



Mechanistic investigation of the addition-cyclization between diacylacetylene and thiourea: A DFT study

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In this project, the mechanism of the addition-cyclization reaction between thiourea and diacylacetylene in the gas phase and the presence of acetone was theoretically investigated using B3LYP/6-311++G(d,p) level of theory. The geometry of all the structures participated during the reaction path, the rate-determining step, potential competitive routes during the reaction coordinate was evaluated. Also, the solvent effect, the effect of the substituent group on the potential energy surfaces were investigated. For a better understanding of molecular interaction, the natural bond orbital method (NBO) and AIM analysis were applied. Results indicated that the orientation of phenyl groups has significant changes in the potential energy surfaces that are important both kinetically and thermodynamically.

Keywords: Thiourea, diacylacetylene, theoretical study, reaction mechanism.

Introduction

Organosulfurs are considered as important compounds in organic chemistry, some of which include: thions, thioesters, thioethers, thiazoles¹⁻³. Due to its special structure and its heterocycles, thiazoles are widely being used such as medical, antibacterial, biological, and color uses⁴⁻⁷. To synthesis these compounds, many different methods have been presented by researchers so far⁸⁻¹². They indicated that the carbon available between sulfur and nitrogen is highly active in the five-member ring of thiazol. The compounds with thiazol structure are significant heterocyclic compounds in bio-organic chemistry¹³⁻¹⁵. These compounds possess many medical uses¹⁶⁻¹⁸. Therefore, the study of the reaction mechanism and the potential reaction direction are significant.

The reaction being studied include a 1:1 cyclization reaction between thiourea **1** and diacy acetylene **2** to produce 2-amino, 4-hydroxyl, 4-phenylthiazol, 5-(4*H*)-ylidene, 1-phenylethanone **P**¹⁹.

The reaction mechanism probably includes thiourea nucleophilic attach to diacylacetylene which will lead to the formation of different intermediate and finally will cause cycloaddition and stable products (Fig. 1). In this study, for in-

vestigating the potential energy levels of the structures participating in the reaction path, determine the rate-determining step for the reaction and also the effect of substituted groups on the potential energy level of the reaction were evaluated by using a quantum calculation.

Computational details

All geometrical structures were optimized at B3LYP/6-311++G(d,p) level of theory using Gaussian 09 and Gamess suite software package^{20,21}. The corresponding frequencies of the structures were estimated at the same level of theory to check the stationary points without imaginary frequencies and the transition states with only one imaginary frequency. Also, the intrinsic reaction coordinate (IRC) approach^{22,23} was performed to ensure that the given transition state connects with the corresponding reactants and products.

Calculations have been carried out both in the gas phase and considering solvent effects (acetone and dichloromethane) with the PCM model²⁴⁻²⁶. Natural bond orbital (NBO) analysis was carried out at B3LYP/6-311++G(d,p) level of theory using version 3.1 of the NBO package²⁷. Besides, the topological electron charge density was analyzed by the atoms in molecules (AIM) method, using AIM2000 program

