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Computational investigation of water as catalyst and solvent in aromatic nucleophilic substitution reaction of 2-bromopyridine

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We have computationally investigated the role of water as a catalyst and solvent in the aromatic nucleophilic substitution reaction of 2-bromopyridine with thiophenol. Water as catalyst significantly lowers the transition state energy by an amount of 5.58 kcal/mol *via* forming hydrogen bonds with reactants and the transition state. The role of water as catalyst is further studied by investigating non-covalent interactions. Results show that water forms hydrogen bonding with reactant 2-bromopyridine (–5.90 kcal/mol) and two hydrogen bonds in the transition state (7.24 and 7.95 kcal/mol) that stabilize the transition state. Reduced density gradient analysis confirms these interactions. Frontier molecular orbital analysis shows water reduces the energy gap in both reactants and transition states thus lowering the reaction's energy requirement. Additionally, the reaction's energy requirement in water is 1.25 kcal/mol lower than in non protic solvent DMSO, further confirming water's dual role as a catalyst and solvent.

Keywords: DFT studies, Nucleophilic substitution, QTAIM, RDG, FMO

Computational organic chemistry has emerged as an important branch of theoretical chemistry, with the prime objective of development and use of reliable mathematical models and algorithms to study organic molecules and investigation of reaction pathways[1-6]. Substituted pyridines are important N-heterocycles compounds which are present in structure of many biologically active compounds as well as in natural products[7-10]. Therefore, there is a strong need for the development of gentle, effective, and adaptable approaches for the synthesis of substituted pyridines. Among variously substituted pyridine derivatives, 2-thiopyridines are highly important because of their wide range of applications especially in pharmaceutical chemistry especially as anti-tuberculosis agents[11-14]. Sreedhar *et al.* reported the green synthesis of 2-thiopyridine derivatives by nucleophilic substitution reaction of 2-halopyridine with thiols by using water as solvent as well as catalyst[15]. The mechanism of this reaction is particularly interesting because water serves both as a catalyst and as a solvent. Computational chemistry methods have been widely used to study and understand the reaction mechanism of nucleophilic substitution reactions[16]. In light of above discussion, we hypothesize that water can perform dual functions in the nucleophilic substitution reaction of 2-halopyridine with thiols by forming hydrogen bonds with reactants and transition states, and that this can be elucidated and understood through computational DFT calculations. This understanding will offer insights into the reaction mechanism and potentially guide the development of new, efficient, and environmentally friendly synthetic methods for heterocyclic compounds.

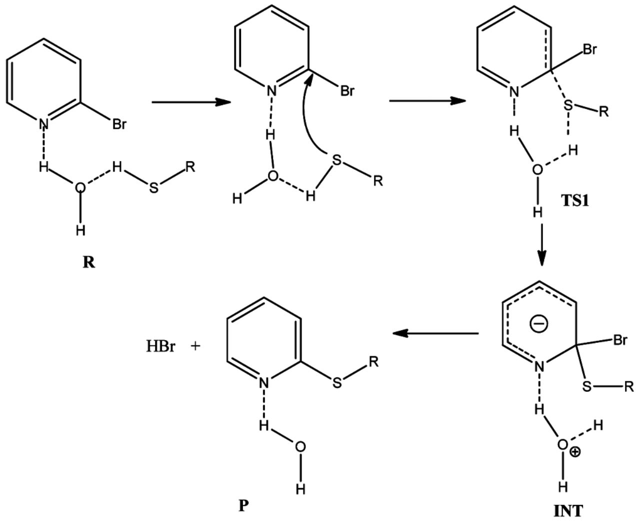
Computational methods

Density functional theory (DFT) calculations were conducted using Becke's three-parameter hybrid functional (B3) for the exchange part and the Lee–Yang–Parr (LYP) correlation function part, along with Pople style basis sets 6-311++G(d,p) implemented in Gaussian 09 software[17, 18]. Structural optimizations were carried out at the same level of theory in both gas and solvent phases, using the IEFPCM solvent model without any geometrical constraints[19, 20]. Frequency calculations were performed to identify transition states, followed by forward and reverse intrinsic reaction coordinate (IRC) calculations on the optimized structures of the transition states in both gas and solvent phases, confirming the connections with stable points[21]. The results from Gaussian 09 were visualized using the GaussView 06 program[22]. ESP, RDG, and QTAIM calculations were conducted using the Multiwfn program[23], with the results visualized using VMD software[24].

Results and Discussion

The plausible reaction mechanism for water catalysed substitution reaction is shown in Scheme 1. Water promotes aromatic nucleophilic substitution reaction of 2-bromopyridine by firstly forming hydrogen bond with nitrogen atom of pyridine ring through hydrogen atom and interacting with hydrogen atom of thiol through oxygen atom. This results in decrease in electron density over ring and also increases nucleophilicity of thiol. The attack of sulphur atom over carbon containing leaving group bromine of pyridine results in formation of intermediate *via* transition state TS1. The intermediate formed then undergoes elimination to form substituted product (Scheme 1).

