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Quantum Chemical and Experimental Studies on the Mechanism of Alkylation of β-Dicarbonyl Compounds. The Synthesis of Five and Six Membered Heterocyclic Spiro Derivatives

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Abstract: The alkylation of β-dicarbonyl compounds in a K_2CO_3/DMSO system was found to afford O- and C-alkylated derivatives, depending on the type of the β-dicarbonyl compound involved. The alkyl derivatives obtained were used in the synthesis of some new spiro barbituric acid derivatives. Quantum chemical calculations were carried out to elucidate the reaction mechanisms for some typical synthesis.

Keywords: Alkylation of β-dicarbonyl compounds; spiro derivatives of barbituric acid, 2-chloro-1-(2- chloroethoxy)ethane; theoretical studies.
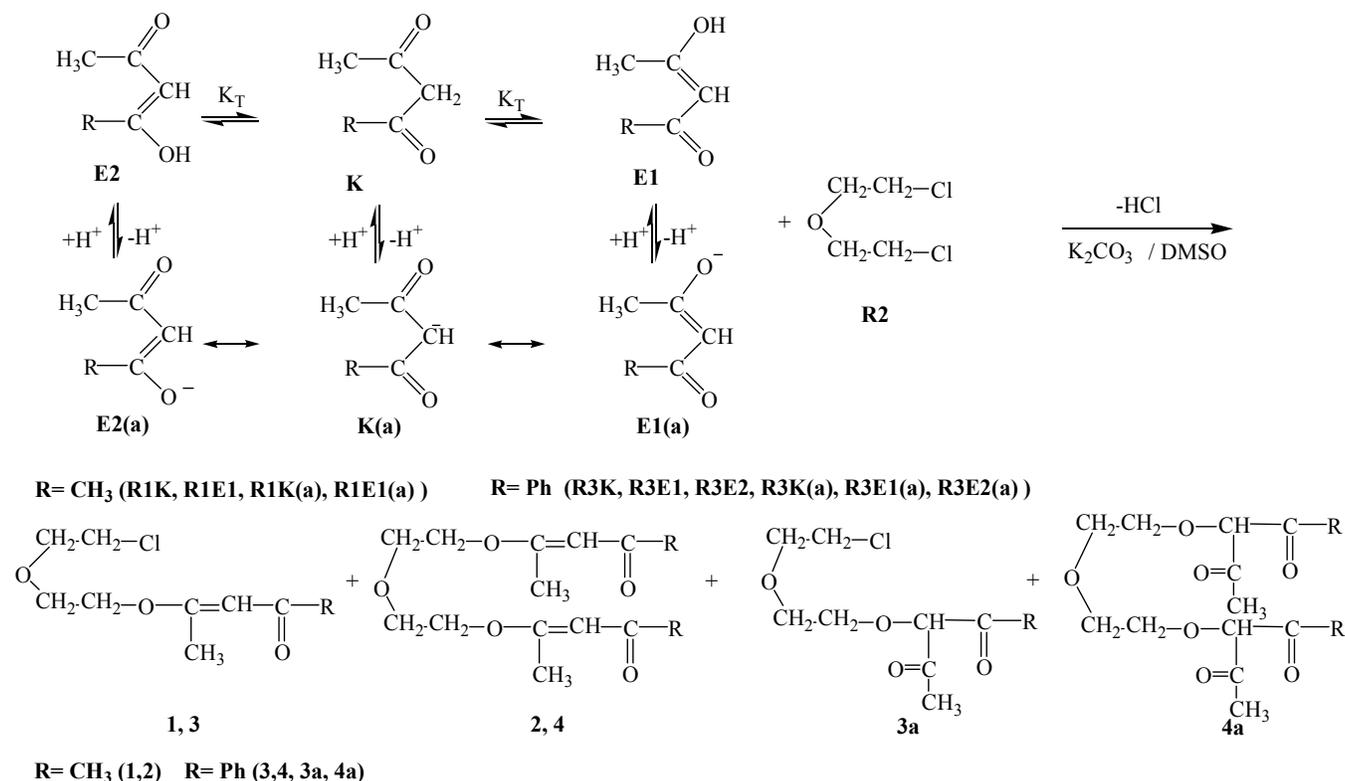
Introduction