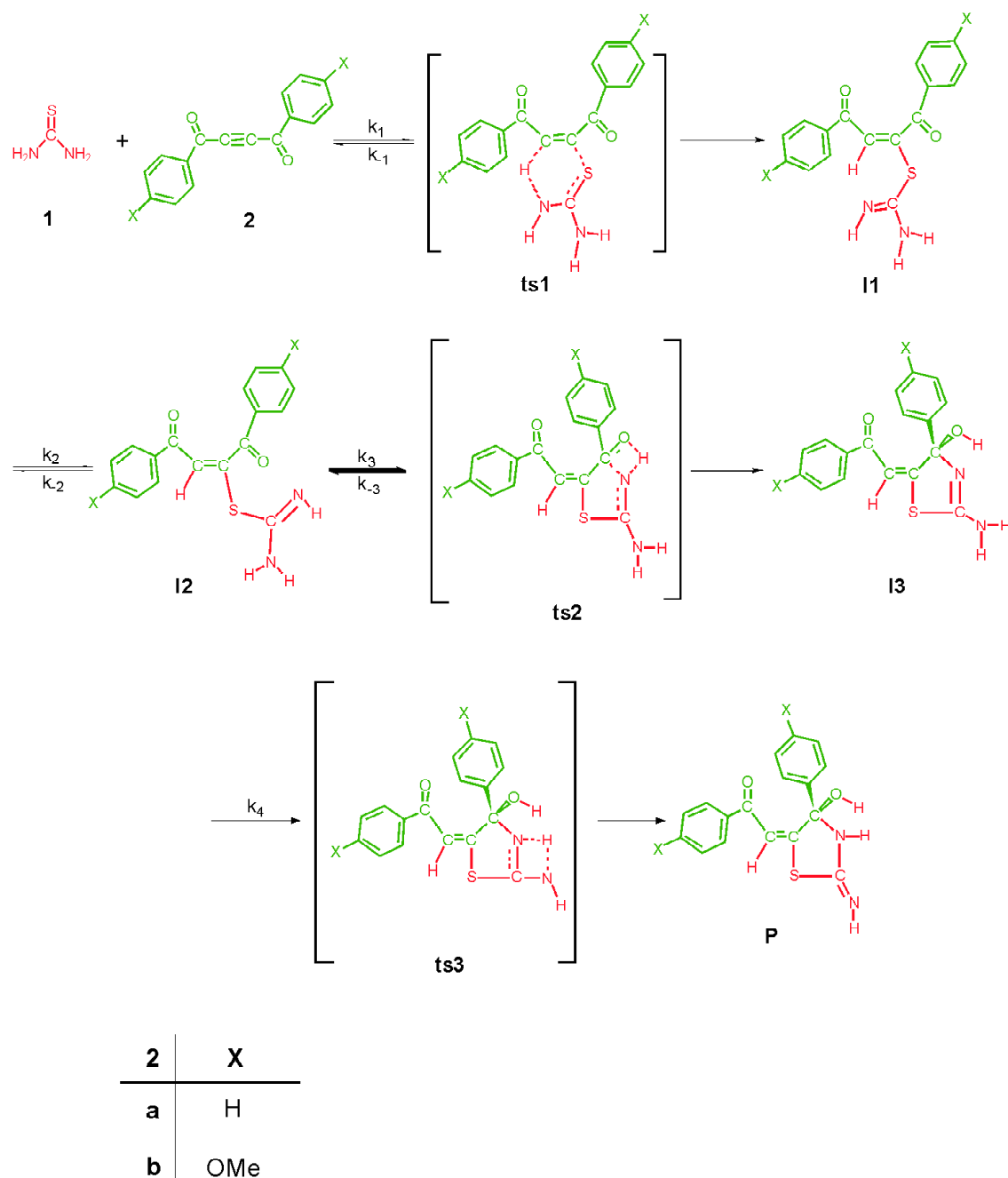


Fig. 1. The reaction between thiourea **1** and diacylacetylene **2**.

on the obtained wave functions at B3LYP/6-311++G(d,p) level²⁸.

Results and discussion

The energies and potential energy surfaces:

Optimized structures of all components involved in the

reaction mechanism are reported in Fig. 2. Atom C14 of dibenzoylacetylene (1,4-diphenyl-2-butyne-1,4-dione) **2-a** can be nucleophilically attacked by S29 atom of thiourea **1** by passing from transition state **TS1-a** will cause the intermediate **I1-a** formation by the energy barrier of 87.29 kJ/mol. The intermediate **I1-a** by rotation around the S29-C15 bond will

