

REACTIONS OF α -OXO KETENES WITH AMIDES: EXPERIMENTAL DATA AND SEMIEMPIRICAL AM1 MOLECULAR ORBITAL CALCULATIONS

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Abstract – The thermal decomposition of 4-acyl substituted furan-2,3-diones (**1a**, **b**) leads to the α -oxo ketenes (**2a**, **b**) as an intermediate which undergoes nucleophilic addition reactions with amides. Some of α -N-acyl-oxo-amide derivatives (**4a-h**) obtained show keto-enol tautomerism. The reaction mechanism of ketene (**R1**) with formamide (**R2**) are calculated by AM1 method. Transition states (**TS1** and **TS2**) were further confirmed by vibrational analysis and characterized by the corresponding imaginary vibration modes and frequencies. According to calculations, intermediate (**IN**) is in the planar zwitterion structure. The transition structure (**TS2**) has almost a planar structure. Analysis of the molecular orbitals indicates that the reaction is best described as pseudopericyclic.

Introduction

The last few years have witnessed the development of a powerful new methodology for the synthesis of substituted aromatic systems and heterocyclic compounds, proceeding through putative ketene intermediates.¹ The chemistry of ketenes has recently been reviewed, notably by Tidwell.² The interaction between ketenes and nucleophiles or radicals has attracted the attention of many experimental³ and theoretical chemists.⁴ Intermolecular reactions of the bisketenes with amines and water proceed efficiently to give ketenylcarboxamides or ketenylcarboxyl acid, which could react intramolecularly to give the succinimides and anhydrides, respectively.⁵ The reaction with nitrogen nucleophiles giving rise to ketene-amine and ketene-imine zwitterions undoubtedly plays a role in several reactions catalyzed by pyridine or tertiary amines.⁶ Wentrup and co-workers observed ketene-pyridine zwitterions directly in cryogenic matrix with IR spectroscopy.^{6a-c,7} Ring opening of electronically excited cyclohexa-2,4-diones

leads to configurationally isomeric diene-ketenes, and then, in the presence of the protic nucleophiles such as amines and alcohols to give the intermediate zwitterions at -150°C .⁸

α -Oxo ketenes (acylketenes) have been demonstrated to be intermediates in a variety of reactions. α -Oxo ketenes are usually generated by thermolysis or photolysis of β -keto esters,⁹ 2-diazo-1,3-dicarbonyl compounds,¹⁰ 1,3-dioxin-4-ones (or 1,3-dioxane-4-6-diones)¹¹ and 2,3-dihydrofuran-2,3-diones.¹² α -Oxoketenes are of considerable current interest not only because of their use as intermediates in organic synthesis but also as the subject of recent kinetic-mechanistic,¹³ spectroscopic^{11f,12a,14} and computational studies.¹⁵ α -Oxo ketenes are highly reactive molecules which can be trapped by nucleophiles to give β -keto carboxylic acid derivatives,^{10,12b,16} or alternatively undergo cycloaddition reactions.^{12b,17} 4-Benzoyl-5-phenylfuran-2,3-dione and some urethanes combine under loss of carbon monoxide yielding the open chain dibenzoylacetic acid derivatives. The keto-enol tautomerism of the products is further investigated with aid of semiempirical quantum chemical calculations.^{16a}

To study the mechanism of the reaction, all calculations were carried out by means of semiempirical AM1 methods with full geometry optimization for reactants, intermediates and products.¹⁸ Transition structures, located with saddle calculations, were refined by minimizing the scalar gradient of energy with respect to the geometry and characterized as saddle points by diagonalising the Hessian Matrix (force constant) and establishing the presence of one and only one negative force constant, whereas the ground state of the reactants, the intermediate, and the products had no imaginary force constants. As a result, the transition states were located with the SADDLE routine in MOPAC and the obtained structures were refined with TS option. The AM1 calculations were carried out with the help of MOPAC 7 program package.¹⁹ Model compounds with alkyl and phenyl groups substituted by hydrogen atoms were used in the theoretical calculations.