To understand the reaction mechanism, we have firstly investigated the reaction between 2-bromopyridine and thiophenol in presence of water as catalyst in gas phase using DFT at B3LYP/6-311++G(d,p) level of theory. The structures of reactants, transition states, intermediates, and products were optimized in gas phase at this level of theory and are shown in Fig. 1. The energy profile diagrams of various reaction species is shown in Fig. 2. The results of DFT calculations show that the structure of reactants *i.e.* thiophenol and 2-bromopyridine is stabilized by presence of water molecule through hydrogen bonding between oxygen (O25) of water and hydrogen (H23) of thiophenol with bond distance of 2.14 Å, while hydrogen (H24) atom of water forms hydrogen bond with nitrogen (N6) of 2-bromopyridine with bond distance of 1.93 Å. This is followed by formation of transition state TS1 by nucleophilic attack of sulphur (S11) atom to carbon (C5) of 2-bromopyridine. The formation of transition state TS1 is confirmed by presence of single imaginary frequency at 339i cm^{-1} which is corresponding to the attack of sulphur (S11) to carbon (C5) of 2-bromopyridine with simultaneous leaving of bromine (Br27). In transition state (TS1) sulphur (S11) forms bond with carbon (C5) at bond distance of 2.13 Å, while C5-Br27 bond starts breaking and elongated to 2.35 Å. The structure of transition state is stabilized by the presence of water through formation of hydrogen bond between oxygen (O25) of water with hydrogen (H23) of thiophenol at bond distance 1.81 Å, while hydrogen (H24) of water forms hydrogen bond with nitrogen (N6) of pyridine ring. The energy of transition state (TS1) is found to be 41.57 kcal/mol higher than energy of reactant molecules. The transition state further gives product 2-(phenylthio)pyridine (P) *via* formation of intermediate (INT). The structure of product formed is also stabilized by the presence of water in the reaction. The overall reaction is found to be exothermic with release of energy of –2.14 kcal/mol.



Scheme 1 — Plausible reaction mechanism for water catalysed substitution reaction between 2-bromopyridine and thiol.

In order to understand the role of water as catalyst in this reaction, we have studied the reaction between 2-bromopyridine and thiophenol in absence of water as catalyst using DFT at B3LYP/6-311++G(d,p) level of theory. The optimized structures of reactants, transition states, intermediates, and products are shown in Fig. 3. The energy profile diagram of various reactive species along reaction coordinates is shown in Fig. 4. In the absence of water as catalyst, the reaction proceeds by initial nucleophilic attack of sulphur (S12) to carbon (C5) of 2-bromopyridine that resulted in a formation of transition state TS1′ with formation of S12-C5 bond with bond length of 2.12 Å while C5-Br11 bond is elongated from 1.92 Å in 2-bromopyridine to 2.44 Å in transition state. The formation of transition state TS1′ is confirmed by single imaginary frequency at 229i cm^{-1} which is corresponding to attack of sulphur (S12) to carbon (C5) of 2-bromopyridine with simultaneous leaving of bromine (Br11). The energy of transition state in absence of water catalyst was found to be 47.15 kcal/mol which is 5.58 kcal/mol higher than energy requirement for reaction in presence of water catalyst. This clearly indicates the presence of water as catalyst