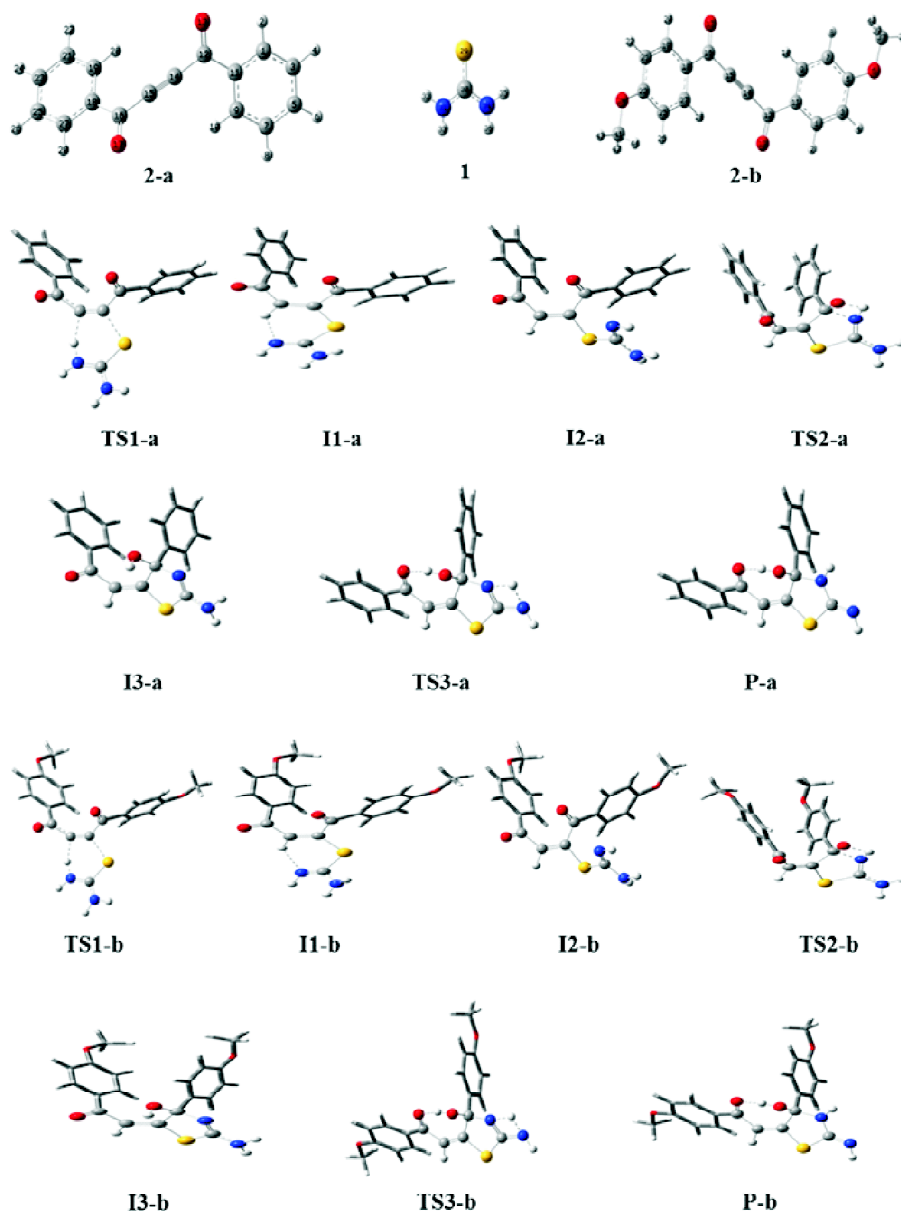


Fig. 2. Optimized structures of all components involved in the reaction between **1** and **2** at B3LYP/6-311++G(d,p) level of theory.

change to intermediate **I2-a**. Then, by the nucleophilic attack of N31 to C12 and the simultaneous transfer of H33 to O13 in the transition state **TS2-a**, the intermediate **I3-a**, with a five-membered ring was formed. The activation energy required for this of the reaction is $151.79 \text{ kJ mol}^{-1}$. In the final step of the reaction mechanism, the final product **P-a** will be formed with the transfer of H36 to N31 by passing from transition state **TS3-a** with an energy barrier of 174.44 kJ/mol . The potential energy diagram related to the structures par-

ticipating in the reaction mechanism is presented in Fig. 3. The first step of the reaction mechanism in the presence of reactant **2-a** is the easiest step and the third step is the hardest, kinetically. The amount of ΔH and ΔG of the reaction suggests that however, the reaction is noticeably exothermic ($\Delta H = -70.2 \text{ kJ mol}^{-1}$), it doesn't tend to be spontaneous ($\Delta G = 0.55 \text{ kJ mol}^{-1}$) and shows that the reaction is entropy controlled.

