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Theoretical Study on the Mechanism of Synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole

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The mechanism of one-pot synthesis among benzene-1,2-diamine, isothiocyanatomethane and 4-methylbenzaldehyde for the synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole was investigated by density functional theory (DFT). The geometries and the frequencies of reactants, intermediates, transition states and products were calculated at the B3LYP/6-311G(d) level. The vibration analysis and the IRC analysis verified the authenticity of transition states. The reaction processes were confirmed by the changes of charge density at the bond-forming critical point. The results indicated that (1) IM2C → IM2D is rate-determining step; (2) The activation energy of the reaction is 351.53 Kj mol^{-1}.

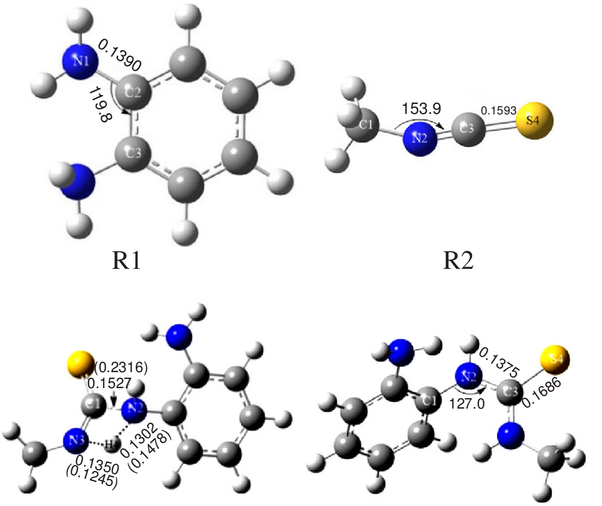
Keywords: Density functional theory, 2-(*p*-tolyl)-1*H*-benzo[d]imidazole, One-pot synthesis, Transition state, Reaction mechanism.

INTRODUCTION

2-(*p*-tolyl)-1*H*-benzo[d]imidazole and their derivatives are the important inter-mediate of a series of drugs. Many of them show antifungal and antibacterial activity[1,2], antiinflammatory activity and analgesic activity[3,4], antitubercular activity[5], antidepressant activity[6], anticancer activity[7], antiviral activity[8], and antilishmanial activity[9]. Imidazole is incorporated into many important biological molecules. The most important is the amino acid histidine, which has an imidazole side chain. Histidine is present in many proteins and enzymes play a vital role in the structure and binding functions of hemoglobin. Therefore, the imidazole compounds attracted the interest of medicinal researchers. One-pot synthesis method is used to the synthesis of imidazole and their derivatives[10-13]. 2-(*p*-tolyl)-1*H*-benzo[d]imidazole was synthesized from multi-component condensation of benzene-1,2-diamine, isothiocyanato methane and 4-methyl benzaldehyde by one-pot synthesis method[14]. There is no literature about the mechanism of synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole The main purposes of this paper are as follows: (1) to investigate the microscopic mechanism of reaction among benzene-1,2-diamine, isothiocyanato methane and 4-methyl benzaldehyde for the synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole by way of density functional theory (DFT); (2) confirm the rate-determining step of the reaction.

