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Theoretical Study on Reaction Mechanism of Tautomerization of Indazole and 3-halogeno-indazole

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(Dated: Received on June 2, 2005; Accepted on September 27, 2005)

The molecular structures of indazole and 3-halogeno-indazole tautomers were calculated by the B3LYP method at the 6-311G** level, both in the gaseous and aqueous phases, with full geometry optimization. The geometry and electronic structure of the tautomers of indazole, 3-halogeno-indazole and their transition states were obtained. The Onsager solvate theory model was employed for the aqueous solution calculations. The results of the calculation indicated that the N1-H form of the studied molecule is more stable than that of the N2-H form. The influences of the different 3-halogeno and solvent effects on the geometry, energy, charge and activation energy were discussed. The reaction mechanism of the tautomerization of indazole and 3-halogeno-indazole was also studied and a three-membered cyclic transition state of the tautomer reaction has been obtained.

Key words: 3-halogeno-indazole, Tautomers, Transition states, Activation energy, DFT

I. INTRODUCTION

The effects of tautomerism of heterocyclic compounds on their chemical/biological and pharmacological properties are of great interest to many researchers especially to medical chemists, if the tautomerism is related to pharmacological properties. The tautomeric equilibria of heterocyclic compounds have been investigated by many experimental and theoretical methods [1-7]. Indazole derivatives are mainly used as anti-inflammatory and analgesic medicines. There have been many studies on indazole and its derivatives, such as Catlan *et al.* [8]. Their research included the biological properties of indazole-derived drugs, aromaticity studies and lone pair-lone pair interactions in the solution at both the ground and the excited states. Ogretir *et al.* studied the effect of 3C substituents on geometries, relative stabilities, acidity constant and proton affinities of indazole derivatives tautomers in the gaseous and aqueous phases using AM1, PM3 and MNDO methods [9,10]. Latosinska *et al.* studied thermodynamic stability by *ab initio* and NMR [11]; Anandan *et al.* discussed the tautomerism of indazole in the gaseous and aqueous phases using *ab initio* and DFT methods [12], but we did not come across any details about theoretical studies on the reaction mechanism of tautomerization of indazole and 3-halogeno-indazole. In this paper, we report the reaction mechanism of the tautomerization of indazole and 3-halogeno-indazole (-F, -Cl and -Br), based on the study of the molecular structures of transition

states, using the B3LYP method at the 6-311G** level in the gaseous and aqueous phases.

II. METHOD OF CALCULATION

All species were optimized with the GAUSSIAN 98W program employing the electron correlated Becke3LYP function of the density function theory by implementing the 6-311G** basis set. Molecular structures of indazole and 3-halogeno-indazole tautomers and their transition states (Fig.1) were calculated, both in the gaseous and aqueous phases, with full geometry optimization. The solvent effects were calculated using the Onsager solvate theory model with a dielectric constant of 78.39 to simulate the water solvent. The total energy, enthalpy, Gibbs free energy and dipole moments have been calculated for all the optimized molecular structures. The predicted transition states were verified by establishing that the Hessians have only one negative eigen value. In addition, the TS→reactants and TS→products reaction paths were followed using the IRC (intrinsic reaction coordinate) procedure. The calculated TSs match the corresponding TS with the reactants and products and hence we can conclude that real TSs were found.

III. RESULTS AND DISCUSSION

A. Geometries

The optimized geometry parameters (i.e. bond lengths R , bond angles A and dihedral angles D) of all the studied molecular structures were obtained by using the B3LYP method at the 6-311G** level, in both

