |
| 7 (7) | 56.44 | 49.54 | 47.99 | 46.28 | 40.04 | 17.56 |
| 8 (8) | 54.27 | 48.83 | 47.20 | 45.81 | 38.24 | 14.81 |

for (**6**) to be absorbed from the equatorial side than from the axial side of the molecule (Scheme 1) [10]. So, (**8**) is produced prior to (**7**). Certainly, the margin of energies of these two routes (1.88 kJ/mol) also makes it easier to change from (**6**) to (**8**) than (**6**) to (**7**), though it is not the major cause. Furthermore, the conformation of (**2**) is more stable than the conformation of (**1**), because the energy of (**2**) is lower than that of (**1**). So, it is easier to change from (**6**) to (**2**) than from (**6**) to (**1**). In the pathway, the *cis*-isomer (**1**) changes to the *trans*-isomer (**2**) easily. So the *trans*-isomer is the predominant product in the experiments. It must be noted that the value of free energy (ΔG_{298}) is approximately represented by the value of enthalpy (ΔH_{298}) for explaining the reaction equation, since the term of TS is commonly little, which determines that the value of enthalpy (ΔH_{298}) is close to the value of free energy (ΔG_{298}).

The interaction energies of the reactants, intermediates and solvents as well as products and solvents increase with increasing polarity of the solvent (Table 3). It explains that

Table 4
The calculated energies (kJ/mol) of the reactants, intermediates and products' optimized conformations at different temperatures and pressures.

| | (1) | (2) | (3) | (4) | (5) |
|-----------------|-------------|-------------|-------------|-------------|-------------|
| -273 K, 0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 348 K, 1.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 348 K, 3.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 348 K, 5.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 348 K, 10.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 398 K, 1.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 398 K, 3.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 398 K, 5.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 398 K, 10.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 448 K, 1.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 448 K, 3.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 448 K, 5.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| 448 K, 10.0 atm | -1362898.87 | -1362899.04 | -1361180.24 | -1361172.74 | -1359748.83 |
| | (6) | (7) | (8) | (9) | |
| -273 K, 0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 348 K, 1.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 348 K, 3.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 348 K, 5.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 348 K, 10.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 398 K, 1.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 398 K, 3.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 398 K, 5.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 398 K, 10.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 448 K, 1.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 448 K, 3.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 448 K, 5.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |
| 448 K, 10.0 atm | -1359747.29 | -1361154.41 | -1361156.29 | -1313.47 | |

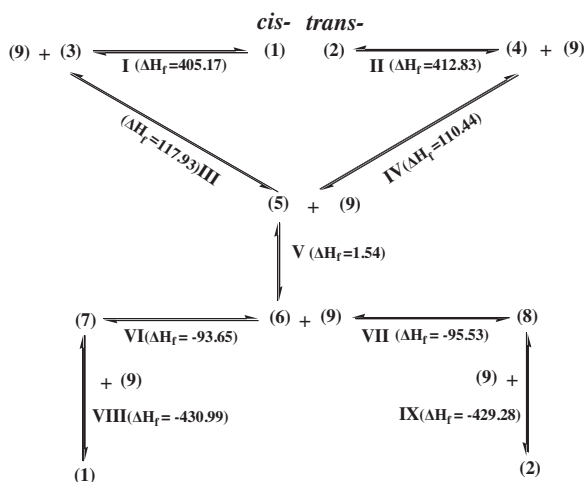


Fig. 1. The energy change (KJ/mol) diagram of the reaction.

increasing the solvent polarity could facilitate the formation of the intermediates and products. In addition, temperature and pressure have no effect on the reaction pathway (Table 4). The computation results determine that water and 1.0 atm are the most optimized conditions for the experiments, which is in good accordance with the experimental results.

5. Conclusion

The mechanism of *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization was investigated with theoretical calculations at the B3LYP/6-31G^{*} level. The calculation results indicate that the reaction proceeds through the

cis-, *trans*-free radical and 4-acetamide-cyclohexanone intermediate pathway.

The effect of solvent on the reaction pathway that involves the formation of radicals was investigated using the PCM model. The calculation results indicate that the solvent plays an important role in the reaction by stabilizing the radicals and provide an alternate and lower energy pathway by which the reaction may proceed. From the analysis of the solvent effect on *N*-(4-hydroxycyclohexyl)-acetamide *cis-trans* epimerization, we can conclude that the ratio of the *trans*- to *cis*-isomer increases with increasing polarity of the solvent, which is in good agreement with the experimental results on solvent polarity. In addition, temperature and pressure has no effect on the reaction pathway.

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