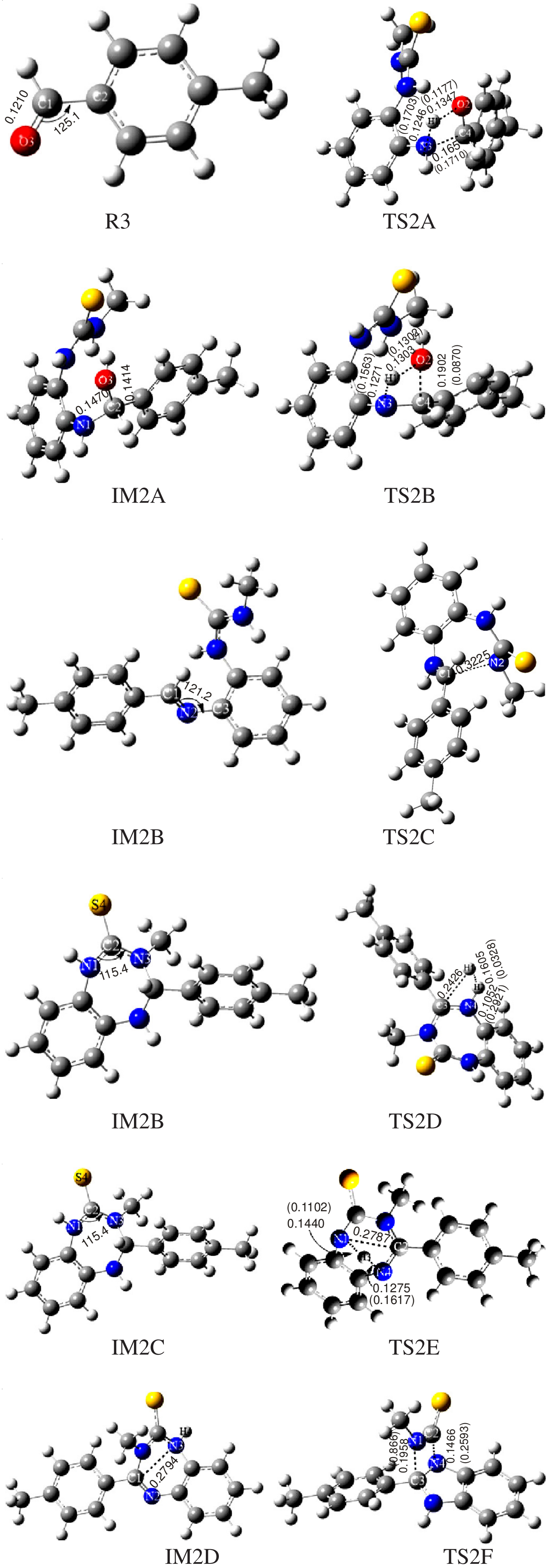
COMPUTATIONAL METHODOLOGY

The mechanism of reaction among benzene-1,2-diamine, isothiocyanato methane and 4-methyl benzaldehyde for the synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole was investigated by density functional theory (DFT). The geometries and the frequencies of reactants, intermediates, transition states and products were calculated at the B3LYP/6-311G(d) level. Stable structures were obtained. The parameters of geometry configuration are shown in Fig.1 (R1-P3). The vibration analysis and the IRC analysis proved the authenticity of intermediates and transition states. The reaction processes were confirmed by the changes of charge density at the bond-forming critical point (as shown by the numeric value in the parentheses in Fig. 1)[15-16]. All calculations were carried out with the Gaussian 03 program[17].



R1 R2

TS1A IM1A



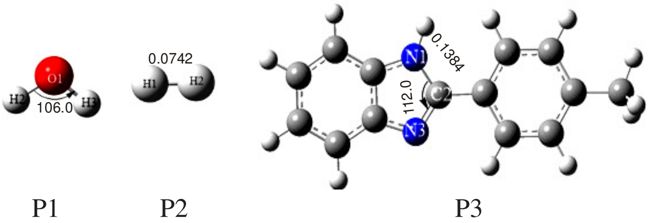


Fig. 1. Optimized geometric configurations of various compounds in the reaction: bond length in nanometers, bond angle in degree, charge density at bond-forming critical point in a.u.

RESULTS AND DISCUSSION

The calculated energies (E) and relative energies (E_{rel}) of reactants, intermediates, transition states and products are listed in Table-1. All energies (E) include zero-point energy (ZPE) corrections. Vibration frequencies of reactants, intermediates and products are positive and vibration frequencies of all transition states have only one imaginary frequency. Fig. 2 is a schematic map of energy levels for the reaction.

