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Theoretical study of the mechanism of thieno[3,2-*b*]benzofuran bromination

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Abstract: The bromination reaction of thieno[3,2-*b*]benzofuran was studied theoretically. Stationary points on the reaction potential energy profile including intermediates and transition states were successfully located employing hybrid DFT procedure at the B3LYP/6-31G* level of theory. The bromination proceeds in two steps at the C(2) carbon of thiophene ring. Initially, a π -complex forms between bromine molecule and thiophene ring. Further the π -complex with high activation barrier 69.9 kcal/mol transforms to σ -complex intermediate. Finally the σ -complex with 4.6 kcal/mol activation transforms to product 2-bromothieno[3,2-*b*]benzofuran.

Introduction

Electrophilic substitution reaction of benzofused heterocycles is one of the most thoroughly studied reactions in organic chemistry owing to its wide range of applications from medicine to material sciences [1]. Many theories have been extensively developed in this field. However mechanism of the electrophilic bromination of aromatic compounds and benzofused heterocycles to be the subject of active research and some controversy [2, 3]. A problem in theoretical study is the lack of the fully optimized structures of transition states on the potential energy profile of electrophilic substitution with bromine. There are some kinetic and quantum mechanic studies of the reactivity of aromatic and benzofused heterocycles that reports the qualitative prediction of reactive sites of compounds in the electrophilic substitution reactions [4].

Continuing our interest in benzofused thienofurans as materials of great practical value, we embarked on study of bromination mechanism of thieno[3,2-*b*]benzofuran. Recently we reported our findings concerning investigation of Hartree-Fock and Density Functional Theory (DFT) based reactivity descriptors for benzofused isomeric thieno[3,2-*b*]furans toward electrophilic substitution reactions [5]. The results of theoretical calculations were in good agreement with experimental observations and provided explanation of exceptional reactivity of C(2) atom on thiophene ring in molecule of thieno[3,2-*b*]benzofuran. Also we reported that delocalized π -electron surface of molecule consists of stable aromatic system between benzene ring and thiophene heterocycle. This

result suggests the presumable possibility of aromatic electrophilic substitution mechanism scenario for thieno[3,2-*b*]benzofuran. As continuation, we extended our investigation on the detailed understanding of reaction mechanism for bromination reaction of thieno[3,2-*b*]benzofuran. In the present work, we selected this reaction as a model to study mechanism of electrophilic substitution with Br₂ by theoretical calculations [6]. The main aim was to search the possible mechanism of reaction. Furthermore, based on the selected mode we also tried to estimate the reacting species changes, such as charge and bond character in the transformation from π -complex to σ -complex on reaction paths.

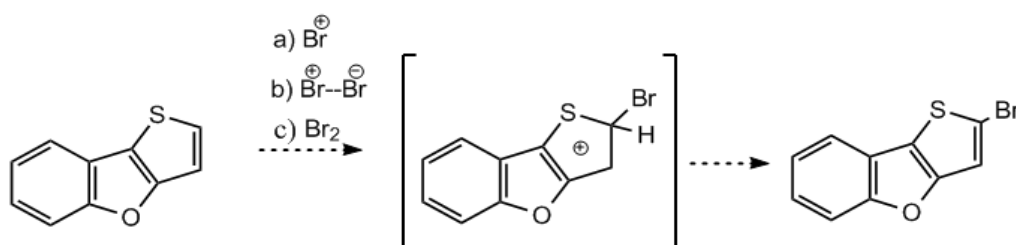
Computational details

It is well known that DFT methods particularly B3LYP [7] have been successfully used in the theoretical understanding of heterocyclic molecules. Recently this method was reported to yield excellent results for prediction of reactivity and electronic structure of complicated partially bonded ionic heterocyclic species [8]. Therefore in this study we chose the B3LYP method for geometry optimizations and frequency calculations. The geometries were optimized at the B3LYP/ 6-31G* level [9]. Transition states were located using linear synchronous transit method [10]. Frequency calculations were performed following each optimization to characterize all stationary points located on the potential energy surface [9]. Intrinsic reaction coordinate was performed to confirm the relationship the transition states with reactants and products at the B3LYP/ 6-31G* level [11].

Results and Discussions

Structure and energy

In the present work we selected electrophilic bromination reaction of thieno[3,2-*b*]benzofuran in dioxane as a model to study the reaction mechanism by theoretical calculations. Electrophilic bromination of this reaction has been reported to undergo exclusive bromination with high regioselectivity of C(2) atom of thiophene ring [6].



