The Biginelli reaction in different solvents and in presence of bismuth nitrate: Thermodynamical investigation into the mechanism by means of DFT calculation and experimental results

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Abstract: The Biginelli reaction has been studied by means of theoretical computations and experimental approaches to determine its mechanism. Experimentally, different starting conditions were considered for a better comprehension of the mechanism. In the computation section, we investigated different approaches using B3LYP/6-311G++(d,p) basis sets in gas phase and IEFPCM model to simulate the effect of solvent (acetonitrile, dichloromethane, ethanol, methanol, THF, toluene and water). For each solvent two temperatures were studied computationally: 298K and under solvent evaporation temperature (reflux conditions). Our computations showed that the reaction starts with the condensation of urea and aldehyde which provides anacylimine intermediate. This last reaction reacts with 1,3-dicarbonyl compound to give, after cyclization and dehydration, the Biginelli product. This step is followed by dehydration and cyclization to release the Biginelli product. The role of $Bi(NO_3)_3$ into the mechanism process has also been taken in consideration during our study.

Keywords: Biginelli reaction; mechanism; B3LYP;$Bi(NO_3)_3$.

INTRODUCTION

Multicomponent reactions (MCRs) [1-4] are of great importance in organic synthesis and medicinal chemistry [5-9]. These reactions offer one-pot combination of three or more reactants allowing in a single step direct access to complex molecules [10-13]. One of the most cited MCRs is the Biginelli reaction, reported for the first time in 1893 by the Italian Chemist Pietro Biginelli [14]. This reaction leads to the formation of 3,4-dihydropyrimidin-2 (1H)-one in one-pot condensation of benzaldehyde, ethylacetoacetate and urea under acid catalysis [14]. Then, the Biginelli reaction has been extended to include variations in all of its components allowing access to a large number of dihydropyrimidinone derivatives [3,15-19]. Dihydropyrimidinones have been becoming very interesting due to their pharmacological and biological properties [5,8,20-22]. Because to their medicinal properties, the synthesis of the dihydropyrimidinones has attracted the attention of researchers to establish efficient and rapid procedures for their synthesis. This has led to the development of several methodologies by the three component Biginelli reaction [12,18,23-25]. However, since its discovery, several reaction pathways has been reported for the Biginelli reaction. The proposed pathway by Cepanac et al. [17] includes the formation of a C=N bond from aldehyde and urea, followed by addition of β-ketoester and cyclodehydration yielding the corresponding dihydropyrimidinone. The same pathway has been reported previously by Folkers and Johnson [26], Sweet and Fisskis [27] and Kappe [28]. Recently, Slimi et al. [29] reported the same pathway for Biginelli reaction catalyzed by bismuth nitrate in acetonitrile.

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We wish to report, here, a mechanistic study of the three-component Biginelli reaction of acetaldehyde, pentan-2,4-dione and urea catalyzed by bismuth nitrate in different solvents (acetonitrile, dichloro-methane, ethanol, methanol, THF, toluene and water). Density functional theory calculations were used to verify the proposed pathway for the Biginelli reaction. We scoop to carry out three usual Biginelli pathways and their intermediates, studying thermodynamical constants at different temperatures as well as the spectroscopic properties. Hence, we intend to determine which pathway or pathways are probably involved at different temperatures.

EXPERIMENTAL

All compounds were characterized by IR, ^{1}H NMR spectra and ^{13}C NMR spectra. The IR spectra were recorded in KBr with a JASCO FT-IR-420 spectrometer, with a precision of ±2 cm^{-1} in the range 400-4000 cm^{-1}. The ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were obtained on a Bruker AC300 spectrometer using DMSO-d_6 as solvent and TMS as an internal standard, chemical shift are given in ppm. Melting points were taken on a Reichert-Heizbank apparatus.

1. Procedure

Acetonitrile (20 mL) and $Bi(NO_3)_3$ (0.4 mmol) are introduced into a round-bottomed flask equipped with a cooling device. The acetaldehyde (12 mmol), urea (12 mmol), and pentane-2,4-dione (8 mmol) are added and the solution is permitted to react for 2.5 h with magnetic stirring at room temperature. The mixture is then washed with water and filtered. The resulting product is recrystallized in ethanol.

5-Acetyl-4,6-dimethyl-3,4-dihydropyrimidin-2 (1H)–one: ^{1}H-NMR (300 MHz, DMSO-d_6) δ_H:1.23 (d, *J*= 6.3Hz, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 4.20 (q, *J*= 6.3Hz, 1H), 5.44 (b, 1H), 5.69 (b, 1H). ^{13}C-NMR (75MHz, DMSO-d_6)δ_C: 18.78, 21.95, 23.07, 46.31, 111.56, 146.97, 158.10, 194.08.