TABLE-1
ENERGIES (E) AND RELATIVE ENERGIES (E_{REL}) OF VARIOUS SPECIES AND IMAGINARY FREQUENCY OF TRANSITIONS

Species	E (a.u.)	E_{rel} (kJ mol^{-1})	ν (cm^{-1})
R1'(R1 + R2 + R3)	-1258.697785	0.00	
IS1A'(TS1A + R3)	-1258.653043	117.47	-1767.71
IM1A'(IM1A + R3)	-1258.721789	-63.02	
TS2A'(TS2A)	-1258.646442	134.80	-1755.21
IM2A'(IM2A)	-1258.704724	-18.22	
TS2B'(TS2B)	-1258.624072	193.53	-1933.93
IM2B'(IM2B + P1)	-1258.701926	-10.87	
TS2C'(TS2C + P1)	-1258.642538	145.05	-67.30
IM2C'(IM2C + P1)	-1258.693203	12.03	
TS2D'(TS2D + P1)	-1258.559463	363.16	-816.84
IM2D'(IM2D + P1 + P2)	-1258.681428	42.95	
TS2E'(TS2E + P1+ P2)	-1258.581790	304.54	-1624.75
IM2E'(IM2E + P1 + P2)	-1258.651491	121.54	
TS2F'(TS2F + P1 + P2)	-1258.634969	164.92	-225.54
P3'(P3 + R2 + P1 + P2)	-1258.696321	3.84	

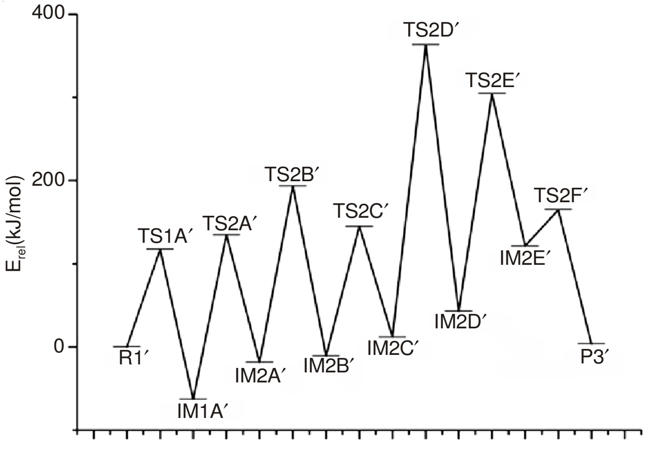


Fig. 2. Schematic map of energy levels in the reaction

Reaction mechanism and energies analysis of synthesis of IM1A: Firstly, R1 reacts R2 to form IM1A through transition state TS1A. This is a nucleophilic reaction. In TS1A, the bond length and the charge density at the bond-forming critical point of C1-N2, H4-N2, N3-H4 are 0.1527 nm and 0.2316 a.u., 0.1302 nm and 0.1478 a.u. and 0.1350 nm and 0.1245 a.u., respectively and the activation energy is 117.47 kJ mol^{-1}. The mechanism of the reaction is: R1 + R2 → TS1A → IM1A.

Reaction mechanism and energies analysis of synthesis of P3: IM1A reacts with R3 to form IM2A through transition state TS2A. This is a concerted reaction process with the bond-forming of N3-C4 and the transfer of a hydrogen atom. In TS2A, the bond length and the charge density at the bond-forming critical point of H1-N3, H1-O2, N3-C4 are 0.1246 nm and 0.1703 a.u., 0.1347 nm and 0.1177 a.u. and 0.1651 nm and 0.1710 a.u., respectively, the charge densities of critical points of (3, +1) rings of H1-O2, O2-C4, C4-N3 and N3-H1 is 0.0769 a.u. and the activation energy is 197.82 kJ mol^{-1}.

IM2A forms IM2B and water through transition state TS2B: This is a dehydration processes. In TS2B, the bond length and the charge density at the bond-forming critical point of H1-N3, H1-O2, O2-C4 are 0.1271 nm and 0.1563 a.u., 0.1303 nm and 0.1302 a.u. and 0.1902 nm and 0.0870 a.u., respectively, and the activation energy is 211.75 kJ mol^{-1}.