The alkylation reactions of β-dicarbonyl derivatives with dibromide and 1,2,3-trihalopropane derivatives have been studied in detail [1-3] and the products obtained have been used in the

synthesis of various heterocyclic compounds. Although many researchers have been working on synthesis of novel spiro derivatives [4-22], we did not come across any studies of the alkylation of β-dicarbonyl derivatives with 2-chloro-1-(2-chloroethoxy)ethane in the literature. We now report our studies on alkylation reactions of β-dicarbonyl derivatives with 2-chloro-1-(2-chloroethoxy)ethane in a K_2CO_3/DMSO system and the synthesis of new spiro derivatives of barbituric acid. Some additional theoretical work had been carried out to elucidate the reaction mechanisms of some typical and novel syntheses.

Results and Discussion

The reaction of acetylacetone (**R1**) with 2-chloro-1-(2-chloroethoxy)ethane (**R2**) at 70°C for 20 h afforded 4-[2-(2-chloroethoxy)ethoxy]pent-3-en-2-one (**1**) in 59% percent yield via O-alkylation. 4-{2-[2(1-methyl-3-oxobut-1-enyloxy)ethoxy]pent-3-en-2-en (**2**) was also obtained in low yield (i.e. 15 %) as a side product, along with compound **1** (Scheme 1). Similarly, the reaction of benzoylacetone (**R3**) with compound **R2** under the same conditions afforded the O-alkylation product 3-[2-(2-chloro-ethoxy)ethoxy]-1-phenylbut-2-en-1-one (**3**) in 57% yield, along with 3-{2-[2(1-methyl-3-oxo-3-phenylprop-1-enyloxy)ethoxy]ethoxy}-1-phenylbut-2-en-1-one (**4**) formed as a side product in 16% yield (Scheme 1).

Scheme 1

R= CH₃ (R1K, R1E1, R1K(a), R1E1(a))   R= Ph (R3K, R3E1, R3E2, R3K(a), R3E1(a), R3E2(a))

R= CH₃ (1,2)   R= Ph (3,4, 3a, 4a)

The presence of the olefinic protons (i.e. 5.31-5.36 ppm) in the ^{1}H-NMR spectra indicates the formation of enol ethers. Formation of 2-[2-(2-chloroethoxy)ethyl]-1-phenylbutane-1,3-dione (**3a**) and 2-{2-[4-oxo-3-(phenylcarbonyl)pentyloxy]ethyl}-1-phenybutane-1,3-dione (**4a**) along with **3** and **4** are expected during the alkylation of benzoylacetone. It seems that enolization occurs at the acetyl carbonyl but not in the benzoyl fragment, due to the interrelation of the benzoyl fragment with the aromatic ring.