The considered temperatures are 298 K, as the standard temperature; and some reflux tempera-tures of usual solvents where the reaction takes place, such as, dichloromethane (313 K), methanol (338 K), THF (339 K), ethanol (351 K), acetone-trile (355 K), water (373 K) and toluene (384 K).

2. Computational details

The electronic calculations were done using the GAUSSIAN package [30]. The reaction was studied at 298 K in the gas phase and under IEFPCM [31] simulation at 298 K and solvent's boiling temperature.

3. Geometry optimizations

We searched for stationary points determining equilibrium geometries and a set of spectroscopic parameters (rotational constant, harmonic wave numbers) using the B3LYP/6-311G++(d,p) [32] as well as implemented in the Gaussian code.

IEFPCM calculations were carried out at 298K and the ebullition temperature of each solvent. Geometry optimizations and harmonic frequencies calculations were done at the C1 point group.

Calculations involving Bismuth were carried out using CAM-B3LYP [33], we used LanL2DZ basis sets also as implemented in the Gaussian code [34-37].

3. RESULTS AND DISCUSSION

3.1. Experimental section

We have studied the Biginelli one pot condensation of acetaldehyde with pentane-2,4-dione and urea in acetonitrile using bismuth nitrate as catalyst at room temperature (Figure 1).

The reaction mechanism is most likely to unfold in three possible outcomes (Figure 2):

- Pathway 1: The first step is a condensation between the aldehyde and urea to give an acylimine-type intermediate. This last one reacts with the dicarbonyl derivative to give, after cyclization and dehydration, the final dihydropyrimidinone.
- Pathway 2: The reaction starts with the condensation between urea and dicarbonyl derivative to give theintermediate, which by further condensation with the aldehyde provides the dihydropyrimidinone.
- Pathway 3: The first step of the reaction is a Knoevenagel condensation between the aldehyde and the 1,3-dicarbonyl compound. Knoevenagel product obtained, reacts with urea to yield the final dihydropyrimidinone.

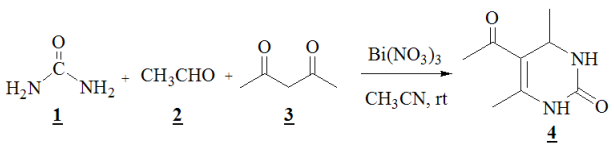


Figure 1. Biginelli reaction of acetaldehyde, pentan-2,4-dione and urea.

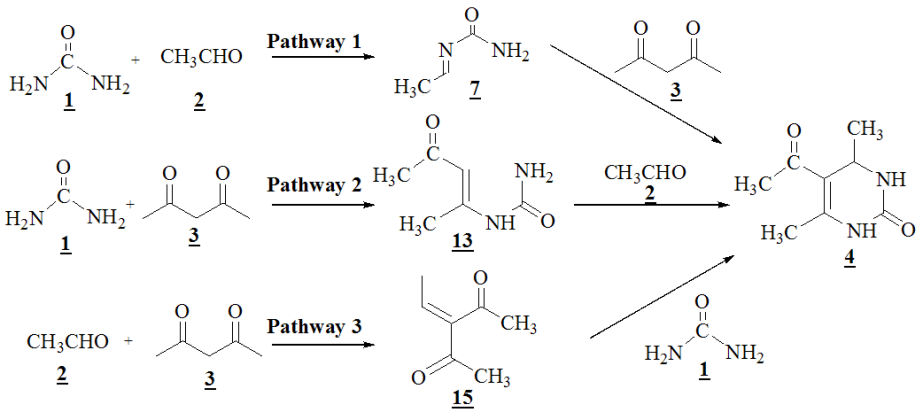


Figure 2. Possible pathways of Biginelli reaction.

In order to determine the most likely mechanism for our case, we performed in the same experimental conditions the reaction involving the following reactants:

- the reaction between acetaldehyde and urea;
- the reaction between acetaldehyde and pentane-2,4-dione;
- the reaction between urea and pentane-2,4-dione.

The monitoring of these three reactions shows that only the condensation between the aldehyde and urea provides a product that can be isolated and identified. This interpretation confirms that the most likely mechanism for the Biginelli reaction is that which corresponds to the first proposal. These results are in good agreement with those found by Hu et al. [38]. Thus, the activation of the Biginelli reaction by bismuth nitrate in acetonitrile starts with the condensation of urea and aldehyde, which is an acylimine type condensation. This last one reacts with the 1,3-dicarbonyl compound to give, after cyclization and dehydration, the Biginelli product. In this respect, the mechanism of the Biginelli reaction involving acetaldehyde, urea and pentane-2,4-dione can be summarized as follows (Figure 3) [29].