Scheme. Bromination reaction of thieno[3,2-*b*]benzofuran

It is known that the structure of attacking species in electrophilic bromination depends on the reaction conditions: when a strong Lewis acid is used with the bromine, the attacking

electrophile may be positive bromonium cation Br^+ . In the presence of moderate catalyst, the attacking electrophile may be a polarized Br_2 molecule [12]. In the absence of catalyst the attacking Br_2 can be polarized by the π -electron rich aromatic ring [13]. In the dioxane dibromide complex, the bromine molecule is slightly polarized, the bond length Br–Br is 2.31 Å, while in the Br_2 molecule the distance between bromine atoms is 2.28 Å [14]. In a study of phenols and phenol ethers bromination with dioxane dibromide it was postulated that the reaction is of third order, i.e. it proceeds by a mechanism not completely understood yet [15]. Therefore we make attempts to clarify the most likely structure of attacking electrophile originated from dioxane dibromide. It can be elucidated through the estimation of electron density transfer, that may be represented by molecular orbital occupancy of the starting electrophilic species (fig. 1). From the figure 1 one can see, that when bromine interacts with dioxane forming dioxane dibromide complex, electron density flows from the lone electron pair of nonbonding occupied orbital of bromine to unoccupied orbitals on dioxane unit, whereas the lowest unoccupied σ^* orbital remains unchanged on isolated bromine and on the dioxane dibromide complex.

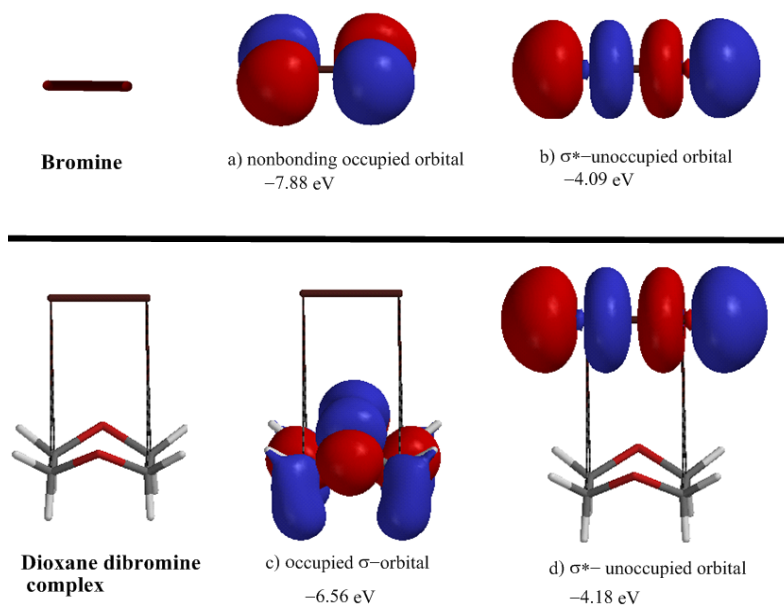


Figure 1. Selected molecular orbitals and their energies for bromine and bromine dioxane complex: a) lone electron pair nonbonding occupied orbital of bromine, b) σ^* - lowest unoccupied orbital of bromine, c) σ -highest occupied orbital of dioxane dibromide complex, d) σ^* -lowest unoccupied orbital of dioxane dibromide complex

It suggests that attacking electrophile derived from dioxane dibromide complex may be neutral bromine molecule with an enhanced electrophilicity power, which is agreement with the earlier findings [14]. Therefore the reaction model with neutral bromine molecule as attacking electrophile seems to be correct.

The calculated geometries of all stationary points along the reaction coordinate are shown in figures 2 and 3. Selected structural parameters are listed in the table 1. Total electronic energies are listed in table 2.

The reaction starts with interaction of Br(1)–Br(2) and thieno[3,2-*b*]benzofuran

under formation of a π -complex (π -R). This process leads to a slight energy lowering. The π -R structure has an oblique structure between Br(1)–Br(2) and thieno[3,2-*b*]benzofuran and the Br(1) atom is facing to C(2) atom of the thiophene ring plane. The reacting C(2) atom is coplanar with the ring plane of thiophene and benzofuran rings.