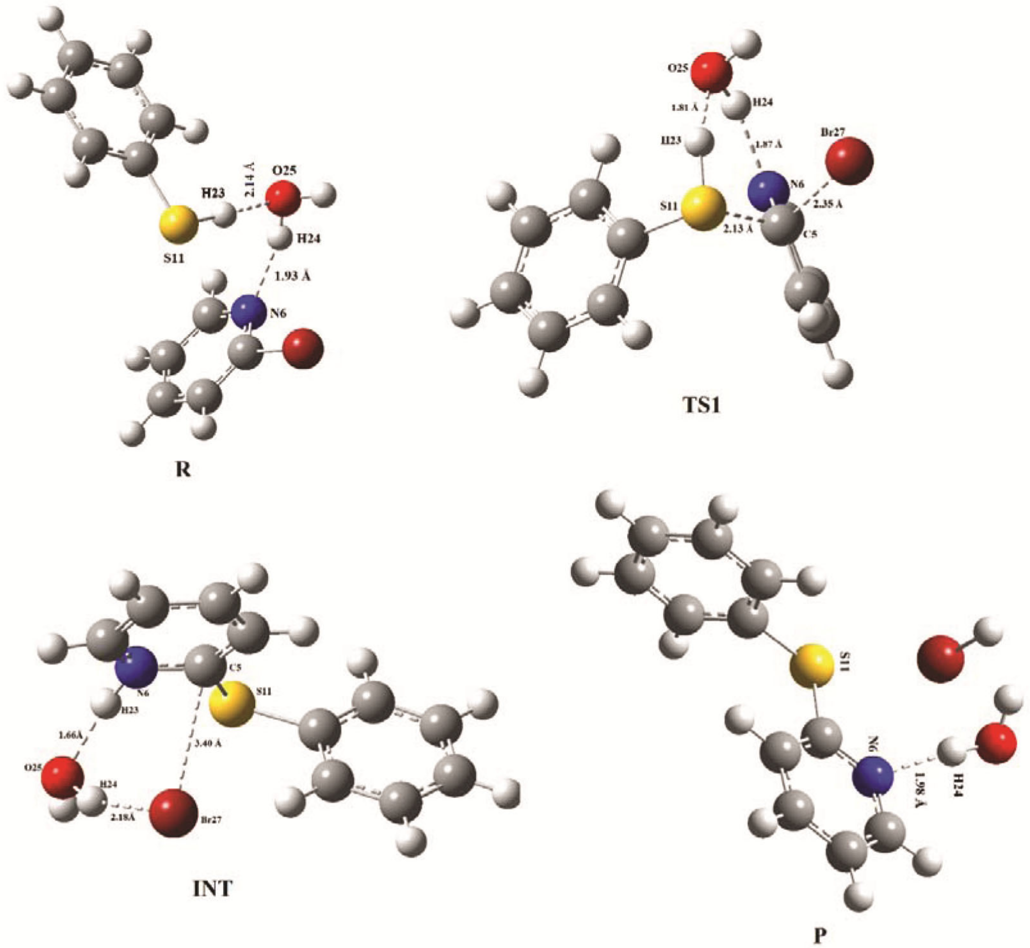


Fig. 1 — Optimized structures of reactants, transition state, intermediate and product for reaction between 2-bromopyridine and thiophenol in presence of water as catalyst in gas phase using DFT at B3LYP/6-311++G(d,p) level of theory.

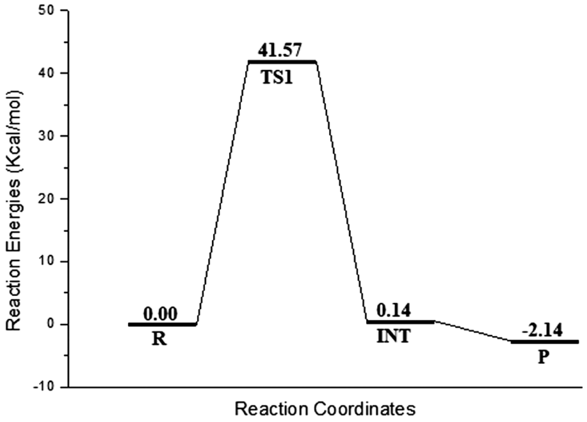


Fig. 2 — The energy profile diagrams for reaction between 2-bromopyridine and thiophenol in the presence of water as catalyst in gas phase using DFT at B3LYP/6-311++G(d,p) level of theory.

plays important role in lowering the energy of transition state by stabilizing its structure through hydrogen bonding. The transition state formed proceed to product 2-(phenylthio)pyridine (P) *via* formation of intermediate (Fig. 3). The energy of product (4.19 kcal/mol) in absence of water catalyst was also found higher than in presence of water as catalyst (–2.14 kcal/mol) indicating the role of water in stabilization of structure of product also.

The reaction mechanism and the impact of water were further investigated by studying non-covalent interactions, such as hydrogen bonding, intra- and intermolecular interactions, in both reactants and transition states. This analysis was conducted using the Quantum Theory of Atoms in Molecules (QTAIM), developed by Richard Bader[25]. QTAIM distinguishes between covalent and non-covalent interactions based on the electron density (ρ) at the bond critical point (BCP). In covalent interactions, the electron density is high, while the Laplacian ($\nabla^2\rho$) at the BCP is negative. Non-covalent interactions, on the other hand, have a low electron density with a positive $\nabla^2\rho$ value[25]. Additionally, the local electronic energy density (HBCP) can further differentiate