The mechanism starts by obtaining the acylimine intermediate, followed by an enolization of pentane-2,4-dione, before the condensation between the enolized pentane-2,4-dione and the acylimine intermediate, to form an intermediate which undergoes cyclization and dehydration to give the final dihydropyrimidinone.

To briefly recapitulate: only the reaction between aldehyde and urea provides the product, $Bi(NO_3)_3$ is primordial for the reaction, but it works as a catalyst not as a reactant, since the reaction works even with reduced quantities of this salt.

3.2. Theoretical section

3.2.1. Part 1: Computations neglecting the role of $Bi(NO_3)_3$

Since the studied reaction uses $Bi(NO_3)_3$ as a catalyst, we provide into this part the reaction with a classical thermodynamical parameters study.

Recently, Rodrugo et al. [39] studied theoretically this reaction using B3LYP/6-31G* basis set and

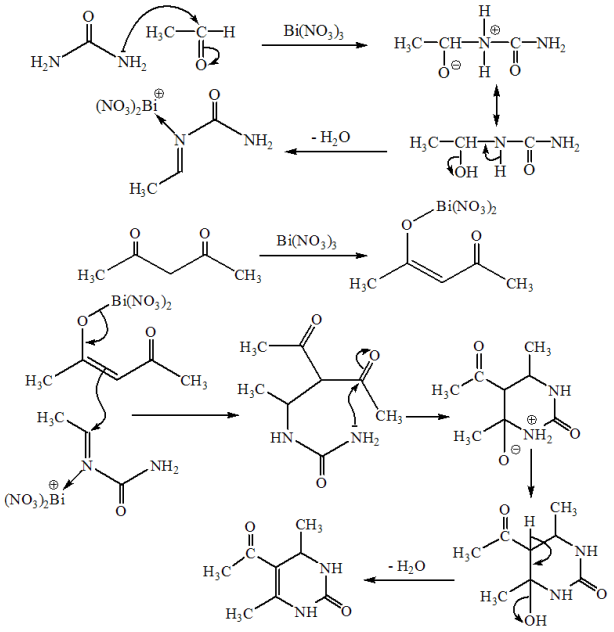
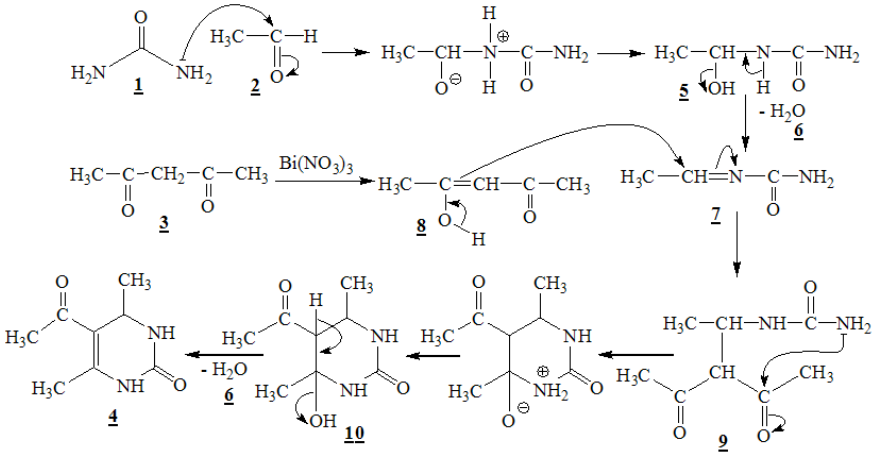


Figure 3. Proposed mechanism for the Biginelli reaction catalyzed by $Bi(NO_3)_3$.