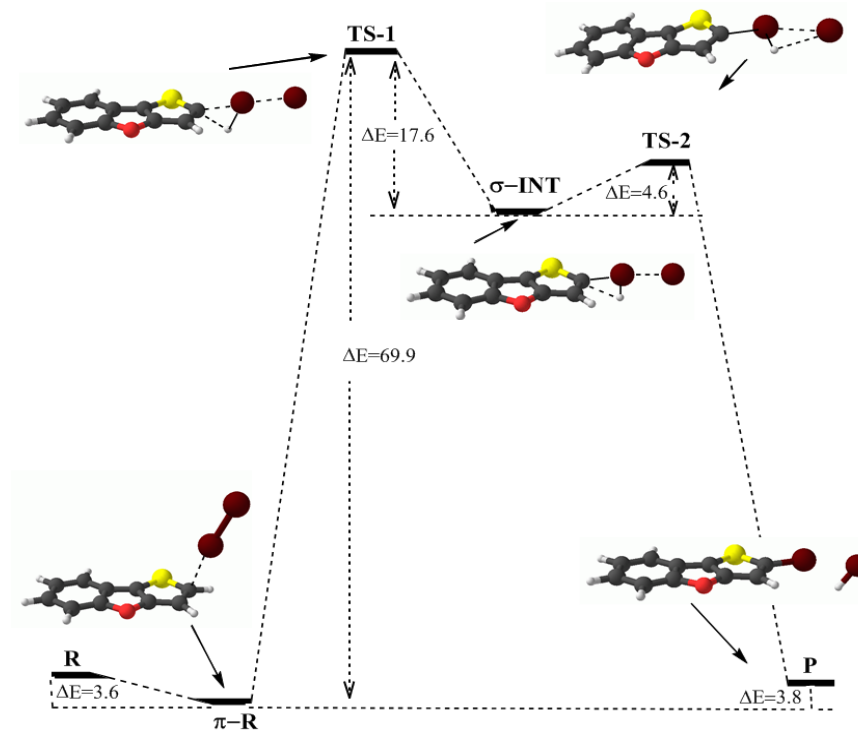


Figure 2. Bromination reaction potential energy profile. Energies in kcal/mol

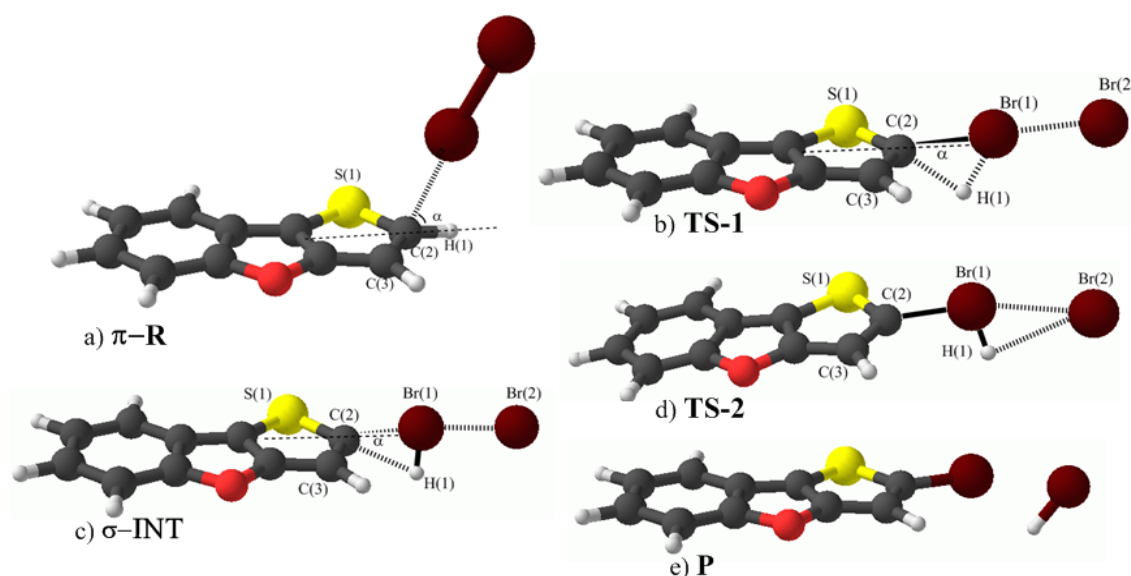


Figure 3. Structures of reaction stationary points presented in figure 2: a) π -complex (π -R),

b) transition state (TS-1), c) σ -complex intermediate (σ -INT), d) transition state (TS-2), e) reaction products (P)