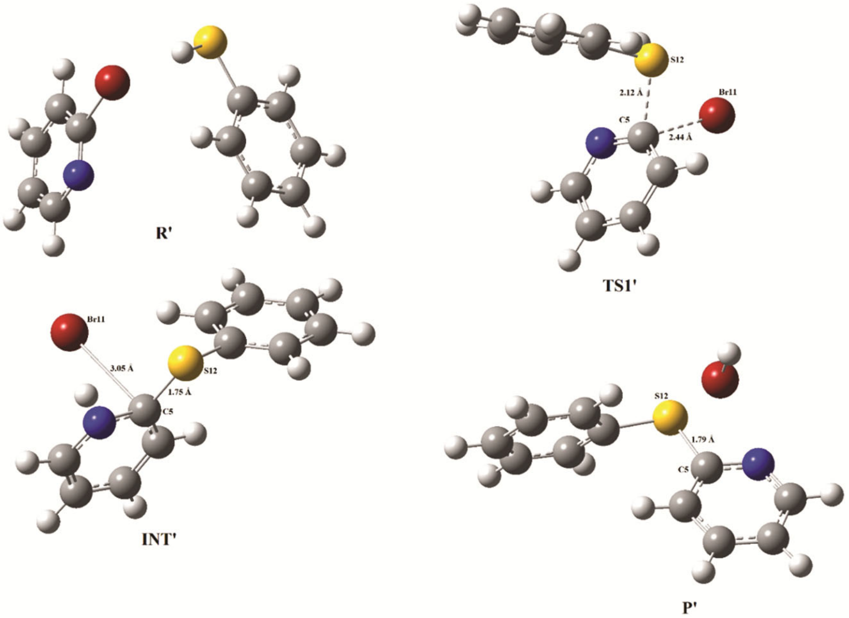


Fig. 3 — Optimized structures of reactants, transition state, intermediate and product for reaction between 2-bromopyridine and thiophenol in absence of water as catalyst in gas phase using DFT at B3LYP/6-311++G(d,p) level of theory.

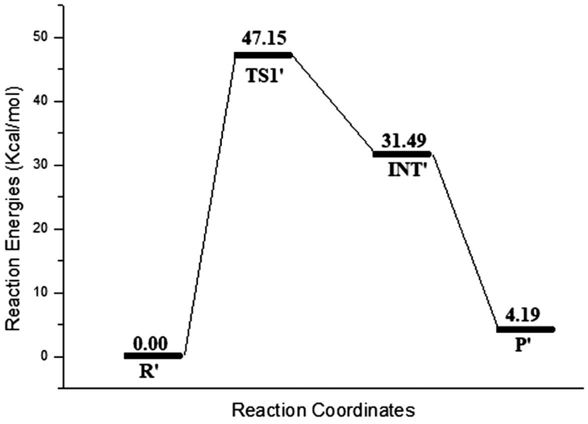


Fig. 4 — The energy profile diagrams for reaction between 2-bromopyridine and thiophenol in absence of water as catalyst in gas phase using DFT at B3LYP/6-311++G(d,p) level of theory.

between covalent and non-covalent interactions, along with the Laplacian of the electron density at the BCP ($\nabla^2\rho$). Covalent interactions exhibit $\nabla^2\rho BCP < 0$ and $HBCP < 0$, while partially covalent interactions have ($\nabla^2\rho BCP > 0$ and $HBCP < 0$), and electrostatic interactions have $\nabla^2\rho BCP > 0$ and $HBCP > 0$[25].

The AIM analysis of reactants and transition state showing attractors and various critical points is shown in Fig. 5. The values of topological parameters *i.e.* electron density (ρ), its Laplacian $\nabla^2\rho$, local electronic energy density (H_{BCP}), and elipticity (ε) for some important bond interactions are shown in Table 1. The AIM analysis of reactants *i.e.* 2-bromopyridine, thiophenol and water catalyst resulted in total 61 critical points which includes 27 atomic critical points (3,–3) except hydrogen, 33 bond critical points-between two neighboring atoms-bonds (3,–1) (BCP), and 01 ring critical points (3,+1) (RCP) between middle of bonds forming ring (Fig. 5). The AIM analysis of transition state (TS1) also gives total 61 critical points (CP) (Fig. 5) which includes 27 atomic critical points (3,–3) except hydrogen, and 34 bond critical points-between two neighboring atoms-bonds (3,–1) (BCP).

The results of AIM analysis show that in the reactants, the strongest hydrogen bond interaction occur between hydrogen atom (H24) of water with nitrogen atom (N6) of 4-bromopyridine. Interaction between H24---N6 has electron density (ρ) value of 00.02979 and its Laplacian while values of $\nabla^2\rho$ have calculated to be 0.07603 with local electronic energy density (H_{BCP}) –0.00028 and elipticity of 0.05027. The bond energy of hydrogen bond was calculated by using equation $-223.08 \times \rho BCP/a.u. + 0.7423$ kcal/mol[26]. Using this equation, the value of hydrogen bond energy was found to be –5.90 kcal/mol which indicates that strong hydrogen bond interactions exist between N6---H24. This strong hydrogen bond interaction helps to stabilize the structure of reactant molecules. Presence of water further stabilize the structure of reactant molecules by hydrogen bond interaction between oxygen (O25) atom of water molecule with hydrogen (H23) atom of thiophenol with bond strength of 3.65 kcal/mol. The presence of