The alkylation of dimedone (**R4**) with **R2** under similar conditions (Scheme 2) afforded both an O-alkyl derivative, 3-[2-(2-chloroethoxy)-ethoxy]-5,5-dimethylcyclohex-2-en-1-one (**5**), formed in 46% yield, and the C-cyclization products 3,3-dimethyl-9-oxaspiro[5.5]undacane-1,5-dione (**6,** 28 %) and 3-{2-[2-(5,5-dimethyl-3-oxocyclohex-1-enyloxy)ethoxy]ethyl}-5,5-dimethyl-cyclohex-2-en-1-one (**7,** 12%).
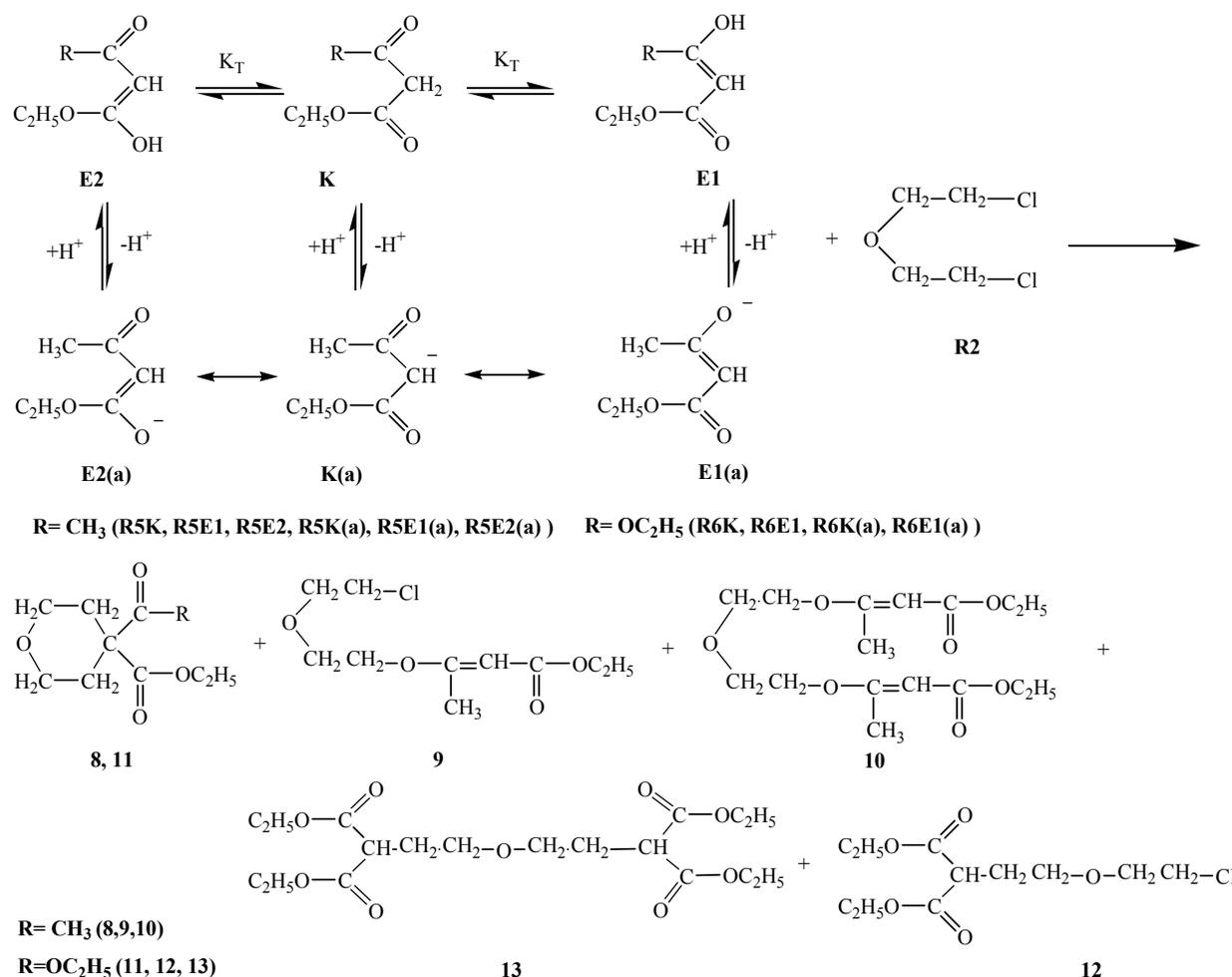
Scheme 2
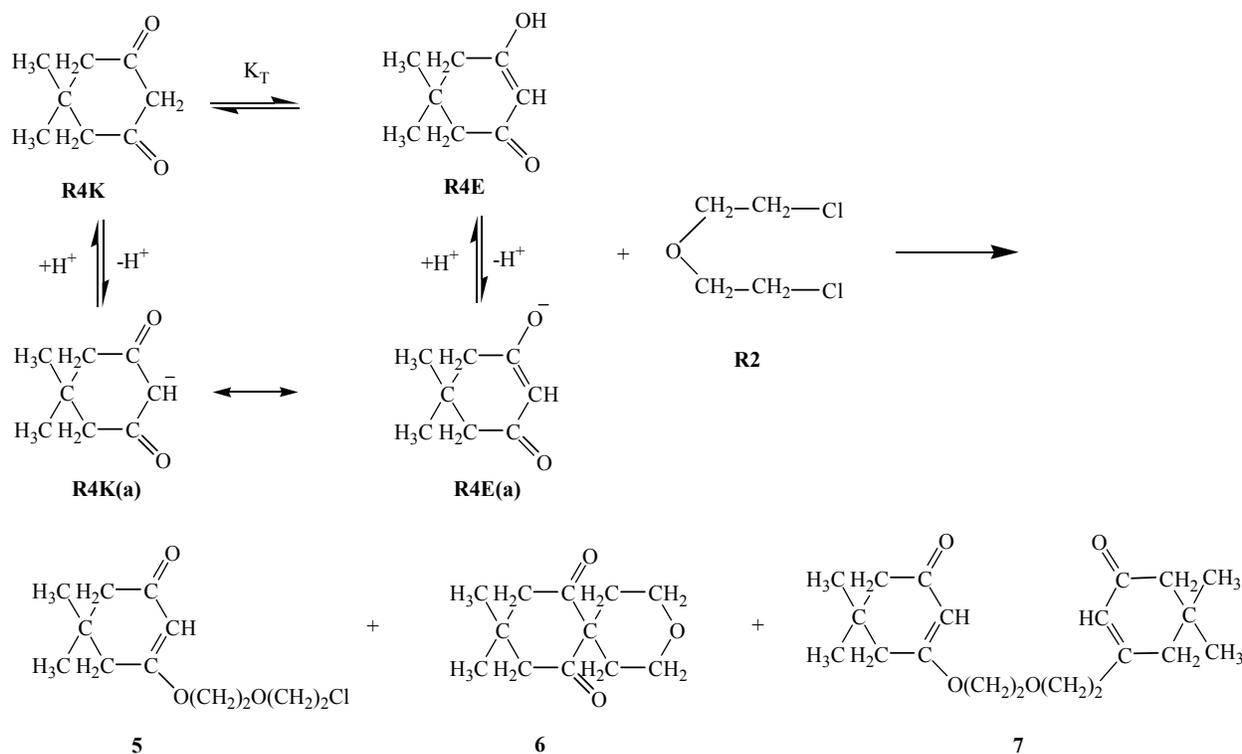
When acetyl acetate (**R5**) was used instead of dimedone the mechanism changed, C,C-cyclo-alkylation now became feasible and 1-(4-acetylperhydro-2H-pyran-4-yl)ethan-1-one (**8**) was produced in 55 % yield. Along with compound **8** the O-alkylation products ethyl 3-[2-(2-chloroethoxy)-ethoxy]but-2-enoate (**9**) and ethyl 3-(2-{2-[2-(ethoxycarbonyl)-1-methylvinyloxy]ethoxy}ethoxy)-but-2-enoate (**10**) were obtained in yields of 23 and 10 %, respectively (Scheme 3).