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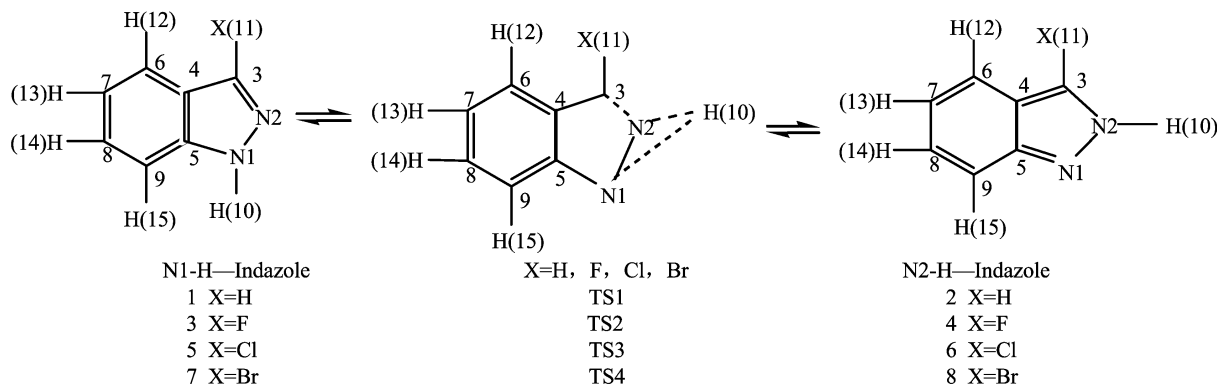


FIG. 1 Possible tautomeric structures of the studied molecules with atom numbering.

TABLE I Optimized bond lengths (nm), bond angles ($^{\circ}$) and dihedral angles ($^{\circ}$) for the transition states of indazole and 3-halogeno-indazole in gaseous and aqueous phases

	Gaseous phase				Aqueous phase			
	TS1	TS2	TS3	TS4	TS1	TS2	TS3	TS4
R_{1-2}	0.1460	0.1476	0.1465	0.1466	0.1466	0.1481	0.1468	0.1471
R_{2-3}	0.1339	0.1327	0.1333	0.1333	0.1340	0.1328	0.1334	0.1334
R_{1-10}	0.1281	0.1291	0.1286	0.1286	0.1282	0.1293	0.1288	0.1289
R_{3-11}	0.1081	0.1329	0.1728	0.1886	0.1081	0.1331	0.1730	0.1889
A_{1-2-3}	108.30	106.70	107.35	107.42	108.09	106.48	107.16	107.12
A_{2-3-4}	110.60	113.03	111.95	111.87	110.78	113.27	112.16	112.19
A_{1-2-10}	51.74	50.84	51.46	51.44	51.48	50.54	51.26	51.15
A_{2-3-11}	119.94	120.26	120.93	120.94	119.95	119.95	120.75	120.75
$D_{1-2-3-4}$	3.14	3.11	3.21	3.21	3.06	2.95	3.09	3.05
$D_{1-2-3-5}$	-0.11	-0.03	-0.18	-0.17	-0.10	0.05	-0.12	-0.09
$D_{10-1-2-3}$	117.63	116.32	116.63	116.72	116.48	115.27	115.86	115.55
$D_{11-1-2-3}$	-177.94	-177.81	-177.54	-177.53	-177.67	-177.90	-177.55	-177.47

The molecular structures of TS1, TS2, TS3 and TS4 were shown in Fig.1.

gaseous and aqueous phases. Some geometric parameters of the transition states are given in Table I.

As for the stationary points, the bond lengths had no noticeably changes, except for the R_{3-11} bond length, which increased greatly due to the increase in atomic radius of halogen, for example, the variation of R_{3-11} ranges from 0.1072 nm to 0.1880 nm; the 3C substituents (H, F, Cl and Br) have little effect on dihedral angle and the variation of dihedral angles are all less than 0.004° . This revealed that all atoms of the reactant and the product are basically on a molecular plane. It also indicated that the 3C substituents have almost no effect on the molecular structures, which is corroborated by others' work [13,14]. According to Table I, the variations of R_{1-10} of the transition states are about 0.03-0.05 nm larger than that of their stationary points; Compared with stationary points, A_{1-2-10} bond angle decreased about 65° - 70° , dihedral angles of $D_{1-2-3-4}$ and $D_{10-1-2-3-5}$ deviated from the molec-

ular plane about 3° and 60° - 70° , respectively, and the variations of $D_{11-1-2-3}$ and $D_{1-2-3-5}$ are about 0.1° , 0.3° , respectively. This suggests that C(3) and X(11) were still on the molecular plane, but that N(1) and N(2) deviated from the plane, and at the same time the transition states corresponding to $N(2)\cdots H(10)$ bond formation accompanied by the hydrogen atom (H(10)) transfer and the migration of H(10), a deviation of about 60° - 70° from the molecular plane occurs. This is a three-member ring consisting of N(1), N(2) and H(10).