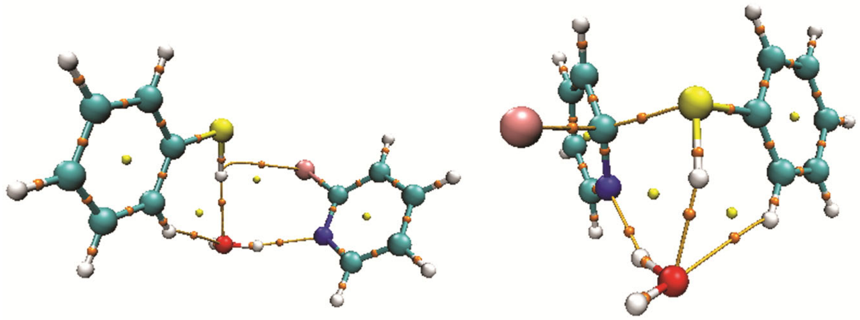


Fig. 5 — AIM analysis of reactants and transition state showing attractors and various critical points (color scheme: attractors-purple, BCP-magenta, RCP-yellow and CCP-green).

Table 1 — Topological parameters of reactants and transition state

Interaction	ρ_{BCP}	$\nabla^2\rho_{BCP}$	H_{BCP}	E
Reactants				
N6---H24	0.02979	0.07603	–0.00028	0.05027
O25---H23	0.01970	0.04624	–0.00107	0.04103
Br27---H23	0.00262	0.00856	0.00051	2.08567
Transition state				
C5---S12 CP45	0.09709	–0.01353	0.03450	0.02098
C5---Br11 CP47	0.06743	0.04981	–0.01480	0.04647
N6---H24 CP 40	0.03582	0.08663	–0.00129	0.02675
O25---H23CP 30	0.03895	0.09439	–0.00135	0.03504

water further stabilize the transition state (TS1) by formation of two hydrogen bonds between H24 and O25 with nitrogen atom (N6) of 4-bromopyridine and hydrogen (H23) of thiophenol, respectively. The strength of hydrogen bond interactions between H24---N6 and O25---H23 was calculated to be 7.24 kcal/mol and 7.95 kcal/mol, respectively. These strong interactions helps in stabilizing transition state, thus confirming the catalytic effect of water in this reaction.

The results of AIM analysis are further supplemented by reduced density gradient (RDG) analysis. The non-covalent interactions present in structure of reactants and transition state (TS1) in presence of water are further investigated by reduced density gradient analysis. This method is based upon electron density function ($\rho(r)$) which refers to the distribution of electron density within a molecule and is calculated from density functional theory (DFT) calculations[27]. The reduced density gradient RDG (r) is obtained from the electron density($\rho(r)$) and its first derivative ($|\Delta\rho(r)|$) by using equation 1 which gives dimensionless quantity[27].

$$\text{RDG (r)} = \frac{|\Delta\rho(r)|}{2(3\pi^2)^{1/3}\rho(r)^{4/3}} \qquad \ldots(1)$$

Identification and visualization of different kind of weak interactions is possible by using scattered plot between RDG (r) and the electron density multiplied by the sign of the second Hessian eigen value *i.e.* sign(λ_2)ρ. The scattered RDG plot results in different spikes, the types of interactions can be determined by the locations and colour of these spikes[26]. The strong repulsive interactions such as steric effects are indicated by large positive values of sign(λ_2)ρ with red colour, while large negative values of sign(λ_2)ρ with blue colour indicates strong attractive interactions, such as hydrogen bond or halogen bond. The Van der Waals interaction are indicated by green coloured spikes with less negative values of sign(λ_2)ρ. Sharp spikes indicate the presence of strong interaction while small spikes indicate the weak interaction. The coloured scattered RDG plot and corresponding iso surfaces for reactants and transition state are shown in Fig. 6 and in Fig. 7, respectively.

The coloured RDG scattered plot (Fig. 6) of reactants shows sharp red coloured spikes at value of +0.02 au while transition state (TS1) shows sharp red coloured spikes at +0.022 au, which indicates the steric repulsive interactions are slightly more strong in transition state as compared to reactants. The presence of sharp peaks in blue region at –0.031au in reactants and at –0.036 au in transition state (TS1) suggests presence of strong hydrogen bonding interactions in transition state (TS1) compared to reactant. The nature and position of interactions present in reactants and in transition state are further visualized by plotting RDG iso-surface with help of VMD program (Fig. 7). The blue coloured circle in RDG iso-surface indicates the presence of strong hydrogen bonding interaction between atoms in reactants and in transition state.