To study the substituted effect on the potential energy

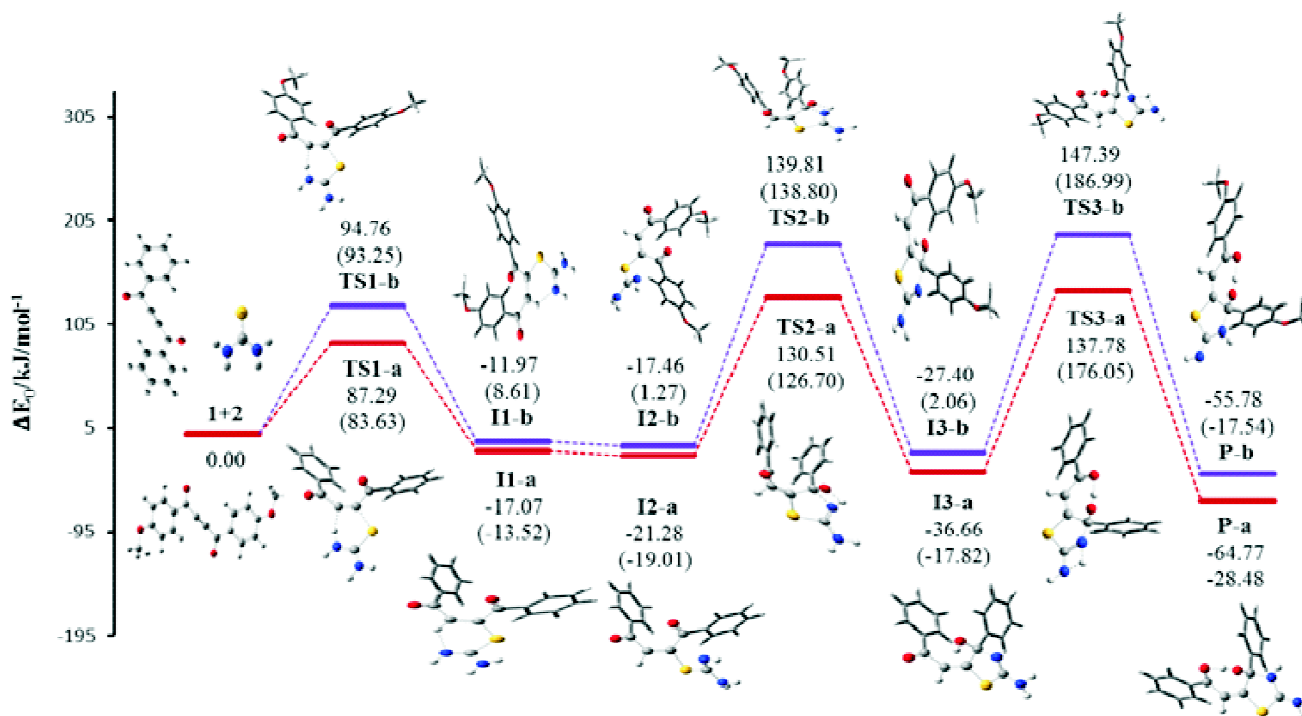


Fig. 3. The potential energy profile of the reaction in the presence of **2-a** and **2-b** (data in acetone are in parentheses).

levels, the reaction was studied in the presence of reactant **2-b** (1,4-bis(4-methoxyphenyl)but-2-yne-1,4-dione). Concerning the results, the potential energy levels of all the structures participating in the reaction mechanism increased. It was observed that, except energy barriers of the third steps of the reaction mechanism which almost stays unchangeable, the first and second energy barriers of the mechanism were increased. The value of the energy barrier in the first, second, and third steps increases to 94.76, 157.27, and 174.79 kJ mol⁻¹. The values of ΔH and ΔG in the presence of **2-b** suggest that the reaction is still exothermic and non-spontaneous. The results show that in this kinetic pathway, the first and third steps of the reaction were also the easiest and the most difficult ones, respectively. Perhaps the question arises as to what is the thermodynamic reason for the intramolecular proton transfer in the final step? The results show that although the energy barrier of this step of the reaction in the presence of **2-a** increased by 22.65 kJ mol⁻¹ compared to the second step, but a 28.11 kJ mol⁻¹ stability was achieved compared to the intermediate **I3-a**. The results in the presence of **2-b** also show that for a 17.52 kJ mol⁻¹ kinetic instability, a 28.38 kJ mol⁻¹ thermodynamic

stability was obtained in the third step of the reaction mechanism.