Pathway 1:

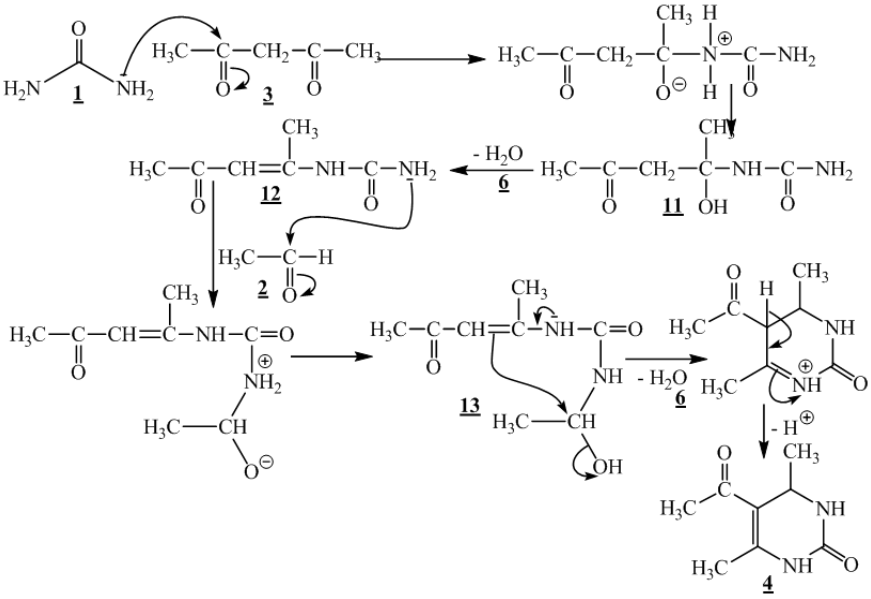
Step 1a: 1+2=5

Step 1b: 5=6+7

Step 1c: 7+8=9

Step 1d: 9=10

Step 1e: 10=4+6



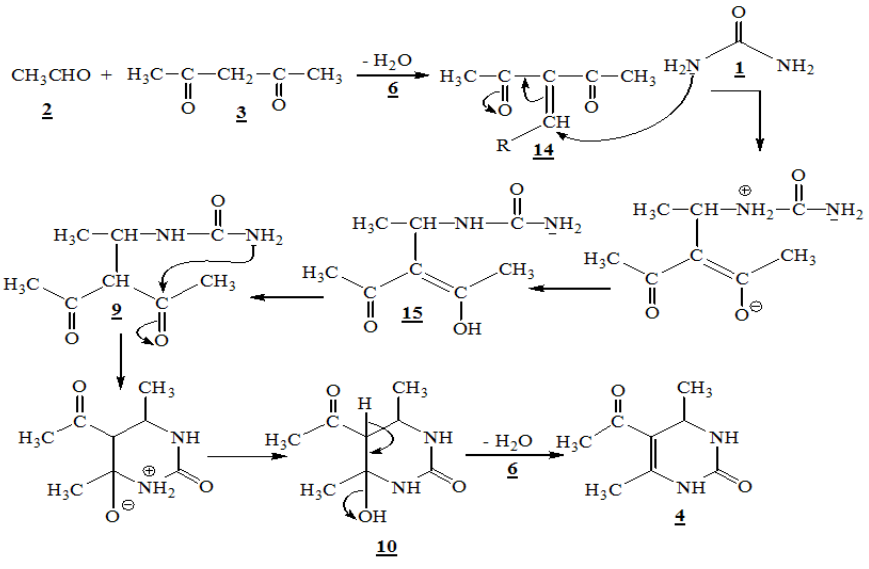
Pathway 2:

Step 2a: 1+3=11

Step 2b: 11=6+12

Step 2c: 2+12=13

Step 2d: 13=4+6



Pathway 3:

Step 3a: 2+3=6+14

Step 3b: 1+14=15

Step 3c: 15=9

Step 3d: 9=10

Step 3e: 10=4+6

Figure 4. Studied Biginelli mechanisms: (a) Pathway 1; (b) Pathway 2; (c) Pathway 3.

focusing their argument to transition state description.

In our work we consider each mechanism as a succession of elementary steps. The following mechanisms, named pathways 1, 2 and 3 represented in Figure 4, were taken under consideration. Each pathway was fractioned on a multitude of steps describing the main

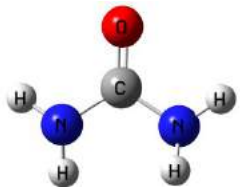
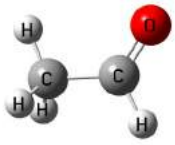
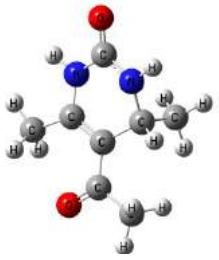
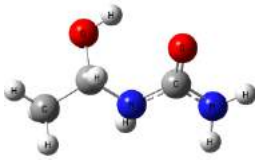
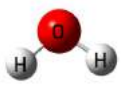
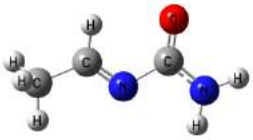
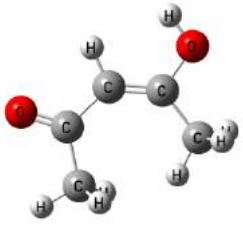
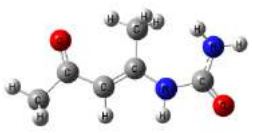
			