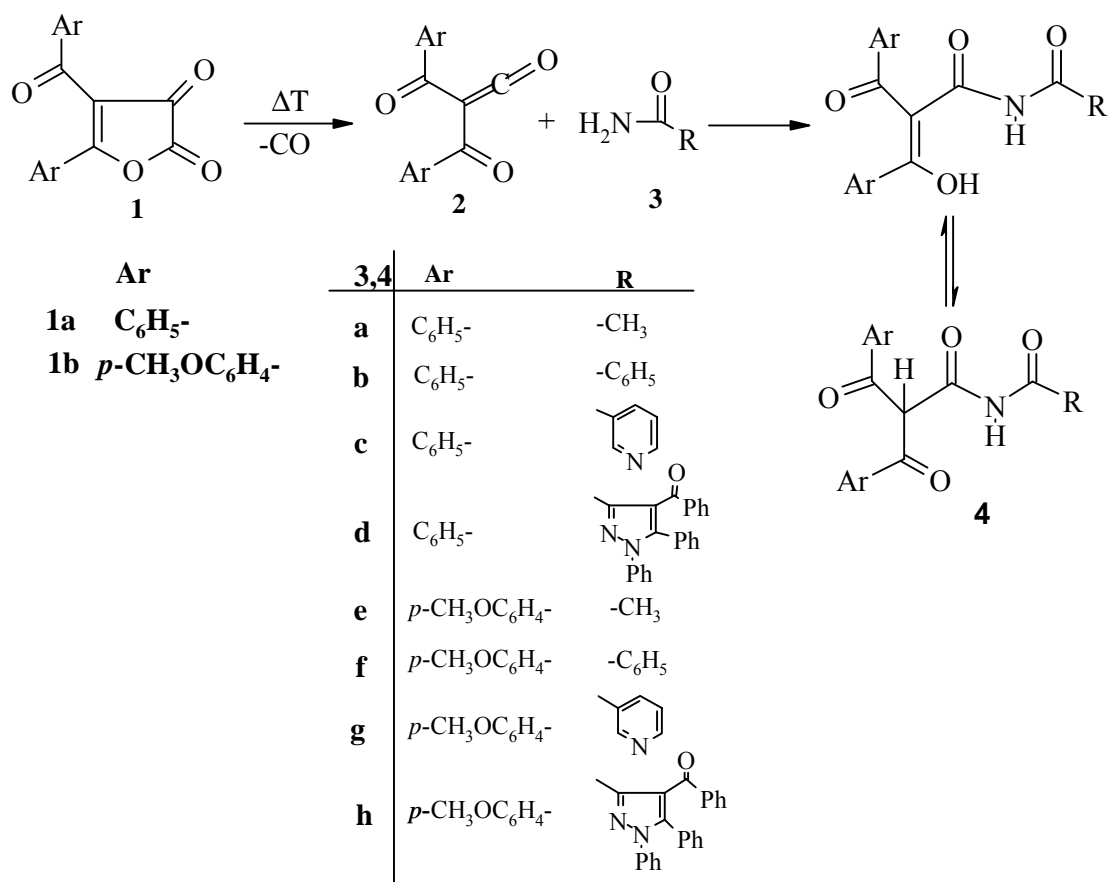
In the present study, we carry out the reactions between various amides and furan-2,3-dione derivatives and the reaction mechanism for selected model structures have been resulted by AM1 calculations. The results of the calculations (relative energies, ΔE_{rel} , kcal.mol⁻¹; dipole moments, μ , debye; HOMO orbital energies, $-E_{HOMO}$, eV; and imaginary frequencies, ν , icm⁻¹; for the reactants (**R1**, **R2**), transition states (**TS1**, **TS2**), intermediate (**IN**), and keto-enol tautomers (**P1-P7**)) are given in Table 1.

Results and Discussion

The reactions of the furan-2,3-diones (**1a,b**) with amide derivatives (**3a-d**) yields α -*N*-acyl-oxo-amide derivatives (**4a-h**) in boiling benzene and toluene (see EXPERIMENTAL). The reaction equations are shown in Scheme 1. Compounds (**4a-h**) were obtained by the addition of amides to α -oxo ketenes (**2**) which is formed by heating **1a-b**. The structures of **4a-h** were confirmed by elemental analysis, IR, ¹H

and ^{13}C NMR spectral data. Product (**4a**) was obtained by treating **1a** with acetamide (**3a**) in 40% yield. In the IR spectra of compound (**4a**), the C=O absorption bands are found to be at about 1727, 1720, 1685 and 1675 cm^{-1} . The -NH and -OH absorption bands are found to be at about 3260 and 3160 cm^{-1} , respectively.

Scheme 1



Important structural information about **4a** can be obtained from its ^1H NMR spectrum. Chemical shift values of very close analogs of α -oxocarboxylic acid derivatives are found to be at between 6.82 and 5.02 ppm for the protons at $-\text{CH}$ in the keto form. It was previously stated that the products, dibenzoylacetate-N-carboxyalkylamide derivatives, obtained by the reaction of dibenzoylketene (**2a**) with oximes are in keto form in solution.²⁰ But the products that were obtained by the reaction of **2a** with urethanes were detected in enol form in solution, whereas keto forms were formed in solid phase.^{16a} Pivaloylmalonic ester amide derivative which was obtained by the reaction between carbomethoxypivaloylketene and amine does not show any tendency to enolize structure in CDCl_3 .^{12b} The IR and NMR spectral data of

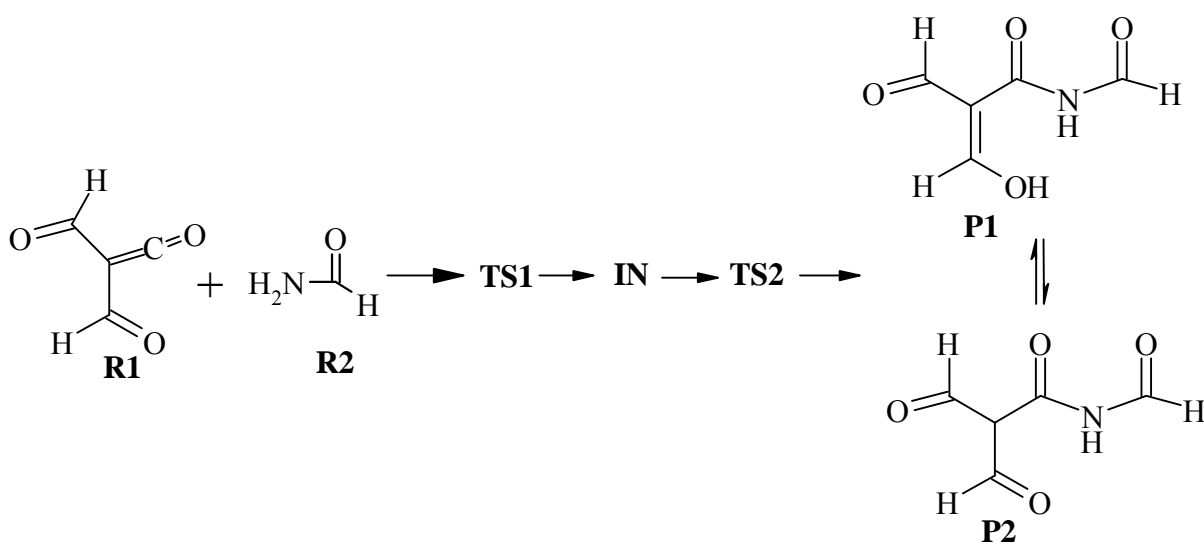
compound (**4a**) indicate the existence of keto-enol tautomerism in this compound. The ^1H NMR peak of **4a** observed at 6.95 ppm belongs to the $-\text{CH}$ in the keto form. The peaks at 9.47 ppm are thought to represent the $-\text{OH}$ in the enol form. The broad peak at 10.80 represents the $-\text{NH}$. This indicates the existence of a keto-enol tautomerism. The proportion of the keto-enol form is found to be about 3/1 for **4a** in CDCl_3 solution. In the ^{13}C NMR spectrum of **4a**, the peak at 26.92 ppm belongs to the methyl group the peak at 67.16 ppm (d, $^1J=132$ Hz) represents the $-\text{CH}$ in the diketo form. The peaks corresponding to 172.80 and 192.43 ppm indicate the presence of imide- $\text{C}=\text{O}$ and benzoyl- $\text{C}=\text{O}$, respectively. More information about spectra of **4b-h** is given in the experimental section. Remarkably, **4b** and **4h** compounds do not show any tendency to enolize in CDCl_3 solution although enols should be stabilized by intramolecular hydrogen bonding. Pyrazole amide derivative (**4d**) used in this work was synthesized by Akçamur and co-workers in our laboratory.²¹ In general, pyrazole nuclei have biological activities.²² Due to the pharmacological importance of these types of compounds, the reactions of **1a-b** with **3d** were studied, and derivatives (**4d** and **4h**) were obtained. The yields for the products (**4a-h**) are in the range 35%-45%. The side products may be 1,3-dioxin-4-ones and α -pyrones derivatives formed by [4+2] cycloaddition dimerization of oxoketenes.^{12a,b,17a} In general, α -oxo ketenes are mixtures of *s-Z* and *s-E* isomers. Ab initio and semiempirical calculations on a series of differently substituted α -oxoketenes were used to investigate *E/Z*-isomerism and rotational barriers in these molecules.^{15a,d} In this study, theoretical calculations were carried out by using the *s-EZ* isomer of **R1**.