IM2B forms IM2C through transition state TS2C: This is a closing-ring processes. In TS2C, the bond length of C1-N2 is 0.3225 nm and the activation energy is 155.92 kJ mol^{-1}. IM2C forms IM2D and hydrogen gas through transition state TS2D. This is a dehydrogenating processes. In TS2D, the bond length and the charge density at the bond-forming critical point of H1-H2, H1-C3, H2-N4 are 0.1605 nm and 0.0328 a.u., 0.2426 nm and 0.1052 nm and 0.2921 a.u., respectively and the activation energy is 351.13 kJ mol^{-1}. This is the determining step.

IM2D forms IM2E through transition state TS2E: This is a concerted reaction process with the closing-ring and the transfer of a hydrogen atom. In this processes, the hydrogen atom of N1 is transferred to position of the N2 atom and a newly ring is formed. In TS2E,the bond length and the charge density at the bond-forming critical point of N1-H3, H3-N4, N1-C2 are 0.1440 nm and 0.1102 a.u., 0.1275 nm and 0.1617 a.u. and 0.2787 nm, respectively and the activation energy is 261.60 kJ mol^{-1}.

IM2E forms P3 and R2 through transition state TS2F. In TS2F, the bond length and the charge density at the bond-forming critical point of N1-C3, C2-N4 are 0.1958 nm and 0.0866 a.u., 0.1466nm and 0.2593 a.u., respectively and the activation energy is 43.38 kJ mol^{-1}.

Mechanism of the reaction is: IM1A + R3 → TS2A → IM2A → TS2B → IM2B + P1→TS2C + P1 → IM2C + P1 → TS 2D + P1 → IM2D + P1+P2 → TS2E + P1 + P2 → IM2E + P1 + P2 → TS2F + P1+ P2 → P1 + P2 + P3 + R2.

The overall reaction is R1 + R2 + R3 → P1 + P2 + P3 + R2.

The details of the reaction mechanism of the reaction are shown as Fig. 3.

Conclusion

The mechanism of reaction among benzene-1,2-diamine, isothiocyanatomethane and 4-methylbenzaldehyde for the synthesis of 2-(*p*-tolyl)-1*H*-benzo[d]imidazole was investigated by density functional theory (DFT). IM2C → IM2D is the rate-determining step. The activation energy of the reaction is 351.13 kJ mol^{-1}. It is identical with Babu *et al.*[14] conclusions.