To investigate the solvent effect on the potential energy levels, all structures in two kinetic pathways **a** and **b** have been optimized in acetone. The results indicate that the energy barriers of the first and the second steps from the path **a** were decreased compared to the gas phase, but the energy barrier of the third step was increased. In the solvent phase, the third step of the reaction in two kinetic pathways **a** and **b** was kinetically and thermodynamically less favorable than the gaseous phase. The energy barrier of the third step of the reaction in the solvent phase in two paths **a** and **b** was increased by 19.43 and 10.14 kJ mol⁻¹, respectively, compared to the gas phase. Also, the thermodynamic stability of the product in the solvent phase in the two pathways **a** and **b** was reduced by 36.29 and 38.24 kJ mol⁻¹, respectively, compared to the gas phase. Despite the kinetic and thermodynamic instability created in the solvent for the proton transfer process in the third step, this process is still thermodynamically desirable, because the two kinetic pathways still have thermodynamic stability of 28.48 and 17.54 kJ mol⁻¹, respectively.

The analysis of natural bond orbital (NBO) and atoms in molecule (AIM):

To achieve more precise information about the nature of hydrogen bonds, the values of electron density $\rho(r)$, Laplacian of the electron density $\nabla^2\rho(r)$, total electron density $H(r)$, and electronic kinetic energy density $G(r)$ at critical points (BCPs) in the gas phase at the theoretical level of B3LYP/6-311++G(d,p) by using the theory of atoms in molecules (AIM) have been calculated and are reported in Table 1. Charge analysis of the participating atoms in the reaction mechanism in the gas phase is reported in Table 2. The **TS1-a** is the result of a nucleophilic attack of **1** to **2-a** in a certain direction. By S29 nucleophilic attack to C14, simultaneously H32 proton transfers to C15. In this structure, a charge transfer was happening from the structures **1** to **2-a** by 0.575 a.u. This value of charge transfer in the structure **TS1-b** was reduced to 0.534 a.u. Results show that the atomic charge of C14 and C15 atoms in the structure **2-b** was increased compared to **2-a**. This increase of the charge can be the result of

the electron-donating of the substituted groups of O-Me in the structure **2-b**. Therefore, increment of the electronic charges of C14 and C15 atoms causes a decreasing value of charge transfer in **TS1-b** than **TS1-a** structure. By S29 nucleophilic attack to C14, the C14 atomic charge considerably increased and the S29 atomic charge considerably decreased. As was expected, there was a significant accumulation of the electronic charge on C15 and its value in the structure **TS1-b** is more than **TS1-a**. By more accumulation of the electronic charge on C15 in the structure **TS1-b**, it is expected to be a stronger hydrogen bond interaction between C15...H32 compare to **TS1-a**. From Table 1, the electron density ($\rho(r)$) of C15...H32 interaction in **TS1-b** and **TS1-a** are respectively equal to 0.060 a.u. and 0.065 a.u., which show a stronger hydrogen bond in **TS1-b**. Studies suggest that the density of C14-S29 interaction in **TS1-b** (0.1022 a.u.) is also more than **TS1-a** (0.1020 a.u.).