Under the proper conditions the reaction of malonic esters **R6** with **R2** efforts only the C-alkylation ester products ethyl 4-(ethoxycarbonyl)perhydro-2H-pyran-4-carboxylate (**11**), diethyl 2-[2-(2-chloro-ethoxy)ethyl]propane-1,3-dioate (**12**) and diethyl 2-{2-[3,3-bis(ethoxycarbonyl)-propoxy]ethyl} propane-1,3-dioate (**13**) in yields of 57, 10 and 14 %, respectively (Scheme 3).

Scheme 3

E2   K   E1

R= CH$_3$ (R5K, R5E1, R5E2, R5K(a), R5E1(a), R5E2(a))   R= OC$_2$H$_5$ (R6K, R6E1, R6K(a), R6E1(a))

E2(a)   K(a)   E1(a)

R2

8, 11   9   10
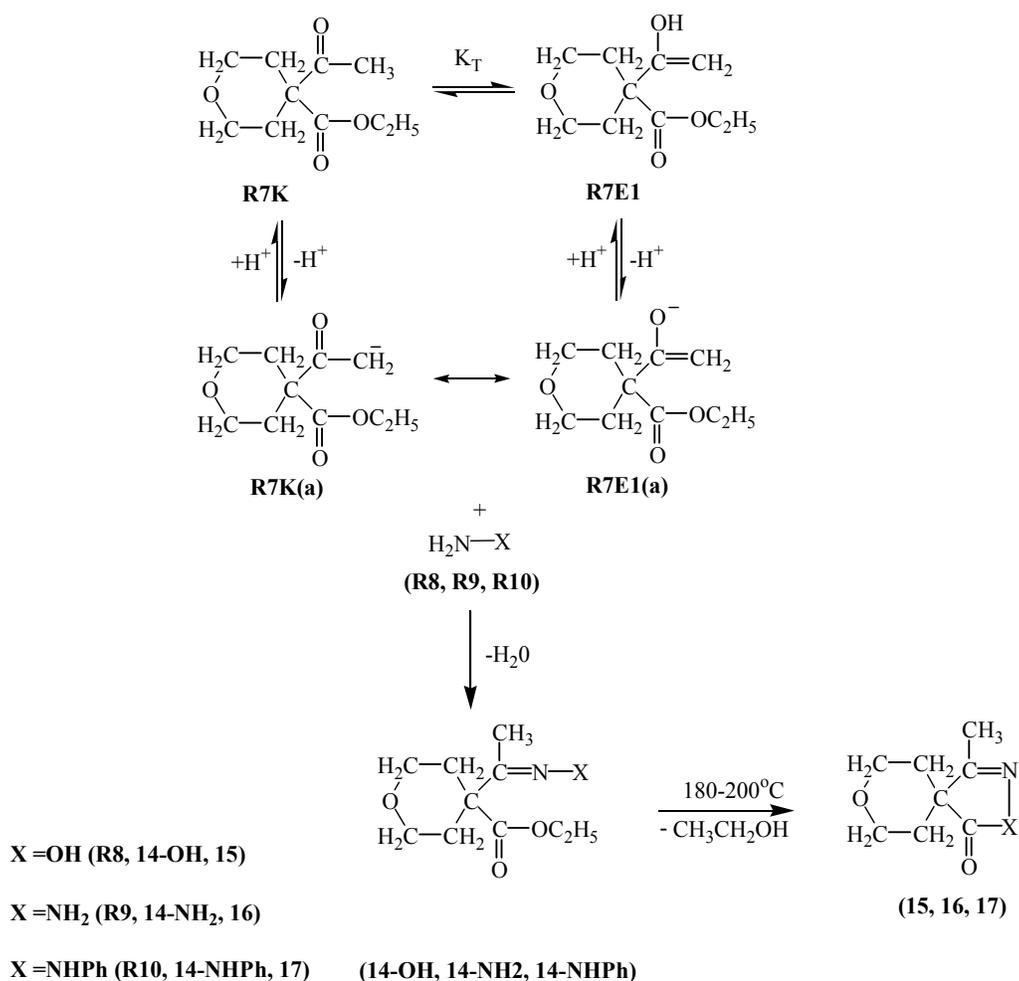
R= CH$_3$ (8,9,10)
R=OC$_2$H$_5$ (11, 12, 13)

13   12

In this way it was proven that the mechanisms of the alkylation reactions basically depend on the β-dicarbonyl compound used, as indicated above. It seems that when the keto-enol equilibrium shifts toward the keto side the formation of O-alkylated products decreases, whereas the formation of C-alkylated products increases.

It is well known that the classical technique for synthesis of 1,2-azolones and barbuturic acid is condensation of acetoacetic and malonic esters with NH$_2$-X type compounds (X=-OH, -NH$_2$, -CONH$_2$, -CSNH$_2$) [23]. To synthesize new spiro derivatives of 1,2-azolone and barbuturic acids the ketoester **8** and diester **11** were condensed with the above mentioned groups.

The reaction of ketoester **8** at 90-95°C with hydroxylamine hydrochloride (**R8**) in 10 % sodium acetate solution affords the oxime of 4-acetyl-4-tetrahydropyran carbamic acid ethyl ester (**14**) as a stable compound in a high yield. When this oxime was heated at 180-200°C to distill off the ethyl alcohol formed upon cyclization, then the compound 3-aza-4-methyl-2,8-dioxaspiro[4.5]dec-3-en-1-one (**15**) was isolated (Scheme 4). The ethoxy and hydroxyl peaks that were observed in the ^{1}H-NMR of compound **14** were absent in the ^{1}H-NMR of compound **15**.

Under similar conditions compound **8** gives condensation reactions with the hydrochloride salts of ketohydrazine and phenylhydrazine to afford 2,3-diaza-4-methyl-8-oxaspiro[4.5]dec-3-en-1-one (**16**) and 2,3-diaza-4-methyl-8-oxa-2-phenylspiro[4.5]dec-3-en-1-one (**17**), respectively, in yields of 71 and 90 %. Diester **11** easily condenses with carbamide or thiocarbamate in absolute ethanol and in the presence of sodium ethoxide to afford the sodium salts of 2,4-diaza-3-hydroxy-9-oxaspiro[4.5]undec-2-ene-1,5-dione (**18**) and 2,4-diaza-9-oxa-3-sulfanylspiro[4.5]undec-2-ene-1,5-dione (**19**), respectively (Scheme 5). When the salts thus obtained were dissolved in water and these solutions were made weakly acidic with HCl they were converted in high yield into 2,4-diaza-9-oxaspiro[4.5]undecane-1,3,5-trione (**20**) and 2,4-diaza-9-oxa-3-thioxospiro[4.5]undecane-1,5-dione (**21**). The above mentioned reactions can be viewed as a simple synthetic method for preparing 1,2-azolones and spiro derivatives of barbituric acids from easily obtainable ketoester (**8**) and diester (**11**) compounds.