Table 1: Relative energies, dipole moments, HOMO and LUMO orbital energies and imaginary frequencies for the reactants, transition states, intermediate and keto-enol tautomers.

Compounds	E_{rel} kcalmol $^{-1}$	μ Debye	E_{HOMO} eV	E_{LUMO} eV	ν icm $^{-1}$
R1		2.92	-10.56	-0.93	
R2		3.70	-10.67	1.57	
R1+R2	0.00				
TS1	16.57	3.86	-9.93	-0.84	-444.25
IN	15.95	5.87	-9.38	-1.30	
TS2	24.79	3.70	-9.71	-0.72	-1656.41
P1	-19.47	1.45	-10.82	-0.90	
P2	-16.52	1.71	-11.19	-0.37	
P3	-23.64	1.90	-10.71	-0.93	
P4	-23.77	1.59	-10.65	-0.89	
P5	-21.96	2.13	-10.01	-0.97	
P6	-25.06	5.07	-10.69	-1.01	
P7	-18.61	4.22	-9.85	-0.98	

The main stages of the presumptive mechanism of the reaction are presented in Scheme 2. The spatial dispositions of atoms for the reactants (**R1**, **R2**), intermediate (**IN**), transition states (**TS1**, **TS2**) and the products (**P1-P7**) are shown in Figure 1. To ease the consideration of changes in the systems, the same numbering of atoms is kept for reactants, the transition states, intermediate and final products of the reaction. According to Scheme 2, the interaction of the nucleophile formamide (**R2**) with α -oxoketene (**R1**) goes through several stages. Each stage of the reaction is characterized by the electronic properties and energy states (see Table 1). The changes in bond orders are matched by the changes in bond lengths (Table 2) during the process of reaction. The lengthening of the bonds couples with the lowering of bond orders or *vice versa*. As noticed in Table 3, zero bond order between C2 and N1 atoms in the species (**R1+R2**), might be an indicative of the fact that there is no formation of the bond, C2-N1.

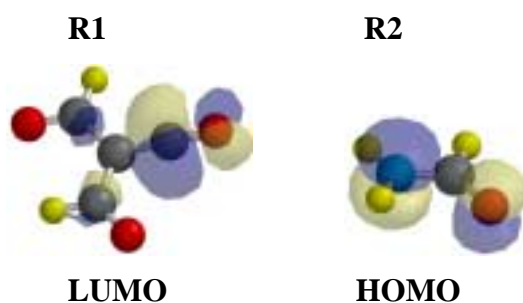
Scheme 2



The calculated energies of the frontier orbitals are presented in Table 1. According to frontier orbital theory the molecular orbital overlap in the transition state will occur and the interaction will be productive when the orbitals have proper symmetry and they have similar energies. The LUMO of α -oxoketene (**R1**), $\pi^*_{C=C=O}$, which is a π antibonding orbital, is strongly polarized toward the C2 atom (the coefficient of C2- P_x , -0.71, is larger than the coefficient of O6- P_x , +0.49, see Figure 2) and is relatively low in energy (-0.93 eV), at least compared with π^* orbital of amide (**R2**) (1.57 eV). Thus, the larger coefficient of the C2- P_x orbital means that the carbonyl π^* orbital of **R1** will interact strongly with HOMO of formamide (**R2**) (-10.67 eV), since the HOMO is localized on the N2 atom (the coefficient of N2- P_z is -0.82, is larger than

the coefficient of O14-P_z, +0.52). During this interactions changes in the charge of the atoms are presented in Table 3.