In addition, we have further conducted frontier molecular orbital (FMO) analysis of reactants and

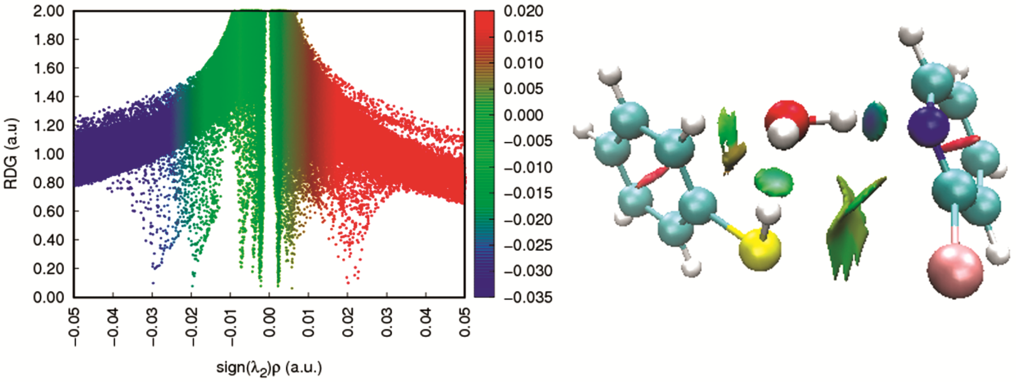


Fig. 6 — The coloured scattered RDG plot and corresponding iso surfaces for reactant molecules

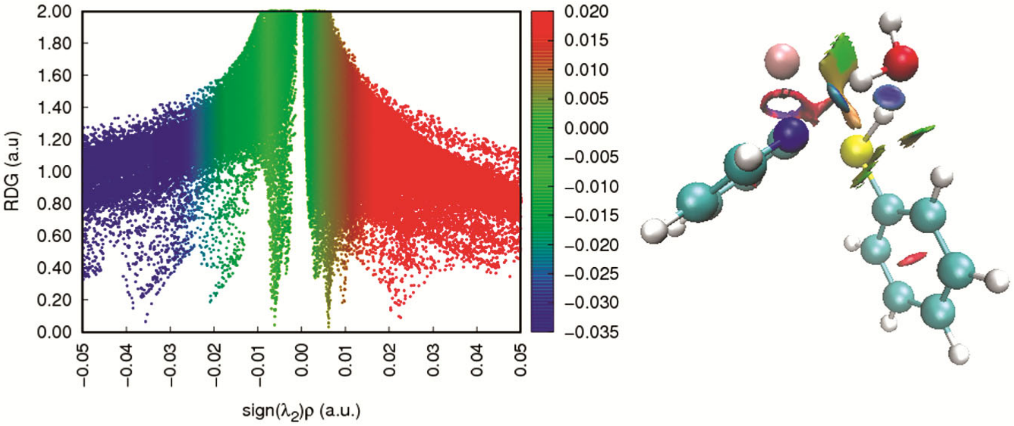
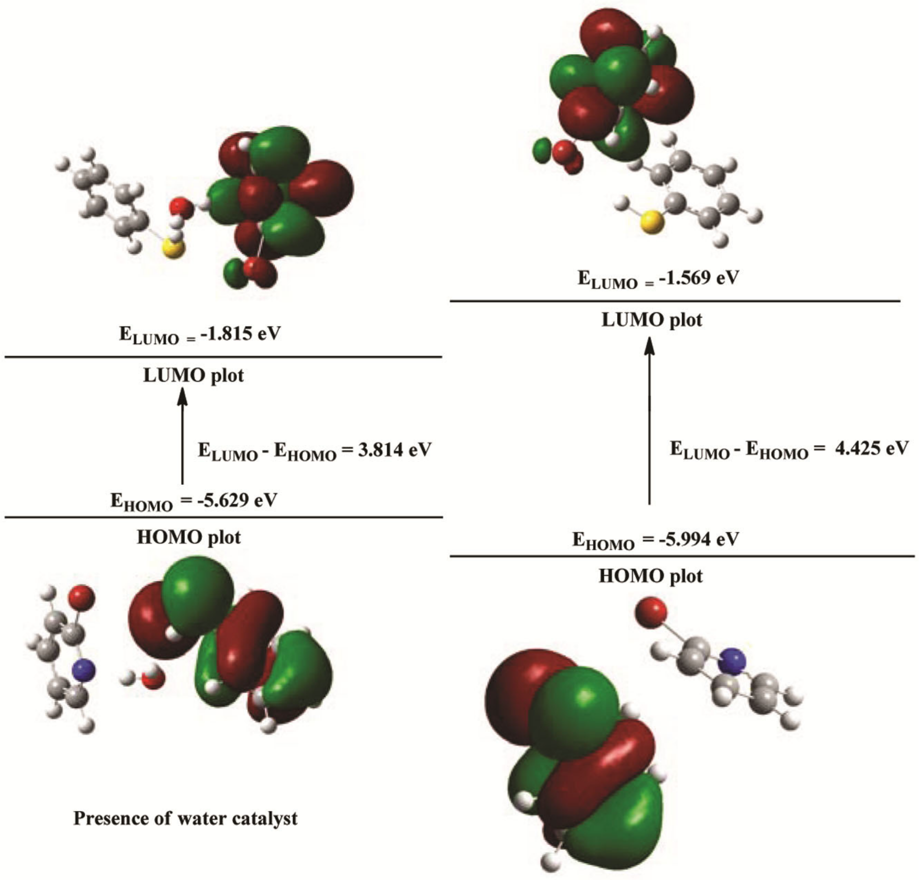