B. Thermodynamic parameters

The calculated tautomeric relative total energies ΔE , relative total energies corrected for the corresponding zero-point energy ΔE_0 , and relative enthalpies ΔH^{\ominus} , relative free energies ΔG^{\ominus} for the N1H \rightarrow N2H tau-

TABLE II Calculated tautomeric relative energies for the N1H→N2H tautomerization of indazole and 3-halogeno-indazole in the gaseous and aqueous phases (kJ/mol)

	Gaseous phase				Aqueous phase			
	ΔE	ΔE_0	ΔH^\ominus	ΔG^\ominus	ΔE	ΔE_0	ΔH^\ominus	ΔG^\ominus
1→2	20.65	21.36	20.99	21.65	11.26	10.55	10.49	10.90
3→4	37.11	37.96	37.47	38.35	42.41	56.96	57.70	55.54
5→6	27.04	31.43	32.58	30.16	32.35	31.91	31.60	32.04
7→8	25.19	26.21	25.88	26.29	30.24	413.33	413.67	413.82

TABLE III Kinetic parameters for the transition states of indazole and 3-halogeno-indazole in the gaseous and aqueous phases (kJ/mol)

	Gaseous phase				Aqueous phase			
	ΔE^\ddagger	ΔE_0^\ddagger	ΔH^\ddagger	ΔG^\ddagger	ΔE^\ddagger	ΔE_0^\ddagger	ΔH^\ddagger	ΔG^\ddagger
1→TS1	224.03	208.16	256.06	256.92	214.88	197.71	254.00	254.91
2→TS1	203.37	186.80	222.82	222.96	203.62	187.16	222.83	222.92
3→TS2	226.86	211.71	260.92	262.51	228.87	213.63	261.31	262.88
4→TS2	189.75	173.75	259.39	211.80	186.46	156.67	261.31	205.31
5→TS3	225.21	200.77	259.39	260.35	227.66	210.99	260.61	261.51
6→TS3	198.17	169.34	259.39	219.02	195.31	179.08	260.61	214.63
7→TS4	224.46	208.87	258.93	259.84	225.96	234.39	259.50	260.37
8→TS4	199.27	182.66	258.93	220.08	195.72	179.28	259.50	216.72

tomomerization of indazole and 3-halogeno-indazole in the gaseous and aqueous phases at the B3LYP/6-311G** level are shown in Table II.

We can see from Table II that the relative total energy (ΔE), zero-point energy corrected total energies difference (ΔE_0), enthalpy difference (ΔH^\ominus), and free energy difference (ΔG^\ominus) are all positive. This revealed that, in the gaseous and aqueous phases, the N1H form was computed to be more stable than the N2H form, which is supported by the references [9,10]. In addition, the energy difference for the N1H→N2H tautomerization of indazole and 3-halogeno-indazole in the gaseous phase are all higher than that in the aqueous phase. Moreover, all thermodynamic energy differences for the 3→4, 5→6, 7→8 tautomerization decreased in turn. Also, according to Table II, energy differences for the N1H→N2H tautomerization of 3-halogeno-indazole in the gaseous and aqueous phases are all higher than those of the parent molecule.