Figure 2. Orbitals of R1 (LUMO: -0.93 eV) and R2 (HOMO: -10.67 eV)

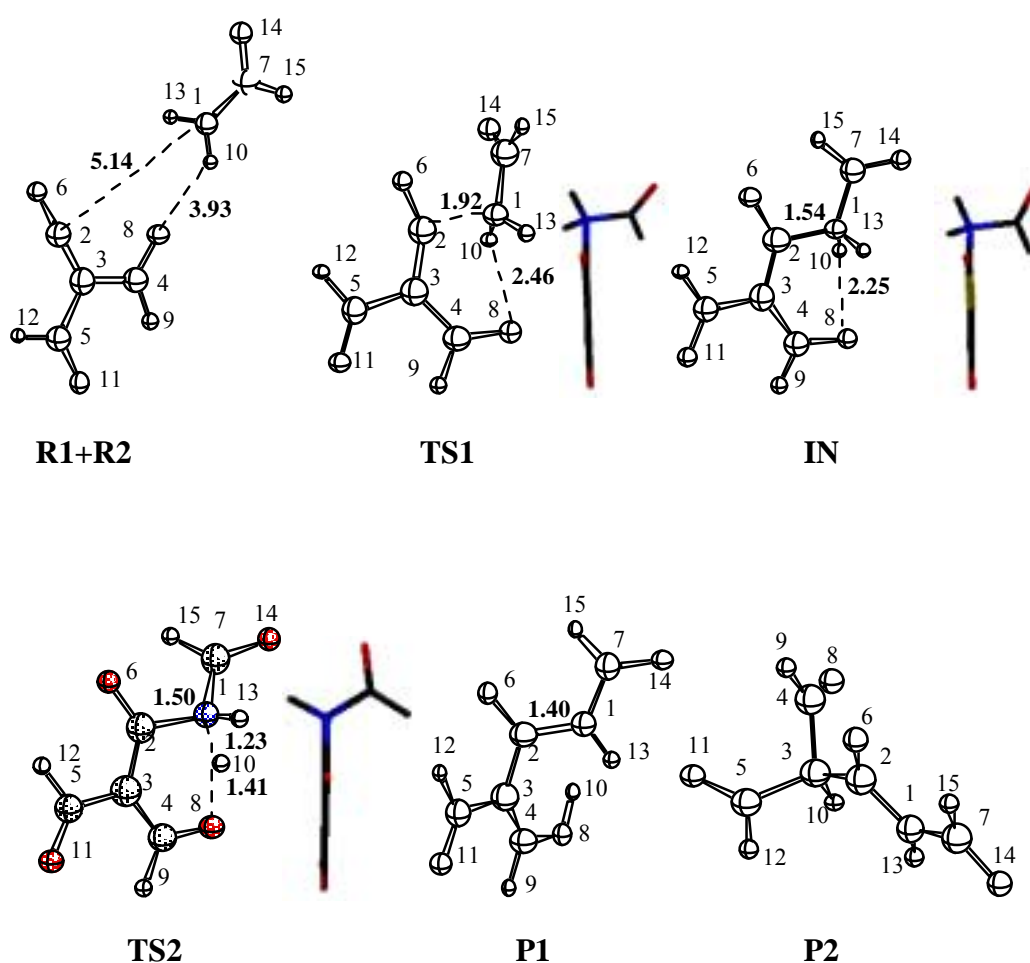


The first transition structure (**TS1**) (see Figure 1) corresponds to the nucleophilic addition of the formamide's amino group to the sp-hybridized carbon atom of the electrophilic α -oxo ketene (**R1**). The N1-C2 bond length and bond order for **TS1** ($\Delta E_{\text{rel}} = 16.57 \text{ kcal.mol}^{-1}$, see Table 1) become 1.92Å and 0.32 (see Tables 2, 3), respectively. Molecular planes of **R1** and **R2** molecules approach at an angle of 55.22° and the H10-N1-C2-C3 atoms are not coplanar. The bond length and bond order of H10-O8 are 2.46Å and 0.00, respectively. For the **TS1** we found one imaginary frequency at 444.25 icm^{-1} . When the bond length of N1-C2 becomes 1.54Å, formation of intermediate (**IN**) is observed. At the same time the torsion angle of H10-N1-C2-C3 is calculated to be 40.33° (see Table 2). Bond order of the N1-C2 and O8-H10 are 0.69 and 0.01, respectively. The bond order of N1-C2 shows that the value for the bond is less than the value of a single bond. The agreement in the energy levels between **IN** ($\Delta E_{\text{rel}} = 15.95 \text{ kcal.mol}^{-1}$) and **TS1** leads to the assumption that these molecule structures are similar. Although **IN** has high energy, it should exist as an unstable reaction intermediate, i.e., a local minimum on the potential energy surface. In theoretical chemistry, we are able to strictly distinguish between reaction intermediates and transition states in terms of vibrational analyses. Since these species have no imaginary frequency modes, it is a stable point on the potential energy surface.

Analysis of charges shows that the N1 becomes more positively charged ($\Delta q = 0.25 \text{ e}$) in the α -oxo ketenes (**IN**) relative to the reactants. The O6 atom shares more electrons ($\Delta q = -0.29 \text{ e}$) in **IN** as does the central carbon atom of ketene ($\Delta q = -0.07 \text{ e}$). The charges on both the C2 of α -oxo ketenes and the central C7 of formamide remain almost constant throughout the reaction pathway. The intermediate (**IN**) is in the structure of zwitterions and this zwitterion has a planar structure (torsion angle of O8-H10-N1-C2 in **TS1**, **IN** and **TS2** is -60.79, -61.92, and 5.02°) and is characterized by an N1-C2 bond distance 1.54Å significantly longer than a typical N-C single bond 1.40. This structure display zwitterionic character as

evidenced by their large dipole moment 5.87 D which is similar to the value of the ketene-pyridine zwitterions found before.^{6b} This dipole moment value is higher than that of **TS1** and **TS2**. The dipole moment differences which result from the N1-C2 and C3-C2-O6 group dipoles may be used for a distinction between transition states and intermediate.

Figure 1: Atom-numbering scheme and structures of the reactants, transition states, intermediate and products (see table 2 for structural data). Two side views, rotated by approximately 90°, are given for **TS1**, **TS2** and **IN**.