Fig. 7 — The coloured scattered RDG plot and corresponding iso surfaces for transition states

transition states in presence and in absence of water catalyst to understand the role of water to promote the reaction mechanism. The energy gap between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is a key parameter in determining the reactivity and mechanism of chemical reactions[28,29]. Molecules with smaller gaps are generally more reactive because they can more easily donate or accept electrons. A smaller gap means that less activation energy is required which facilitates rate of reaction. Molecules with larger gaps are typically less reactive. The higher energy barrier makes it more difficult for the molecule to participate in electron transfer processes. The FMO analysis of reactants and transition states in presence and absence of water was performed by DFT calculations at B3LYP/6-311++G(d,p) level of theory. The FMO diagrams of reactant molecules in presence and in absence of water catalyst are shown in Fig. 8.

As it can be observed from Fig. 8, due to the presence of water the nucleophilicity of substrates is enhanced, as conformed from increase in highest occupied molecular orbital (HOMO) energy level of substrate with water catalyst (–5.629 eV) by an amount of 0.365 eV as compared to substrate without water catalyst (–5.994 eV). Further there is a decrease in LUMO energy level by amount of 0.246 eV of substrates in absence of water catalyst (–1.569 eV) when compared with substrates with water catalyst (–1.815 eV). In presence of water as catalyst the energy gap between HOMO-LUMO has also been reduced to 0.611 eV, which is due to formation of hydrogen bonding by water molecules with reactants. The FMO analysis of transition states is shown in Fig. 9. In presence of water molecule, the energy of HOMO of transition state (–5.629 eV) increased by amount of 0.365 eV as compared to in the absence of water (–5.994 eV). While energy of LUMO in presence of water (–1.815 eV) decreased by amount of 0.246 eV when compared to LUMO energy in absence of water (–1.569 eV). Thus the presence of water molecules as catalyst lowers the energy gap between HOMO and



Presence of water catalyst

Absence of water catalyst

Fig. 8 — The FMO diagrams of reactant molecules in presence and in absence of water catalyst

LUMO by an amount of 0.141 eV. This reduction in the HOMO-LUMO energy gap results in a lower activation energy which plays a pivotal role in enhancing the reactivity and efficiency through easier transition from reactants to the transition state of the nucleophilic substitution reaction of 2-bromopyridine with thiophenol.

In order to understand the effect of water as catalyst as well as solvent both over reaction mechanism, the reaction between 2-bromopyridine and thiophenol in presence of water catalyst is investigated in polar protic solvent water and polar aprotic solvent DMSO using DFT at B3LYP/6-311++G(d,p) level of theory. Firstly, reaction was investigated in water as solvent using IEPCM method by optimizing structures of reactants, transition states and product with any geometrical constraint. The energy profile diagram for reaction in water is shown in Fig. 10. As it can be observed from energy profile diagram, the energy requirement for reaction in presence of water as solvent as well as catalyst is 39.53 kcal/mol which is 2.04 kcal/mol lower than energy demand for same reaction in gas phase (41.57 kcal/mol). This result indicates that polar water solvent plays an important role in stabilizing structure of transition state. Further, structure of product also gets highly stabilized by an amount of 13.09 kcal/mol in water as solvent as compared to gas phase reaction.

Then, the reaction was further investigated in polar aprotic solvent DMSO by optimizing the structures of reactants, transition states and products without any geometrical constraints using DFT at B3LYP/6-311++G(d,p) level of theory. The results of DFT analysis shows that reaction requires higher energy by an amount of 1.25 kcal/mol presence of DMSO as solvent (40.78 kcal/mol) when compared to water as solvent (39.53 kcal/mol). These results confirm that water plays role of both catalyst as well as solvent in this reaction; moreover these results are also supported by experimental studies[15].