C. Kinetic parameters

The calculated tautomeric activation energies, enthalpies, free energies, and zero-point energies for the N1H→TS, TS→N2H in the gaseous and aqueous phases at the B3LYP/6-311G** level are shown in Table III. With increasing charges of fluorin, chlorine and bromine carried, the activation energies for the N1H→TS of the studied molecules(except for 1→TS1) decreased gradually in the gaseous and aqueous phases, while TS→N2H

(except for TS1→2) increased in turn. In addition, the activation energies for the N1H→TS in the aqueous phase were larger than those in the gaseous phase, increasing 1.99 kJ/mol on average, or about 0.8%. On the contrary, activation energies for the TS→N2H in the aqueous phase were lower than that in the gaseous phase, decreasing 3.20 kJ/mol, or about 1.7%, which indicated that the influence of the solvent increased the activation energies for the N1H→TS while decreasing those for the TS→N2H. The influence of the solvent facilitated the tautomerization of 3-halogeno-indazole. The calculated tautomeric enthalpies (ΔH^\ddagger) for the stationary point→TS of 3-halogeno-indazole in the gaseous and aqueous phases showed that ΔH^\ddagger in the aqueous phase were only 0.5% higher than that in the gaseous phase. As for tautomeric Gibbs free energies (ΔG^\ddagger), all ΔG^\ddagger for the N1H→TS reactions were higher than that of TS→N2H, but ΔG^\ddagger for the tautomerization reactions in the gaseous phase nearly the same as those in the aqueous phase (e.g. ΔG^\ddagger for the 3→TS2 is 262.51 kJ/mol in the gaseous phase, ΔG^\ddagger is 262.88 kJ/mol in the aqueous phase). This indicated that the influence of the solvent effect is not significant on either ΔH^\ddagger or ΔG^\ddagger of the tautomerization.

D. Natural population analysis and dipole moment

The charge distribution in reactants and transition states was analyzed. The natural atomic charges com-

TABLE IV The natural atomic charges and dipole moments (μ) of indazole and 3-halogeno-indazole and their transition states in the gaseous and aqueous phases

	Gaseous phase						Aqueous phase					
	N(1)	N(2)	C(3)	H(10)	X(11)	μ	N(1)	N(2)	C(3)	H(10)	X(11)	μ
1	-0.350	-0.254	-0.010	0.399	0.201	1.7072	-0.349	-0.262	-0.013	0.400	0.195	2.2931
2	-0.298	-0.289	-0.025	0.401	0.210	2.5056	-0.304	-0.285	-0.015	0.405	0.218	3.2738
3	-0.348	-0.305	0.588	0.398	-0.323	3.2748	-0.354	-0.315	0.584	0.405	-0.343	4.3005
4	-0.310	0.342	0.596	0.410	-0.324	1.1562	-0.313	-0.331	0.595	0.406	-0.313	1.5500
5	-0.335	-0.271	0.155	0.399	0.015	3.4730	-0.342	-0.279	0.156	0.406	-0.008	4.5795
6	-0.290	-0.314	0.140	0.411	0.030	0.9325	-0.292	-0.313	0.142	0.411	0.035	1.1631
7	-0.346	-0.272	0.091	0.404	0.081	3.2540	-0.342	-0.281	0.095	0.406	0.052	4.5706
8	-0.288	-0.315	0.072	0.411	0.099	1.1583	-0.293	-0.314	0.073	0.412	0.195	1.6303
TS1	-0.412	-0.422	0.064	0.490	0.192	2.5717	-0.424	-0.436	0.072	0.487	0.193	3.2551
TS2	-0.389	-0.434	0.618	0.469	-0.321	2.9517	-0.394	-0.446	0.615	0.465	-0.324	3.7588
TS3	-0.375	-0.406	0.172	0.471	-0.324	2.9837	-0.377	-0.416	0.173	0.467	0.028	3.6502
TS4	-0.375	-0.408	0.108	0.471	0.103	2.8454	-0.378	-0.422	0.110	0.465	0.092	3.8222

puted are summarized in Table IV.

NBO population analysis indicates the N(1) and N(2) possess negative charges and the migration hydrogen (H(10)) possesses a positive charge (Table IV). Compared with the reactants and products, negative charges of N(1) and N(2) of the transition states all increased, but negative charges of N(2) increased noticeably; positive charge of H(10) also increased substantially. These increases showed that electrons flowed from H(10) to N(1) and N(2), meanwhile a three-member ring as cited in this work, consisting of H(10), N(1) and N(2) came into being. In addition, the negative charges N(1) and N(2) carried in the aqueous phase were greater than those in the gaseous phase. As for the charges of X(11), which augmented gradually with the increasing of the electronegativity of fluorine, chlorine and bromine (e.g. in the gaseous phase the charges the N1-H and N2-H forms carried ranged from $-0.323e$ to $0.081e$, $-0.324e$ to $0.099e$, respectively). Combining this with Table II, we can include that the more charge X(11) possesses, the lower the energy differences for N1-H \rightarrow N2-H tautomerization reactions are.