1: urea	**2:**ethanal	**3:** pentan-2,4-dione	**4:** 5-acetyl-4,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one
			
5: 1-(1-hydroxyethyl)urea	**6:** water	**7:** 1-ethylidenurea	**(*E*)-8:** (*E*)-4-hydroxypent-3-en-2-one
			
(*Z*)-8: (*Z*)-4-hydroxypent-3-en-2-one	**9:**1-(3-acetyl-4-oxopentan-2-yl)urea	**10:** 5-acetyl-6-hydroxy-4,6-dimethyl-tetrahydropyrimidin-2(1H)-one	**11:**1-(2-hydroxy-4-oxopentan-2-yl)urea
			
12: 1-(4-oxopent-2-en-2-yl) urea	**13:** 1-(1-hydroxyethyl)-3-(4-oxopent-2-en-2-yl)urea	**14:** 3-ethylidenpentan-2,4-dione	**15:**1-(3-acetyl-4-hydroxypent-3-en-2-yl)urea

Figure 5. B3LYP/6311++G(d,p) optimized geometries in the gas phase at 298 K.

intermediates. Every intermediate has been assigned to a code number (Figure 4). B3LYP/6-311G++(d,p) was used to compute studied geometries in this section as well in the gas phase as in different solvents (acetonitrile, dichloro-methane, ethanol, methanol, THF, toluene and water) by mean IEFPCM computations. For each solvent, we studied the reaction under 298 K and under its evaporation (reflux) temperature trying to improve temperature conditions for this reaction. We note that compound **8** (4-hydroxypent-3-en-2-one, Figure 4), has been studied separately under configurations (*Z)* and (*E)* forms.
After geometry optimization, no imaginary frequencies were found for all structures.

Structural discussion

Figure 5 gives, as an example, the name and the B3LYP 6-311G++(d,p) equilibrium structure for every computed molecule at 298 K in gas phase. We recapitulate in table I the rotational constants and three characteristic modes of vibration for computed molecules in the same conditions.

In accordance to table I, we note that the computed vibrational values are overestimated by 7-8% compared to usual experimental values. Nevertheless, those results may be helpful to attribute the experimental modes of vibration as well as to compare the influence of the substitution on vibrational modes and the following of the reaction evolution. As an example, we note urea C=O vibrator increases by 4 cm^{-1} between urea (compound **1**) and the final product (compound **4**).
It is also interesting to note that in the compound (*Z*)-**8**, ν_{OH} corresponding to OH stretch was moved from 3780 cm^{-1} in (*E*)-**8** to 3067 cm^{-1} in (*Z*)-**8**. This value is due to the sharing of H between the two carbonyl groups in (*Z*)-**8**.

Energetical discussion

Table II describes the free enthalpy energy exchange calculated during each step for the pathways 1, 2 and 3.
On the pathway 1, we could notice that the reaction involving (*E*)-**8** is the only way leading to the final product. This behavior let to explain that the

Table I. Rotational constants and three characteristic modes of vibration for computed molecules at 298 K.