The $n_{O8} \rightarrow \sigma^*_{N1-H10}$ interaction at **IN** takes place when the lone pair electrons of the oxygen atom n_{O8} delocalise into the antibonding orbital σ^* of N1-H10 atoms. The transition state (**TS2**) is characterized by the presence of a six membered cycle with the bond lengths substantially changed as compared with those of **IN** values. The bond distances N1-C2, C2-C3, C3-C4, O8-H10, N1-H10 and C2-O6 are 1.50, 1.43, 1.41, 1.41, 1.23 and 1.24Å, respectively. Further approach of the atoms N1 and C2 finally leads to the bond formation of N1-C2 and O8-H10 and a breaking of N1-H10 bond. The bond orders of H10-N1 and

H10-O8 of **TS2** are 0.52 and 0.32, respectively. On going from **IN** to **P1** there exist change in charge on H10 from 0.27 to 0.35. The E_{HOMO} and E_{LUMO} values for **TS1** and **TS2** are found to be higher than those of reactants, intermediate and products. This nearly planar (**TS2**) is a dramatic contrast to other pericyclic reactions, where the transition states are usually nonplanar so as to maximize orbital overlap.^{15b} In a recent series of publications, Birney *at al.* have reported a number of examples for thermal pseudopericyclic reactions that include cycloadditions, sigmatropy rearrangements and electrocyclizations.²³ Such pseudopericyclic reactions are typically characterized by planar (or almost planar) transition states and low activation energy.^{15b,f}

Table 2: Selected structural data for the reactants, transition states, intermediates and final products.

Bond Lengths	R1+R2	TS1	IN	TS2	P1	P2
N1-C2	5.14	1.92	1.54	1.50	1.40	1.39
C2-C3	1.34	1.37	1.40	1.43	1.48	1.52
C4-C3	1.46	1.45	1.44	1.41	1.36	1.52
O6-C2	1.18	1.20	1.24	1.24	1.24	1.24
O8-H10	3.93	2.46	2.25	1.41	0.97	2.52
H10-N1	0.98	1.01	1.03	1.23	2.55	2.29
O8-C4	1.24	1.24	1.25	1.28	1.35	1.23
N1-C7	1.36	1.43	1.48	1.45	1.40	1.40
Bond Angle						
O6-C2-C3	179.00	146.59	131.59	129.14	122.65	-
C3-C2-N1	86.55	108.52	115.05	114.35	116.78	117.39
C4-C3-C2	121.12	128.60	125.20	122.03	125.34	108.56
C5-C3-C2	120.53	114.65	116.54	117.71	114.82	109.29
O8-C4-C3	123.66	125.98	124.56	123.20	127.86	121.32
H10-N1-C2	81.47	100.51	107.56	103.72	-	-
H13-N1-C2	51.32	99.92	108.20	110.09	118.38	118.38
Torsion Angle						
C4-C3-C2-N1	-5.57	-2.54	-3.17	1.93	-50.70	-133.84
H10-N1-C2-C3	55.22	40.56	40.33	-3.22	-	-
C2-N1-H10-O8	0.81	-60.79	-61.92	5.02		

The N1-C7 bond length (1.36 Å) of **R1** has some double-bond character due to partial overlap of the p orbitals of the carbonyl group with unshared electron of the nitrogen. The N1-C7 (1.48 Å) bond length of **IN** is longer than that of **TS1** (1.43 Å) and **TS2** (1.45 Å). As shown in Table 2, the reaction results in the rearrangements of bonds and valence angles in the reacting systems. The values of valence angle O6-C2-C3 of **R1+R2**, **TS1**, **IN**, **TS2**, and **P1** are 179.00, 146.59, 131.59, 129.14 and 122.65°, respectively. The transition structure (**TS2**) is the rate determining step and the relative activation energy for this state is found to be 24.79 kcal.mol⁻¹ which is higher than the previously calculated activation energy of formyl-

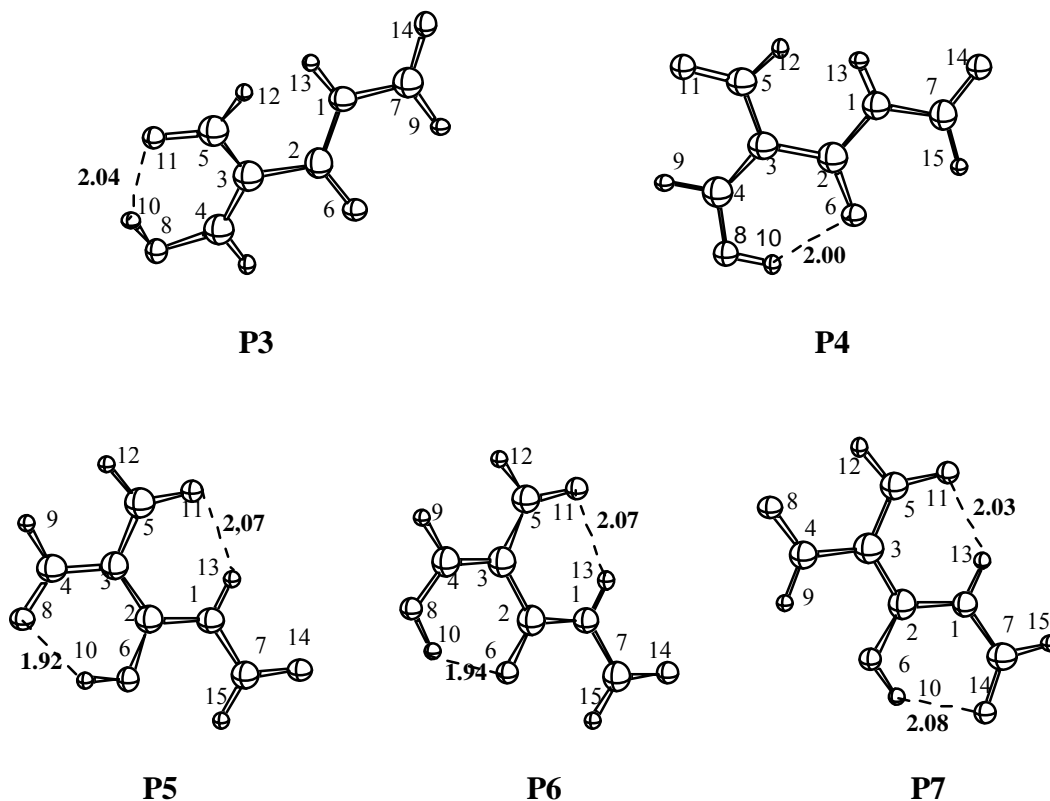
ketene with nucleophiles such as amines, alcohols and aldehydes.^{15f} Since formamide (**R2**) is as nucleophile weaker than amines, alcohols and aldehydes, the tendency of addition to oxo ketenes is low.