Though the influence of solvent made the dipole moments of all studied molecules in the aqueous phase much larger than those in the gaseous phase, the difference of the N1H form of 3-halogeno-indazole ranged from about 1.100-1.300 D, the N2H form ranged from about 0.300-0.400 D and transition states about 0.700 D, respectively. These changes revealed that the solvent has no noticeable effect on the dipole moments of tautomers of 3-halogeno-indazole and their transition states.

E. Vibrational frequencies and potential profile

The harmonic vibrational frequencies of the molecular structures of transition states were calculated at

the B3LYP/6-311G** level in the gaseous and aqueous phases, the lowest frequencies and the vibrational frequencies corresponding to the largest IR intensities were obtained. The lowest frequencies can explain whether the obtained structures had imaginary frequencies. The results of the calculation showed that all TSs had only one imaginary frequency. Lowest frequencies in the gaseous phase were $1727i$, $1721i$, $1733i$, $1733i$, respectively. The frequencies in the aqueous phase were $1715i$, $1709i$, $1724i$, $720i$, respectively. These results indicate that the calculated molecular structures are the real structures of the transition states.

For each transition state, we calculated the intrinsic reaction coordinate (IRC) routes in both directions toward the corresponding minima (using 40 points along the reaction path to examine, step size along the reaction path, in units of $0.01 \text{ amu}^{-1/2}\text{-Bohr}$). The results of the calculation showed that optimizing follow the path only in the backwards direction (i.e. calculation were carried out from the transition state to the reactant). The bond length of R_{1-10} decreased gradually and bond angle of A_{2-1-10} increased little by little, and followed the path only in the reverse direction. A_{1-2-10} augmented gradually. This revealed that the calculated transition states actually connected the reactants with the products. The potential profile in the tautomerization reaction of $1\rightarrow\text{TS1}\rightarrow 2$ is given in Fig.2.

IV. CONCLUSION

Through detailed mathematical modeling of the reaction mechanism of tautomerization of indazole and 3-halogeno-indazole, we were able to draw the following conclusions: (i) The calculations showed that the N1-H form of indazole and 3-halogeno-indazole is more stable

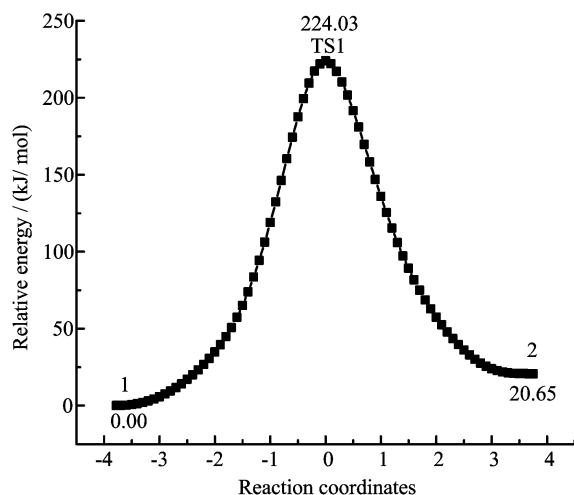


FIG. 2 The potential profile in the isomerization reaction of indazole.

than that of N2-H form. (ii) The molecular structure of transition states of the N1-H→N2-H tautomerization reactions was a three-member ring which consisted of N (1), N (2) and H (10), and the migration H(10) deviated from the molecule plane about 60°-70°. (iii) The influence of a 3-substituent (-F, -Cl and -Br) had no noticeable effect on the geometric structures of the reactants, the transition states nor the products. (iv) The influence of a solvent had no significant effect on the activation energies for the N1H→N2H tautomerization

reactions of the studied species.

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