Code	Rotational constants (gHz)			Some characteristic vibrations (cm^{-1})		
1	11.19	10.32	5.41	$\nu_{(C=O)}$=1786	$\nu_{(NH)a}$=3689	$\nu_{(NH)s}$=3579
2	57.25	10.13	9.09	$\nu_{(C=O)}$=1807	$\nu_{(CH(O))}$=2872	$\delta_{(CH(O))}$=1420
3	4.15	1.93	1.52	$\nu_{(C=O)}$=1794	$\nu_{(C=O)}$=1763	$\nu_{(CH3)a}$=3143
4	1.48	0.74	0.55	$\nu_{(NH)}$= 3623;3618	$\nu_{((C=O)N)}$=1787	$\nu_{((C=O)C)}$=1715
5	5.35	1.71	1.41	$\nu_{(C=O)}$=1748	$\nu_{(OH)}$=3762	$\nu_{(NHRR')}$=3585
6	824.0	429.8	282.5	$\nu_{(OH)a}$=3919	$\nu_{(OH)s}$=3814	$\delta_{(OH)}$=1603
7	9.87	2.09	1.74	$\nu_{(NH)a}$=3743	$\nu_{(NH)s}$=3606	$\nu_{(C=O)}$=1774
(*E*)-8	4.92	1.65	1.26	$\nu_{(OH)}$=3780	$\nu_{(C=O)}$=1705	$\nu_{(C=C)}$=1675
(*Z*)-8	5.82	1.71	1.34	$\nu_{(OH)}$=3067	$\nu_{(C=O)}$=1676	$\nu_{(C=C)}$=1676
9	1.18	0.54	0.46	$\nu_{(NH)a}$=3670	$\nu_{((C=O)N)}$=1758	$\delta_{(NH)}$=1474
10	1.17	0.68	0.52	$\nu_{(OH)}$=3824	$\nu_{(NH)}$= 3630;3614	$\nu_{((C=O)N)}$=1757
11	1.40	0.83	0.66	$\nu_{(OH)}$=3798	$\nu_{(NH)a}$=3663	$\nu_{((C=O)N)}$=1752
12	3.42	0.59	0.51	$\nu_{(NH)a}$=3721	$\nu_{(NH)}$=3589	$\nu_{((C=O)N)}$=1773
13	2.39	0.28	0.25	$\nu_{(OH)}$=3773	$\nu_{((C=O)N)}$=1756	$\nu_{((C=O)C)}$=1732
14	1.91	1.46	0.93	$\nu_{(C=O)}$=1763	$\nu_{(C=O)}$=1733	$\nu_{(C=C)}$=1646
15	1.00	0.57	0.47	$\nu_{(OH)}$=3836	$\nu_{(NH)a}$=3648	$\nu_{((C=O)N)}$=1761

Table II: B3LYP/6-311G++(d,p) computed free enthalpy exchange ΔrG (kJ.mol^{-1}).

Pathway1									
Condition	**T(K)**	**Step 1a**	**Step 1b**	**Step 1c via (*Z*)-8**	**Step 1c via (*E*)-8**	**Step 1d**	**Step 1e**	**Reaction via (*Z*)-8**	**Reaction via (*E*)-8**
Gas	298	29.27	-3.22	39.86	-18.95	18.79	-53.13	31.56	**-27.24**
Acetonitrile	298	46.63	-16.55	37.38	-8.66	21.40	-65.47	23.38	**-22.66**
	355	56.79	-26.71	49.18	3.43	22.99	-74.55	27.70	**-18.06**
Dichloromethane	298	45.38	-14.41	37.16	-10.32	20.83	-64.24	24.72	**-22.77**
	313	48.07	-17.00	40.14	-7.25	21.26	-66.61	25.86	**-21.53**
Ethanol	298	46.51	-15.85	36.95	-9.27	21.34	-65.28	23.67	**-22.55**
	351	55.88	-25.44	48.09	2.16	22.83	-73.76	27.60	**-18.34**
Methanol	298	46.48	-15.99	36.94	-9.15	21.41	-65.36	23.49	**-22.61**
	338	53.60	-23.04	45.16	-0.74	22.53	-71.71	26.54	**-19.35**
THF	298	45.22	-14.05	37.29	-10.92	20.69	-63.93	25.22	**-22.99**
	339	52.67	-21.17	45.44	-2.55	21.89	-70.45	28.38	**-19.62**
Toluene	298	38.41	-9.75	39.69	-10.05	18.55	-59.51	27.39	**-22.35**
	384	54.02	-24.57	56.31	8.01	21.12	-73.11	33.77	**-14.53**
Water	298	46.84	-17.52	37.91	-7.84	21.49	-65.67	23.05	**-22.69**
	373	60.17	-31.12	53.67	8.30	23.57	-77.61	28.68	**-16.69**

Pathway2						
Condition	**T(K)**	**Step 2a**	**Step 2b**	**Step 2c**	**Step 2d**	**Reaction**
Gas	298	81.43	-37.58	25.49	-54.31	15.03
Acetonitrile	298	99.94	-55.39	36.48	-66.97	14.06
	355	111.53	-65.44	46.17	-73.11	19.15
Dichloromethane	298	97.59	-52.72	35.33	-65.83	14.37
	313	100.62	-55.34	37.88	-67.44	15.72
Ethanol	298	99.57	-54.97	36.23	-66.68	14.15
	351	110.30	-64.30	45.29	-72.52	18.78
Methanol	298	99.79	-55.31	36.37	-66.76	14.10
	338	107.92	-62.34	43.16	-71.04	17.70
THF	298	97.23	-52.12	35.19	-65.68	14.63
	339	105.59	-59.31	42.20	-70.13	18.35
Toluene	298	89.55	-45.09	31.89	-62.25	14.11
	384	106.88	-60.17	46.98	-72.00	21.68
Water	298	100.44	-55.96	36.71	-67.13	14.06
	373	115.71	-69.21	49.46	-75.20	20.76