Table 3: Mulliken charge (e) and bond order of selected atoms for the reactants, transition states, intermediates, and final products.

Atom	R1+R2	TS1	IN	TS2	P1	P2
Charge						
N1	-0.44	-0.35	-0.19	-0.31	-0.41	-0.39
C2	0.40	0.43	0.34	0.35	0.36	0.32
C3	-0.47	-0.52	-0.54	-0.53	-0.39	-0.29
C4	0.28	0.27	0.26	0.26	0.14	0.21
O6	-0.07	-0.22	-0.36	-0.32	-0.23	-0.33
C7	0.25	0.23	0.22	0.23	0.27	0.27
O8	-0.35	-0.39	-0.44	-0.41	-0.33	-0.26
H10	0.22	0.23	0.27	0.35	0.24	0.15
O11	-0.28	-0.31	-0.34	-0.34	-0.30	-0.25
Bond Order						
N1-C2	0.00	0.32	0.69	0.79	1.01	1.04
C2-C3	1.47	1.34	1.26	1.11	0.94	0.91
C4-C3	0.96	1.03	1.08	1.26	1.68	0.94
O6-C2	2.17	1.97	1.75	1.82	1.81	1.80
O8-H10	0.00	0.00	0.01	0.32	0.92	0.00
H10-N1	0.91	0.91	0.88	0.52	0.02	0.00
O8-C4	1.87	1.81	1.75	1.53	1.15	1.97
N1-C7	1.15	0.95	0.83	0.88	0.99	0.98

β -keto carboxylic acids and their derivatives in solution are generally present in equilibrium with their enols depending on the solvent and the substituents. Intramolecular hydrogen bonds of these compounds may become a stabilizing factor. Intramolecular hydrogen bonding for **P3-P7** is very responsible for the molecular conformation and intramolecular rearrangement. Several planar conformers are possible for product (**P**) (Figure 1). Ball and stick models of the energy-minimized intramolecularly hydrogen-bonded conformations of **P** are given in Figure 3. There is no hydrogen bond in conformer (**P1**) since the bond distance N1-H10 (2.55 Å) is too long for intramolecular hydrogen bonding. Hydrogen bonds are shown by dashed line for **P3-7**. The calculated heats of formation of enol structures were compared with that of keto structure (**P2**) (Table 1). Enol forms have been proved to be the most stable structure and their extraordinary stabilities are related to the formation of intramolecular hydrogen bond and cyclic pseudo aromatic structures. The results of relative energy (Table 1) show that the hydrogen bond energy was only 2.09 kcal.mol⁻¹ for **P7**, indicating the formation of weak hydrogen bond, but 8.54 kcal/mol for **P6** indicating a stronger hydrogen bond. The dipole moment value of **P6** is largest compared with those of other tautomers indicating intermolecular interaction, more than others.

Figure 3: Ball and stick models of the energy-minimized intramolecularly hydrogen-bonded conformations of **P3-P7**.



The reactivity of α -oxo ketenes depends upon their ability to accept the reactant amide molecule. The ability of nucleophilic formamide molecule to add to the hybridized carbonyl group in α -oxoketenes depend not only on the charge of the carbonyl carbon atom but also on the charge separation between carbon and oxygen of the carbonyl group. Charge separation of the N1, C2, C3, O6 and H10 atoms of all structures is given in the Table 3. Bond orders were calculated as the sum of the squares of density matrix elements connecting two atoms by the bonds routine implemented in MOPAC 7.¹⁹ Bond orders can be used as a measure of the degree of advancement of the transition state along a reaction path.²⁴ Table 3 shows the bond orders throughout the reaction paths of the model reactions used in this study. As going from **R1+R2** to **P1**, N1-C2 and O8-H10 bond strengths decrease and N1-H10 bond strength increases during the reaction. The E_{HOMO} of **IN** is higher than that of **TS1** and **TS2** whereas E_{LUMO} is lower those of both.

EXPERIMENTAL

Solvents were dried by refluxing over the appropriate drying agent and distilled before use. Melting points (mp) were determined by use of Büchi melting point apparatus and are not corrected.

Microanalyses were performed on a Carlo Erba Elemental Analyser Model 1108. The IR spectra were recorded on a Shimadzu Model 435 V-04 apparatus, using potassium bromide pellets. The ^1H and ^{13}C NMR spectra were recorded on Varian 4200 Gemini spectrometer using tetramethylsilane as an internal standard. All experiments were followed by TLC using DC Alufolion kieselgel 60 F 254 Merck and with a Model Camag tlc lamp (254/366 nm).