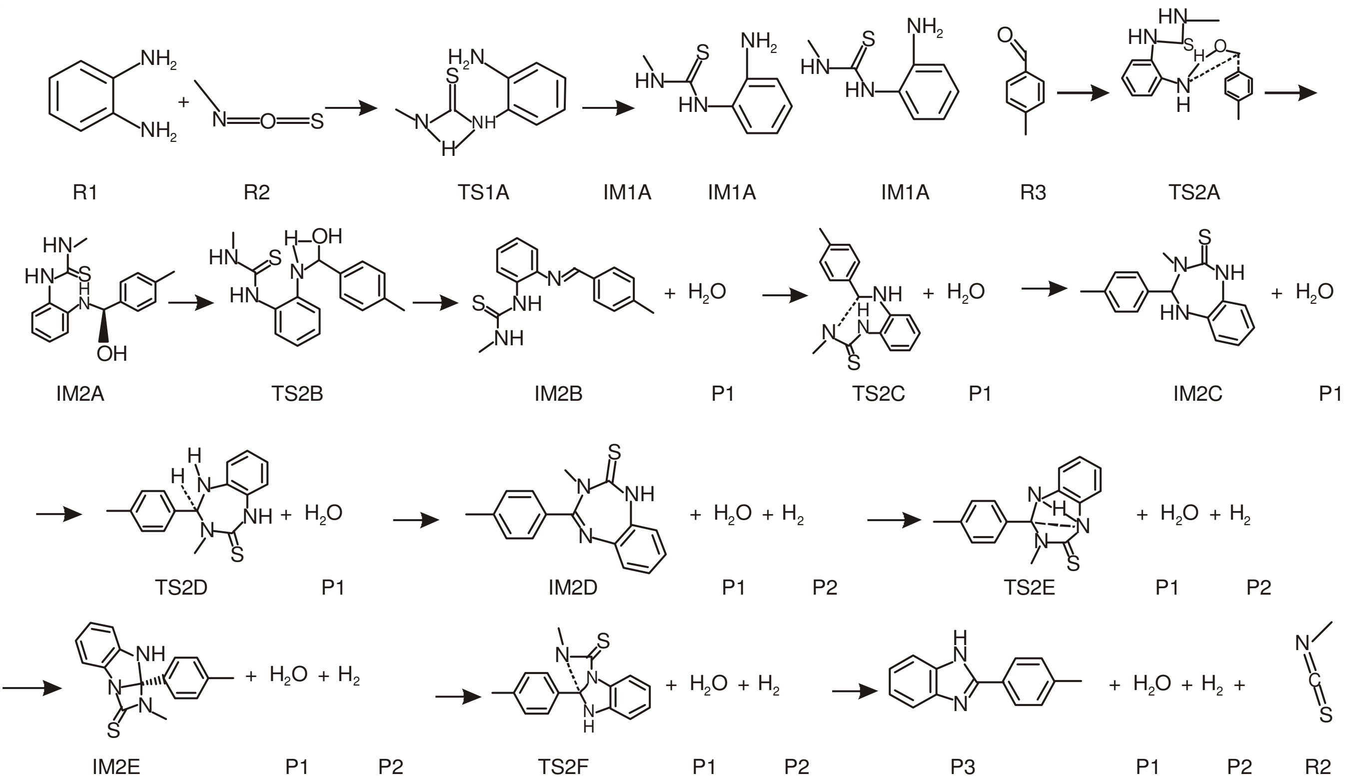


Fig. 3. Mechanism of Synthesis on 2-(*p*-tolyl)-1*H*-benzo[d]imidazole

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REFERENCES

1. R.V. Shingalapur, K.M. Hosamani and R.S. Keri, *Eur. J. Med. Chem.*, **44**, 4244 (2009).
2. D. Zampieri, M.G. Mamolo, L. Vio, E. Banfi, G. Scialino, M. Fermeglia, M. Ferrone and S. Pricl, *Bioorg. Med. Chem.*, **15**, 7444 (2007).
3. A. Puratchikody and M. Doble, *Bioorg. Med. Chem.*, **15**, 1083 (2007).
4. K.C.S. Achar, K.M. Hosamani and H.R. Seetharamareddy, *Eur. J. Med. Chem.*, **45**, 2048 (2010).
5. P. Gupta, S. Hameed and R. Jain, *Eur. J. Med. Chem.*, **39**, 805 (2004).
6. F. Hadizadeh, H. Hosseinzadeh, V. Sadat Motamed-Shariaty, M. Seifi, S. Kazemi, *Iran. J. Pharm. Res.*, **7**, 29 (2008).
7. H.M. Refaat, *Eur. J. Med. Chem.*, **45**, 2949 (2010).
8. D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq and J. Balzarini, *Eur. J. Med. Chem.*, **44**, 2347 (2009).
9. K. Bhandari, N. Srinivas, V.K. Marrapu, A. Verma, S. Srivastava and S. Gupta, *Bioorg. Med. Chem. Lett.*, **20**, 291 (2010).
10. S. Balalaie and A. Arabanian, *Green Chem.*, **2**, 274 (2000).
11. S. Samai, G.C. Nandi, P. Singh and M.S. Singh, *Tetrahedron*, **65**, 10155 (2009).
12. A. Hasaninejad, A. Zare, M. Shekouhy and J. Ameri Rad, *J. Comb. Chem.*, **12**, 844 (2010).
13. A. Davoodnia, M.M. Heravi, Z. Safavi-Rad and N. Tavakoli-Hoseini, *Synth. Commun.*, **40**, 2588 (2010).
14. A. Babu, V. Babu and P. Hanumanthu, *Synth. Commun.*, **31**, 375 (2001).
15. R.F.W. Bader, Atoms in Molecules: A Quantum Theory, Clarendon: Oxford, U.K. (1990).
16. P.L. Prpelier, Atoms in Molecules: An Introduction; Pearson Education: Halow, U.K. (1999).
17. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez and J.A. Pople, Gaussian, Inc., Wallingford CT, Gaussian, Inc.: Pittsburgh, PA (2004).