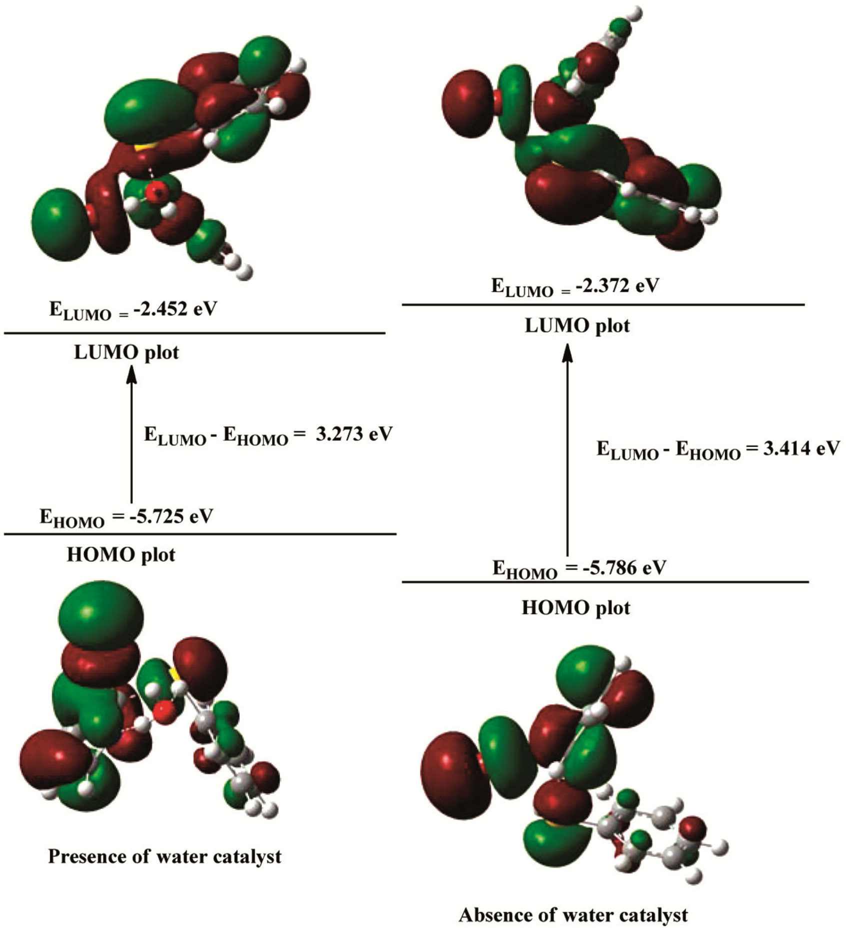


Fig. 9 — The FMO diagrams of transition states in presence and in absence of water catalyst

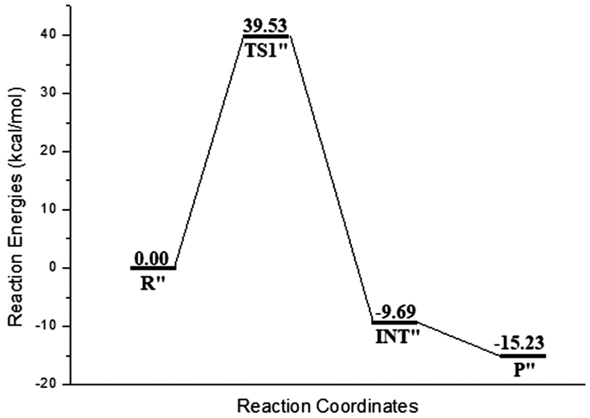


Fig. 10 — The energy profile diagrams for reaction between 2-bromopyridine and thiophenol in presence of water as catalyst in water as solvent using DFT at B3LYP/6-311++G(d,p) level of theory.

Conclusion

In conclusion, we have investigate the role of water as catalyst in aromatic nucleophilic substitution reaction of 2-bromopyridine with thiophenol theoretically using DFT calculations at B3LYP/6-311++G(d,p) level of theory. The results show that water plays an important role as catalyst by forming hydrogen bonding with reactants 2-bromopyridine and thiophenol and also with transition state (TS1) thereby lowering energy of transition state by amount of 5.58 kcal/mol as compared to absence of water as catalyst in gas phase. The role of water as catalyst is further studied by investigating non-covalent interactions (NCI) using AIM and RDG method. The results of AIM analysis shows that water forms hydrogen bonding with nitrogen atom (N6) of 4-bromopyridine in reactants with bond energy of –5.90 kcal/mol and further stabilize the transition state (TS1) by formation of two hydrogen bonds with nitrogen atom (N6) of 4-bromopyridine and hydrogen (H23) of thiophenol with bond strength of 7.24 kcal/mol and 7.95 kcal/mol respectively. These results are further confirmed and visualized by RDG analysis. The FMO analysis of reactants and transition state in presence and absence of water catalyst is also performed, the results shows that presence of water reduces energy gap between HOMO and LUMO in both reactants and in transition states, thus lowering energy requirement for reaction. The dual role water as catalyst and solvent is investigated by studying reaction in polar protic solvent water and polar aprotic solvent DMSO. The energy requirement of reaction was found lower in water as compared to DMSO by an amount of 1.25 kcal/mol, which confirms dual role of water as catalyst and as well as solvent in the reaction. The future aspects of this study's insights on water's catalytic role can guide the selection of catalysts for similar nucleophilic substitutions reactions where hydrogen bonding is crucial, enhancing reaction efficiency and reaction rate. It supports green chemistry by highlighting water's potential as an eco-friendly solvent, encouraging the development of sustainable and efficient reaction protocols.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

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