It indicates that sulfur atom in the thiophene ring adopts hybridization sp^2 , leaving a p-orbital and a pair of electrons to conjugate with π -electron system of heterocycles. It acquires the most negative charge on C(2) carbon atom as shown in the table 3. Furthermore, the angle α in π -R is close to 90° (81.30°) and the bond length $R_{\text{Br}(1)\text{-Br}(2)}$ (2.368 Å) is slightly longer than that of the isolated Br(1)–Br(2) molecule (2.324 Å); the bond orders of $R_{\text{Br}(1)\text{-C}(2)}$ and $R_{\text{Br}(1)\text{-C}(3)}$ are 0.1 and 0.05, resp.. Those facts indicate a weak interaction between C(2) and C(3) atoms of thiophene ring and Br(1) of bromine unit and suggest the existence of a weak non-symmetric three-membered π complex π -R with slightly stronger $R_{\text{Br}(1)\text{-C}(2)}$ bond.

As the system moves on the reaction coordinate to transition state TS-1, considerable structural changes occur. First the Br(1)–Br(2) moiety migrates towards the thiophene ring plane with the bromine Br(1) atom heading towards C(2) and the α changes from 81.30° to 7.30° , indicating that the interaction changes from π - to a σ -bonding character. Second, $R_{\text{Br}(1)\text{-C}(2)}$ is shortened from 2.99 to 2.22 Å and the bond order (bond strength) grew up from 0.1 to 0.5 with the synchronous $R_{\text{Br}(1)\text{-C}(3)}$ lengthening up to 3.2 Å until bond disruption. Whereas $R_{\text{Br}(1)\text{-Br}(2)}$ is lengthened from 2.37 to 2.64 Å with bond order weakening from 0.85 to 0.45, indicating that both the partial C(2)–Br(1) bond formation and Br(1)–Br(2) bond breaking happen in a concerted way. Third, $R_{\text{H}(1)\text{-C}(2)}$ is lengthened from 1.08 to 1.82 Å with bond order weakening from 0.91 to 0.26, whereas $R_{\text{H}(1)\text{-Br}(1)}$ is shortened significantly from 3.1 to 1.5 Å with the bond order growing up to 0.71, indicating formation of a polarized C(1)---H(1)---Br(1) hydrogen bond and significant hydrogen atom migration.

Table 1. Particular structural parameters of reaction stationary points

a) bond lengths in Å and α angle in degrees

Geometry	R	π -R	TS-1	σ -INT	TS-2	P
C(2)-H(1)	1.083	1.082	1.817	2.543	2.628	4.280
C(2)-Br(1)	-	2.997	2.223	2.028	2.007	1.800
Br(1)-Br(2)	2.324	2.368	2.640	2.744	2.775	2.900
Br(1)-H(1)	-	3.090	1.500	1.435	1.510	2.690
Br(2)-H(1)	-	5.293	3.662	2.824	2.270	1.438
α	-	81.30	7.30	5.16	3.09	0.10

b) bond order

Geometry	R	π -R	TS-1	σ -INT	TS-2	P
C(2)-H(1)	0.920	0.909	0.256	0.153	0.005	0.000
C(2)-Br(1)	-	0.090	0.515	0.707	0.732	0.958
Br(1)-Br(2)	0.978	0.848	0.450	0.414	0.320	0.059
Br(1)-H(1)	-	0.001	0.705	0.875	0.691	0.000
Br(2)-H(1)	-	0.000	0.040	0.315	0.417	0.937

The transition of the complex π -R to TS-1 requires 69.9 kcal/mol. Over this barrier, the system goes to the σ -intermediate (σ -INT). The energy of σ -INT is 52.3 kcal/mol relative to π -R. The structure of σ -INT is similar to that of TS-1, with the $R_{\text{Br}(1)\text{-C}(2)}$ further shortened and $R_{\text{Br}(1)\text{-Br}(2)}$ further lengthened slightly. The most remarkable change from TS-1 to σ -INT is the complete migration of H(1) to Br(1), with $R_{\text{H}(1)\text{-Br}(1)}$ 1.44 Å and 0.88 bond order.

Table 2. Calculated electronic energy and relative energies for stationary points

Species	E_e (a.u.)	E_r (kcal/mol)
R	-6005.82530	3.6
π -R	-6005.83072	0
TS-1	-6005.74023	69.93
σ -INT	-6005.74076	52.30
TS-2	-6005.71963	56.9
P	-6005.82500	3.8

Starting from σ -INT, the system can be easily activated to the second transition state (TS-2), which leads to the final product. The energy barrier of the second step is only 4.6 kcal/mol. It is evident that the first step along the reaction path from π -R across TS-1 to σ -INT is the rate limiting step.