Pathway3							
Condition	**T(K)**	**Step 3a**	**Step 3b**	**Step 3c**	**Step 3d**	**Step 3e**	**Reaction**
Gas	298	32.06	68.38	-51.06	18.79	-53.13	15.03
Acetonitrile	298	21.50	76.60	-39.97	21.40	-65.47	14.06
	355	22.80	87.18	-39.26	22.99	-74.55	19.15
Dichloromethane	298	22.61	76.60	-41.43	20.83	-64.24	14.37
	313	23.00	79.28	-41.21	21.26	-66.61	15.72
Ethanol	298	21.64	76.70	-40.25	21.34	-65.28	14.15
	351	22.89	86.63	-39.82	22.83	-73.76	18.78
Methanol	298	21.48	76.50	-39.93	21.41	-65.36	14.10
	338	22.42	83.89	-39.43	22.53	-71.71	17.70
THF	298	22.81	77.88	-42.82	20.69	-63.93	14.63
	339	23.82	85.58	-42.50	21.89	-70.45	18.35
Toluene	298	24.75	73.04	-42.72	18.55	-59.51	14.11
	384	26.70	88.37	-41.41	21.12	-73.11	21.68
Water	298	21.18	76.62	-39.56	21.49	-65.67	14.06
	373	22.88	90.52	-38.60	23.57	-77.61	20.76

system stabilizes in a certain way *(E)*-**8** isomer despite the fact that (*Z*)-**8** is thermodynamically more stable. As an example our computations showed that in the gas phase at 298 K, *(Z)*-**8** is more stable than (*E*)-**8** by -58.80 kJ.mol^{-1}. *(Z)*-**8** is even more stable than its ketonic form (compound **3**, Figure 4) by -16.53 kJ.mol^{-1} under the same conditions. Hence, it becomes obvious here the contribution of $Bi(NO_3)_3$, we see later. It is interesting also to notice that in all studied solvents, the reaction is more thermodynamically favorable at 298 K than at the reflux temperature. This difference ranges between 1and 8 kJmol^{-1}, depending of the solvent, whereas reactions via (*Z*)-**8** intermediate were less unfavorable underreflux temperature than 298 K.

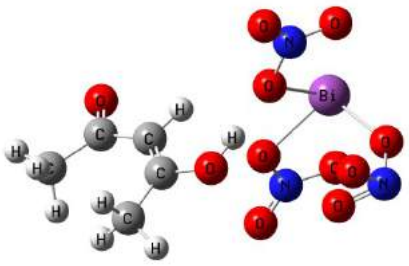
On pathway 2, the reaction seems thermodynamically impossible under considered conditions with 14 <ΔrG < 21 kJ.mol^{-1}. Into this process, step 2a seems to be the main energetical barrier (80 <ΔrG < 120 kJ.mol^{-1}).We note also a similar attitude than reactions via (*Z*)-**8**, where the thermodynamical loss is less important under reflux temperature than 298 K.

Finally, on pathway 3, we have the same behavior as pathway 2, where the reaction seems thermodynamically impossible and the energetical loss is less important under reflux temperature than 298 K.

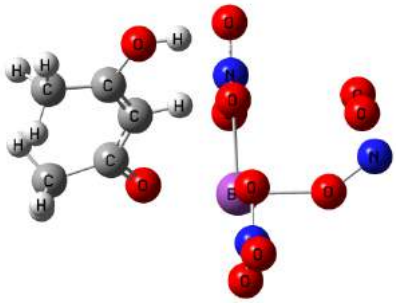
3.2.2. Part 2: Investigations into the role of $Bi(NO_3)_3$

We show in the last section that the only pathway to obtain the desired product is the first pathway, via (E)-4-hydroxypent-3-en-2-one intermediate named (*E*)-**8**, where this intermediate seems less stable than its (*Z*) stereoisomer. Recently, some works tried to explain theoretically the role of Bi $(NO_3)_3$ or some related derivatives as reactant or catalyst [40,41], where $BiCl_3$ and by extrapolation $Bi(NO_3)_3$ reacts with pentan-2,4-dione (**3**) to lead R-O-$BiCl_2$ complex and HCl ; R-O is the alkoxide form of **8** [41].