The study of the S29 electron charge indicates that this atom in **TS1-b** has less tendency for charge transfer, which

Table 1

Structure	Bond	$\rho(r)$	$\nabla^2\rho(r)$	$G(r)$	$V(r)$	$H(r)$
R1	C30-S29	0.214	-0.78794	0.23408	-0.48787	-0.25378
	N31-H32	0.34076	-1.70293	0.5125	-0.52823	-0.01573
R2-a	C14-C15	0.40402	-1.21151	0.26947	-0.84181	-0.57235
R2-b	C14-C15	0.40398	-1.20829	0.27054	-0.84316	-0.57262
TS1-a	C14-C15	0.36069	-1.04233	0.18917	-0.63893	-0.44975
	C15-H32	0.60044	3.91706	0.29173	-0.48554	-0.19381
	C14-S29	0.10204	-0.85079	0.33839	-0.69806	-0.35966
	N31-H32	0.27658	-1.22131	0.55114	-0.41556	0.13559
I1-a	C14-C15	0.33272	-0.94306	0.13881	-0.51339	-0.37458
	C15-H32	0.28367	-0.98785	0.34515	-0.31599	0.02916
	C14-S29	0.18127	-2.74595	0.51016	-0.17068	0.33948
	N31-H32	0.20179	0.68685	0.14612	-0.12053	0.02559
I2-a	C14-S29	0.18797	-3.07118	0.52714	-0.18221	0.34493
TS2-a	C12-O13	0.31827	-0.88585	0.22218	-0.66583	-0.44365
	O13-H33	0.44387	-2.64181	0.68565	-0.66182	0.02382
	N31-H33	0.19972	-0.52894	0.63547	-0.25933	0.37614
	C12-N31	0.22536	-0.45241	0.96516	-0.30613	0.65902
I3-a	O13-H33	0.36356	-2.50677	0.71378	-0.76945	-0.05567
	C30-S29	0.18392	-2.81992	0.54052	-0.1786	0.36192
	C30-N31	0.3894	-1.09533	0.3261	-0.92603	-0.59993
TS3-a	N31-H36	0.1299	-0.89575	0.59322	-0.14104	0.45218
	N34-H36	0.11968	-0.46952	0.57431	-0.1266	0.44771
	C30-S29	0.19675	-3.5084	0.57884	0.20348	0.78232

Table-1 (contd.)

P-a	C30-S29	0.18167	-2.73968	0.50426	-0.16934	0.33492
	O17-H33	0.36488	1.19605	0.30761	-0.3162	-0.00859
	O13-H33	0.34457	-2.4029	0.68517	-0.73776	-0.05259
	N31-C12	0.27396	-0.77072	0.11957	-0.43182	-0.31225
	N31-H32	0.34076	-1.7016	0.51306	-0.52801	-0.01496
TS1-b	C14-C15	0.36039	-1.04154	0.18921	-0.6388	-0.44959
	C15-H32	0.65507	2.91165	0.30703	-0.54128	-0.23424
	C14-S29	0.10221	-0.87608	0.33926	-0.70043	-0.36116
	N31-H32	0.2678	-1.12727	0.5659	-0.395	0.17091
I1-b	C14-C15	0.33282	-0.94218	0.13974	-0.51503	-0.37529
	C15-H32	0.28366	-0.98661	0.34847	-0.31635	0.03212
	C14-S29	0.18095	-2.72558	0.5101	-0.17016	0.33994
	N31-H32	0.19767	0.67276	0.14278	-0.11738	0.02541
I2-b	C14-S29	0.18713	-3.02741	0.52376	-0.18044	0.34332
TS2-b	C12-O13	0.31806	-0.88555	0.22166	-0.6647	-0.44304
	O13-H33	0.98864	1.37918	0.73147	-0.11181	0.61965
	N31-H33	0.20074	-0.53617	0.63608	-0.26126	0.37482
	C12-N31	0.22374	-0.44338	0.95904	-0.30265	0.65638
I3-b	O13-H33	0.36369	-2.50642	0.71462	-0.76953	-0.0549
	C30-S29	0.18389	-2.81738	0.54073	-0.17858	0.36215
	C30-N31	0.38986	-1.09283	0.32832	-0.92985	-0.60153
	Ring1	0.35795	2.14595	0.48242	-0.42835	0.05407
TS3-b	N31-H36	0.12996	-0.88965	0.59454	-0.14115	0.45339
	N34-H36	0.11989	-0.47279	0.57519	-0.12686	0.44833
	C30-S29	0.19682	-3.51091	0.57997	-0.20377	0.37621
P-b	C30-S29	0.18193	-2.75164	0.50563	-0.16992	0.33571
	O17-H33	0.37885	1.22681	0.31978	-0.33286	-0.01308
	O13-H33	0.34346	-2.3921	0.688	-0.73563	-0.04762
	N31-C12	0.27309	-0.76627	0.11923	-0.43003	-0.3108
	C12-O13	0.2736	-0.68086	0.18134	-0.5329	-0.35156