***N*-(2-Benzoyl-3-oxo-3-phenylpropionyl)acetamide (4a).**

4-Benzoyl-5-phenylfuran-2,3-dione (**1a**) (0.5 g, 1.798 mmol) and acetamide (**3a**) (0.11 g, 1.798 mmol) were boiled in benzene (50 mL) for 4 h. The benzene was evaporated and the remaining oily residue was dissolved in ethanol. Petroleum ether was then added into the solution and the whole was left standing for about a day. The white crude product was filtered and recrystallized from *n*-propyl alcohol and dried on P_2O_5 . mp 224°C, yield 0.224 g (40%). IR (KBr): $\nu=3260, 3160$ (N-H, O-H), 1727, 1720, 1685, 1675 (C=O), 1325 cm^{-1} (C-N). ^1H NMR (CDCl_3): $\delta=10.80$ (br, -NH), 9.47 (s, enol-OH), 7.96-7.04 (m, 10H, Ar-H), 6.95 (s, keto-CH), 2.23 (s, CH_3); ^{13}C NMR (CDCl_3): $\delta=192.43$ (Ph-C=O), 172.80 (N-C=O), 168.01 (C1=O), 137.44 (Ph-C3-OH, in enol form) 132.22-129.91 (m, aromatic C), 106.44 (C2), 67.16 (diketo, CH); 26.92 (CH_3). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_4$: C, 69.90; H, 4.85; N, 4.53. Found: C, 70.02; H, 4.88; N, 4.53.

***N*-(2-Benzoyl-3-oxo-3-phenylpropionyl)benzamide (4b).**

4-Benzoyl-5-phenylfuran-2,3-dione (**1a**) (0.5g, 1.798 mmol) and benzamide (**3b**) (0.22 g, 1.798 mmol) were boiled in benzene (50 mL) for 2 h. The benzene was evaporated and the oily residue was treated with dry ether. The crude product was then filtered and recrystallized from *n*-propyl alcohol/acetic acid and dried on P_2O_5 . mp 187°C, yield 0.268 g (40%). IR (KBr): $\nu=3260$ cm^{-1} (N-H, not observed enol-OH), 1720, 1705, 1690, 1680 cm^{-1} (C=O). ^1H NMR (CDCl_3): $\delta=11.00$ (br, -NH), 8.2-7.2 (m, 16H, Ar-H), 6.95 (s, keto-CH, not observed enol-OH). Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{NO}_4$: C, 74.38; H, 4.61; N, 3.77. Found: C, 74.24; H, 4.66; N, 3.65.

***N*-(2-Benzoyl-3-oxo-3-phenylpropionyl)nicotinamide (4c).**

4-Benzoyl-5-phenylfuran-2,3-dione (**1a**) (0.5g, 1.798 mmol) and nicotinamide (**3c**) (0.2g, 1.798 mmol) were boiled in benzene (50 mL) for 4 h. The benzene was evaporated and the oily residue was treated with dry ether. The crude product was then filtered and recrystallized from *n*-propyl alcohol and dried on P_2O_5 . mp 177 °C, yield 0.268 g (40%). IR (KBr): $\nu=3255, 3155$ cm^{-1} (N-H, O-H), 1720, 1705, 1690, 1680 cm^{-1} (C=O). ^1H NMR (CDCl_3): $\delta=12.46$ (br, -NH), 9.28 (s, -OH), 8.85-6.98 (m, 14H, Ar-H), 6.95 (s, keto-CH); ^{13}C NMR (CDCl_3): $\delta= 193.05$ (Ph-C=O), 172.50 (N-C=O), 165.02 (C1=O), 155.56 and 151.25 (C-N=C), 137.57 (Ph-C3-OH, in enol form), 136.31-125.67 (m, aromatic C), 106.44 (C2), 68.33 (diketo, -CH). Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_4$: C, 70.96; H, 4.30; N, 7.52. Found: C, 70.79; H, 4.07; N, 7.39.

***N*-[(4-Benzoyl-1,5-diphenyl-1*H*-3-pyrazolyl)carbonyl]-2-benzoyl-3-oxo-3-phenylpropanamide (4d).**

4-Benzoyl-5-phenylfuran-2,3-dione (**1a**) (0.1 g, 0.36 mmol) and 4-benzoyl-1,5-diphenylpyrazole-3-carboxylic amide (**3d**) (0.132 g, 0.36 mmol) were boiled for 4 h in distilled benzene (50 mL). The benzene was evaporated and the oily residue was treated with dry ether. The precipitate was then filtered and recrystallized from *n*-propyl alcohol and dried on P₂O₅. mp 196°C, yield 0.099 (45%). IR (KBr): $\nu=3250, 3160\text{ cm}^{-1}$ (N-H, O-H), 1710, 1700, 1695, 1680 cm^{-1} (C=O). ¹H NMR (CDCl₃): $\delta=12.53$ (br, -NH), 9.97 (s, -OH), 7.89-7.10 (m, 25H, Ar-H), 7.04 (s, keto, C-H); ¹³C NMR (CDCl₃): $\delta=199.27$ and 193.05 (Ph-C=O), 172.36 (N-C=O), 168.19 (C1=O), 160.16 (140.51 (enol C=O), 139.48-125.08 (m, aromatic C), 139.49 (C=N), 137.83 (Ph-C3-OH, in enol form), 106.71 (C2), 67.23 (diketo, C-H). Anal. Calcd for C₃₉H₂₇N₃O₅: C, 75.85; H, 4.38; N, 6.80. Found: C, 75.55; H, 4.45; N, 6.66.