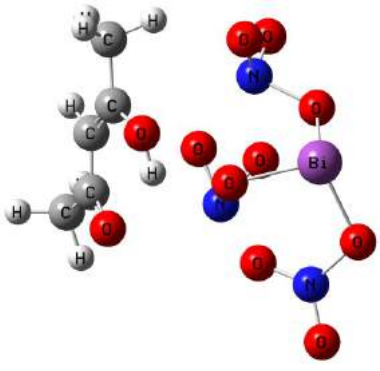
Considering the experimental fact that $Bi(NO_3)_3$ have to be used in catalytic way in our study, we studied its evolution with both (*Z*)-**8** and (*E*)-**8** derivatives. Computations were considered with CAM-B3LYP/LanL2DZ since B3LYP/6-311G++ (d,p) is not available for Bismuth. This approach did not affect our previous results as $Bi(NO_3)_3$ is a



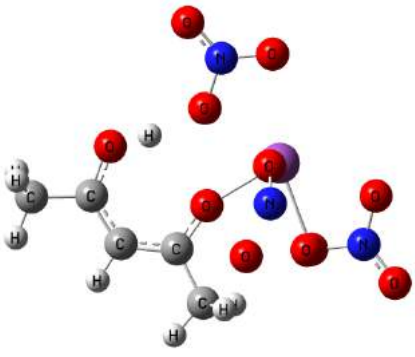
Starting geometry: $Bi(NO_3)_3$ + (*E*)-**8**



Optimized geometry: $Bi(NO_3)_3$ + (*E*)-**8**



Starting geometry: $Bi(NO_3)_3$ + (*Z*)-**8**



Optimized geometry: $Bi(NO_3)_3$ + (*Z*)-**8**

Figure 6. CAM-B3LYP/LanL2DZ optimized geometries for $Bi(NO_3)_3$ with (*E*)-**8** and (*Z*)-**8**

catalyst and did not affect the final thermodynamical energy balance. Thus, we put Bi $(NO_3)_3$ and respectively (*Z*)-**8** and (*E*)-**8** derivatives and let the system fully optimizes energy and geometry.

Structural discussion

Figure 6 gives the starting and optimized geometries computed at gas phase in CAM-B3LYP/LanL2DZ level of calculations between $Bi(NO_3)_3$ and respectively (*Z*)-**8** and (*E*)-**8**. No positive frequencies were reported.

The first remarkable information from Figure 6 is when the reaction between $Bi(NO_3)_3$ + (*E*)-**8** did not note any significant evolution, $Bi(NO_3)_3$ + (*Z*)-**8** leads to the formation of R-O-$Bi(NO_3)_2$ and HNO_3. The initial system is no more stable and leads to new products.

This result is confirmed by ν_{OH} stretch calculated at 2949 cm^{-1} for $Bi(NO_3)_3$ + (*Z*)-**8** due to the sharing of H between the enol function and HNO_3, whereas we found 3706 cm^{-1} for $Bi(NO_3)_3$ + (*E*)-**8** which is a classical O-H vibration.

These results seems to be in accordance with the fact that only $Bi(NO_3)_3$ + (*E*)-**8** let to obtain reached products.

Energetical discussion

Energetically, reaction $Bi(NO_3)_3$ + (*E*)-**8** has a free enthalpy gain of -90.4 $kJ.mol^{-1}$ probably due to Van Der Walls interactions stabilizing this new Bismuth complex.

Reaction between $Bi(NO_3)_3$ + (*Z*)-**8** leading to new compounds has also a high energy gain of -106.5 $kJ.mol^{-1}$. The problem is that this last consideration is not really in accordance with experimental results when$Bi(NO_3)_3$ reacts as a catalyst not a reactant.

Some recent studies suggest a regeneration of $Bi(NO_3)_3$ as R-$Bi(NO_3)_2$ + HNO_3 [40,41], but we think that the formation and the disappears of HNO_3 still have to be confirmed experimentally, at least under the conditions we studied.

Finally, we propose that the role of $Bi(NO_3)_3$ is to stabilize the (*E*)-**8** facilitating the step 1-c attack (Figure 4).

CONCLUSION

Biginelli reaction has been studied theoretically and experimentally under different solvents and temperatures to determine its mechanism. Our results show that both computational and experimental approaches confirm that the first pathway involving a condensation between the aldehyde and urea to give an acylimine-type intermediate, is the easiest way for the Biginelli reaction. The role of $Bi(NO_3)_3$ suggests the stabilization of (*E*)-4-hydroxypent-3-en-2-one isomer, which is theoretically primordial for the reaction process.

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