can be the result of a more electronic charge of atom C14 (-0.190 a.u.) in **TS1-b** than **TS1-a** (-0.178 a.u.). Also, it can be the result of the steric effect of O-Me substituted groups in **TS1-b** structure. More precise studies show that a part of this electronic charge can be the result of an electronic charge of atom H33, because the electronic charge of H33 in **TS2-a** decreased compare to **I2-a** structure. It can be the result of the more electron affinity of O13 atom than N31. Examination of the electron density of new interactions created in structures **TS1-a** and **TS1-b** shows that the electron density of C30-S29...C14 interaction in **Ts1-a** (0.102) is less than **Ts1-b** (0.0103) and also the electron density of N31-H32...C15 interaction in **Ts1-a** (0.060) is less than the **Ts1-**

b (0.065). Also, the study of the electron density of the ring in these two structures shows that the electron density of the ring critical point in the structure of **Ts1-b** is higher than in **Ts1-a**. Despite stronger interactions in **Ts1-b**, this structure has a higher potential energy level than **Ts1-a**. Interestingly, the potential energy level of all structures in the kinetic path **b** is higher than the kinetic path **a** (Fig. 3). The steric factor of substituted methyl groups in all structures involved in path **b** seems to play a more prominent role than their electron donor.

Calculation of the reaction rate constant:

The outcome of a quantum calculation shows that the

Table 2. The NBO analysis includes the natural charge of different atoms in the gas phase

1		2-a		TS1-a		I1-a		I2-a		TS2-a	
atom	charge	atom	charge	atom	charge	atom	charge	atom	charge	atom	charge
S29	-0.242	C12	0.471	C12	0.505	C12	0.529	C12	0.543	C12	0.428
C30	0.257	O13	-0.511	C14	-0.178	C14	-0.225	C14	-0.229	O13	-0.822
N3	-0.793	C14	-0.021	C15	-0.28	C15	-0.257	C15	-0.199	C14	-0.122
H32	0.407	C15	-0.021	S29	0.133	S29	0.262	S29	0.254	S29	0.301
H33	0.378	C16	0.471	C30	0.335	C30	0.318	C30	0.313	C30	0.348
N34	-0.793	O17	-0.511	N31	-0.747	N31	-0.716	N31	-0.709	N31	-0.65
H35	0.407			H32	0.427	H32	0.267	H32	0.23	H32	0.223
H36	0.378			N34	-0.765	N34	-0.816	N34	-0.817	H33	0.473
				H35	0.413	H35	0.398	H35	0.39	N34	-0.757
				CT	0.575	CT	0.436	CT	0.383	CT	0.75
I3-a		TS3-a		P-a		2-b		TS1-b		I1-b	
C12	0.399	C12	0.387	C12	0.386	C 12	0.463	C12	0.507	C12	0.525
O13	-0.722	O13	-0.741	O13	-0.749	O 13	-0.527	C14	-0.19	C14	-0.223
C14	-0.154	C14	-0.27	C14	-0.29	C 14	-0.029	C15	-0.291	C15	-0.261
S29	0.244	S29	0.32	S29	0.282	C 15	-0.026	S29	-0.171	S29	0.259
C30	0.321	C30	0.305	C30	0.331	C 16	0.466	C30	0.985	C30	0.317
N31	-0.568	N31	-0.657	N31	-0.649			N31	-0.809	N31	-0.716
H32	0.226	H32	0.037	H32	0.033			H32	0.433	H32	0.265
H33	0.475	H33	0.492	H33	0.496			N34	-1.069	N34	-0.816
N34	-0.788	N34	-0.828	N34	-0.701			H35	0.403	H35	0.397
CT	0.704	CT	0.524	CT	0.556			CT	0.534	CT	0.426
I2-b		TS2-b		I3-b		TS3-b		P-b			
C12	0.538	C12	0.43	C12	0.401	C12	0.388	C12	0.386		
C14	-0.229	C14	-0.128	C14	-0.159	O13	-0.743	O13	-0.751		
C15	-0.198	C15	-0.272	C15	-0.28	C14	-0.265	C14	-0.291		
S29	0.249	S29	0.296	S29	0.239	S29	0.313	S29	0.274		
C30	0.311	C30	0.347	C30	0.319	C30	0.303	C30	0.33		
N31	-0.707	N31	-0.652	N31	-0.567	N31	-0.656	N31	-0.649		
H32	0.228	H32	0.222	H32	0.225	H32	0.081	H32	0.067		
N34	-0.819	N34	-0.759	N34	-0.789	H33	0.493	H33	0.496		
H35	0.39	H35	0.403	H35	0.391	N34	-0.832	N34	-0.705		
CT	0.370	CT	0.736	CT	0.6925	CT	0.554	CT	0.575		