The migration of H(1) from Br(1) to Br(2) is the dominant structural change in the second step, from σ -INT to TS-2. $R_{\text{H}(1)\text{-Br}(1)}$ is lengthened slightly from 1.44 to 1.51 Å whereas $R_{\text{H}(1)\text{-Br}(2)}$ is shortened from 2.82 to 2.27 Å and strengthened from 0.32 to 0.42. The leaving Br(2) atom in TS-2 is actually hydrogen bonded by H(1) and Br(1)–Br(2) bond (2.78 Å) is remarkably weakened up to 0.32. As H(1) migrates to Br(2) ($R_{\text{H}(1)\text{-Br}(2)}$ 1.44 Å) the bromination completes and the product 2-bromothieno[3,2-*b*]benzofuran is finally loosely associated with HBr.

The demonstrated reaction potential energy profile shows, that during this process a remarkable structural change involves a transfer of H(1) atom from C(2) to Br(1) and finally

to Br(2), accompanying the formation of C(2)–Br(1) bond and breaking the Br(1)–Br(2) bond in bromine molecule. By this route the thieno[3,2-*b*]benzofuran and bromine produce two products, 2-bromothieno[3,2-*b*]benzofuran and HBr. The potential energy profile (fig. 2) is identical to energy profile of aromatic electrophilic substitution with bromine. The high energy barrier of the rate limiting step indicates a lower reactivity of this heterocyclic system, however, solvent effects may play an important role on decreasing the energy barrier of bromination reaction.

Charge transfer

The charge on some selected atoms obtained by natural orbital population analysis (NPA) for all stationary points are summarized in table 3.

Table 3. NPA charges on selected atoms of reacting species

Atom	R	π -R	TS-1	σ -INT	TS-2	P
Br(1)	0.00	-0.031	+0.346	+0.518	+0.516	+0.128
Br(2)	0.00	-0.078	-0.449	-0.609	-0.635	-0.207
C(2)	-0.417	-0.441	-0.451	-0.444	-0.446	-0.351
S(1)	+0.462	+0.493	+0.506	+0.500	+0.508	+0.498
C(3)	-0.309	-0.294	-0.318	-0.304	-0.301	-0.316
H(1)	+0.206	+0.209	+0.266	+0.259	+0.266	+0.207

As the result of first step, the neutral Br(1)–Br(2) unit in π -R approaches to transition state TS-1 and becomes polarized in σ -INT. Simultaneously, the positive charge on the Br(1) atom in bromine unit increases gradually from -0.003 in π -R to +0.35 in TS-1 and to +0.52 in σ -INT, whereas the Br(2) becomes more negative along the same path. The charge separation effect of bromine Br(1)–Br(2) occurs in the rate-limiting step. The TS-1 and σ -INT possess same character similar to a bromoarenium cation. The positive charge is mainly located on the bromine Br(1) atom and sulfur atom of the thiophene ring. This charge separation weakens Br(1)–Br(2) bond and cause positive charge transfer from Br(1) to H(1). The charge separation remains large until system reaches the TS-2. From TS-2 the negative charge of the Br(2) atom reduces, resulting in negative charge flow from Br(2) to Br(1)--H(1) and simultaneous migration of H(1) from Br(1) to Br(2) and decrease of the positive charge in bromine Br(1).

The charge separation effect of Br(1)–Br(2) unit in TS-1, σ -INT, and TS-2 implies that bromination may proceed via an ion pair route.

Conclusion

Bromination of thieno[3,2-*b*]benzofuran proceeds via a mechanism typical for electrophilic aromatic substitution.

The present reaction pathway involves two steps:

first the π -complex is activated to σ -complex intermediate, the barrier of this rate limiting step is about 70 kcal/mol;

second the σ -complex intermediate transforms into the final products 2-bromothieno[3,2-*b*]benzofuran and HBr with the barrier of 3.8 kcal/mol.

Accompanying the C(2)–Br(1) bond formation and Br(1)–Br(2) bond disruption, hydrogen atom migrates from C(2) carbon atom to Br(1) in the first step and from Br(1) to Br(2) in the second course of reaction.

The charge transfer within Br(1)–Br(2) unit is significant, indicating the complicated nature of bonding, which suggest that reaction may undergo via an ionic route.

Acknowledgements

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