***N*-[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropionyl]acetamide (4e).**

4-*p*-Methoxybenzoyl-5-*p*-methoxyphenyl-furan-2,3-dione (**1b**) (0.2 g, 0.59 mmol) and acetamide (**3e**) (0.035 g, 0.59 mmol) were boiled for 4 h in distilled toluene (50 mL). The solvent was evaporated. The remaining oily residue was dissolved in dry ether. Petroleum ether was then added. The white product was then filtered and recrystallized from CCl₄ and dried on P₂O₅. mp 182 °C, yield 0.077 g (35%). IR (KBr): $\nu=3250, 3150\text{ cm}^{-1}$ (N-H, O-H), 2860 cm^{-1} (aliph. -C-H), 1700, 1690, 1630, 1590 cm^{-1} (C=O). ¹H NMR (CDCl₃): $\delta=10.65$ (br, -NH), 9.47 (s, -OH), 7.97-6.91 (m, 8H, Ar-H), 6.68 (s, keto-CH), 3.86 (s, 6H, 2CH₃O), 2.30 (s, -CH₃); ¹³C NMR (CDCl₃): $\delta=190.37$ (Ph-C=O), 172.71 (N-C=O), 133.83 (enol-OH), 133.64-115.32 (m, aromatic C), 66.96 (keto-C=O), 57.57 and 57.31 (CH₃O), 27.18 (metil-C=O). Anal. Calcd for C₂₀H₁₉NO₆: C, 65.04; H, 5.15; N, 3.79. Found: C, 64.71; H, 4.88; N, 3.66.

***N*-[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropionyl]benzamide (4f).**

4-*p*-Methoxybenzoyl-5-*p*-methoxyphenyl-furan-2,3-dione (**1b**) (0.2 g, 0.59 mmol) and benzamide (**3f**) (0.08 g, 0.59 mmol) were boiled for 4 h in distilled benzene (50 mL). The benzene was evaporated and the remaining oily residue was treated with ether. The white crude product was recrystallized from acetic acid and dried on P₂O₅. mp 214°C, yield 0.117 g (45%). IR (KBr): $\nu=3250, 3150\text{ cm}^{-1}$ (N-H, O-H), 3000-2800 cm^{-1} (alifa-C-H), 1730, 1700 cm^{-1} (C=O). ¹H NMR (CDCl₃): $\delta=12.22$ (br, -NH), 10.26 (s, -OH), 8.06-6.97 (m, 13H, Ar-H), 7.26 (s, keto-C-H) 3.86-3.78 (s, 6H, 2CH₃O); ¹³C NMR (CDCl₃): $\delta=198.76$ and 190.55 (Ph-C=O), 172.53 (N-C=O), 166.59 (C1=O), 164.86-133.87 (m, aromatic C), 133.44 (Ph-C3-OH, in enol form), 67.18 (diketo-C-H), 57.59-57.33 (CH₃O). Anal. Calcd for C₂₅H₂₁NO₆: C, 69.59; H, 4.91; N, 3.25. Found: C, 69.20; H, 4.84; N, 2.92.

***N*-[2-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropionyl]nicotinamide (4g).**

4-*p*-Methoxybenzoyl-5-*p*-methoxyphenylfuran-2,3-dione (**1b**) (0.2 g, 0.59 mmol) and nicotinamide (**3g**) (0.08 g, 0.59 mmol) were boiled in distilled toluene (50 mL) for 2 h. The toluene was evaporated and the oily residue was mixed with dry ether. The white crude product was filtered and recrystallized from *n*-

butanol and dried on P₂O₅. mp 196°C, yield 0.104 g (40%). IR (KBr): $\nu=3300-3200\text{ cm}^{-1}$ (N-H, O-H), $3000-2900\text{ cm}^{-1}$ (aliph. C-H), $1630, 1610\text{ cm}^{-1}$ (C=O), $1600-1590\text{ cm}^{-1}$ (C-N). ¹H NMR (CDCl₃): -NH not observed, $\delta=11.85$ (s, -OH), $9.09-7.07$ (m, 12H, Ar-H), 7.21 (s, keto-CH), 3.86 (s, 6H, 2CH₃O); ¹³C NMR (CDCl₃): $\delta=192.15$ (Ph-C=O); 170.14 (N-C=O); 167.39 (C1=O), 155.11 and 151.17 (C-N=C), 138.04 (Ph-C3-OH, in enol form), $132.58-116.04$ (m, aromatic C), 66.37 (diketo, C-H), 57.45 (CH₃O). Anal. Calcd for C₂₄H₂₀N₂O₆: C, 66.66; H, 4.63; N, 6.48. Found: C, 66.69; H, 4.62; N, 6.67.

***N*-[(4-Benzoyl-1,5-diphenyl-1*H*-3-pyrazolyl)carbonyl]-2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-3-oxopropanamide (4h).**

4-*p*-Methoxybenzoyl-5-*p*-methoxyphenylfuran-2,3-dione (**1b**) (0.2 g, 0.59 mmol) and 4-benzoyl-1,5-diphenylpyrazole-3-carboxylic amide (**3h**) (0.217 g, 0.59 mmol) were boiled in distilled toluene (50 mL) for 2 h. The toluene was evaporated and the oily residue was treated with dry ether and stirred for a few days in a cold condition. The white crude product was filtered and recrystallized from *n*-butanol and dried on P₂O₅. mp 169°C, yield 0.16 g (40%). IR (KBr): $\nu=3300, 3200\text{ cm}^{-1}$ (N-H), $2970-2840\text{ cm}^{-1}$ (aliph-C-H), $1610, 1590\text{ cm}^{-1}$ (C=O). ¹H NMR (CDCl₃): $\delta=11.59$ (br, -NH), $7.85-7.05$ (m, 23H, Ar-H), 3.85 (s, 6H, 2CH₃O); ¹³C NMR (CDCl₃): $\delta=191.96$ (Ph-C=O), 167.92 (N-C=O), 165.46 (C1=O), $138.99-116.06$ (m, aromatic C), 66.41 (diketo-C-H), 57.46 (CH₃O). Anal. Calcd for C₄₁H₃₁N₃O₇: C, 72.67; H, 4.58; N, 6.20. Found: C, 72.51; H, 4.76; N, 6.17.

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