energy barrier of the fourth step is the highest in the pathways **a** and **b**, both in the gas phase and in the solvent. This implies that the third step of the reaction is the rate-determining step.

The rate equation of the reaction based on the final product according to Fig. 1 is equal to:

$$\text{Rate} = k_4[\mathbf{I3}] \quad (1)$$

The equilibrium concentration of intermediates **I1**, **I2**, and **I3** can be obtained by using the rate-determining approxima-

tion according to the following equations:

$$K_1 = \frac{k_1}{k_{-1}} = \frac{[\mathbf{I1}]}{[\mathbf{1}][\mathbf{2}]} \rightarrow [\mathbf{I1}] = K_1 [\mathbf{1}][\mathbf{2}] \quad (2)$$

$$K_2 = \frac{k_2}{k_{-2}} = \frac{[\mathbf{I3}]}{[\mathbf{I2}]} \rightarrow [\mathbf{I3}] = K_2 [\mathbf{I2}] \quad (3)$$

Finally, by using eqs. (2) and (3) the final rate equation of the reaction will be obtained as:

Table 3. Rate constant and equilibrium constant values for reaction steps

Path	k_1	k_{-1}	k_2	k_{-2}	K_1	K_2	k_3	k_{ove}
a	2.38E-07	2.42E-07	2.37E-07	2.36E-07	9.84E-01	1.004	2.35E-07	2.32E-07
b	2.38E-07	2.42E-07	2.36E-07	2.36E-07	9.83E-01	1.002	2.33E-07	2.29E-07

$$\text{Rate} = k_{\text{ove}} [\mathbf{1}][\mathbf{2}], k_{\text{ove}} = K_1 K_2 k_3 \quad (4)$$

The final rate equation shows that the reaction is second order with depending on the concentration of two reactants **1** and **2**. The rate constants (k) were calculated within the transition state theory (TST) according to the Eyring equations^{29–31}.

$$k(T) = \frac{k_B T}{h C^\circ} e^{-\Delta G^\ddagger / RT}$$

where k_B is the Boltzmann constant, T the absolute temperature and h the Planck constant. ΔG^\ddagger is the activation free energy for each step. The standard concentration ($C^\circ = 1 \text{ mol/dm}^3$) was considered. The value of the total rate constant of the reaction is reported in Table 3.

Conclusions

The mechanism of the addition-cyclization reaction between thiourea **1** and diacylacetylene **2** both in the gas phase and in the presence of acetone was investigated theoretically. The results are summarized as below:

(i) The final step of the reaction mechanism was recognized as the rate-determining step.

(ii) The values of ΔH and ΔG suggest that the reaction in both paths of the reaction are exothermic and non-spontaneous.

(iii) The results obtained from the calculation of the reaction rate show that in addition to the thermodynamic stability of the kinetic path **a**, this path also has kinetic stability relative to path **b**.

(iv) In the solution phase, the proton transfer in the third step of the path of the reaction is more difficult than the gas phase. This step of the reaction in the solution phase has less thermodynamically and kinetically preference than the gas phase.

(v) The steric factor of substituted methyl groups in all structures involved in path **b** seems to play a more prominent role than their electron-donating effect.

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