Scheme 4

X =OH (R8, 14-OH, 15)

X =NH$_2$ (R9, 14-NH$_2$, 16)

X =NHPh (R10, 14-NHPh, 17)   (14-OH, 14-NH2, 14-NHPh)

Scheme 5

X =O (R12, 18(a), 18E, 20K)

X =S (R13, 19(a), 19E, 21K)
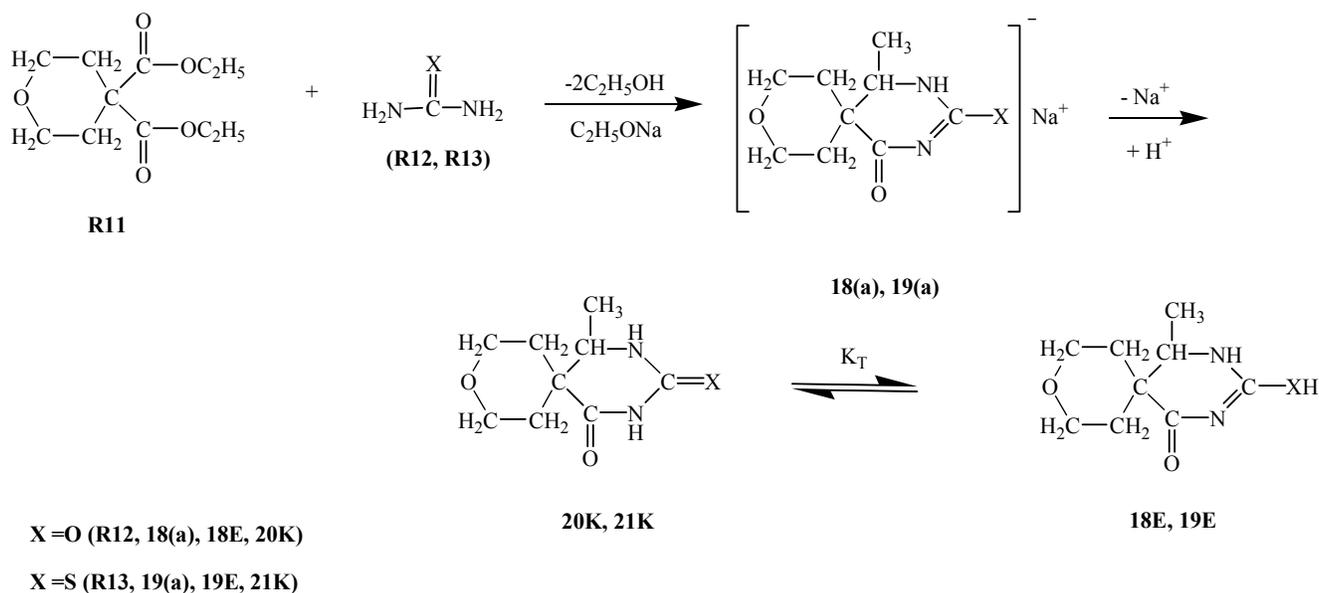
Theoretical Approaches

There is no doubt that one of the most versatile methods for elucidating reaction mechanisms nowadays is the use of theoretical calculations. The superiority of computations comes from the fact that they let us to simultaneously calculate more than one parameter, such as dihedral angles, bond lengths, atomic charges, etc. that are related to structure and thermodynamic parameters, which in turn are related to thermodynamics and kinetics. In the present work we aimed to elucidate the reaction mechanism of some synthesis using semi-empirical calculation approach.

Discussion of Computational Work

The aqueous phase PM3 calculation data are given in Table 1. Using appropriate computed parameters and related equations the tautomeric equilibrium constants, K_T, were calculated for the **Keto ⇌ Enol** tautomerism of the main molecules and the obtained data is collected in Table 2.

For the formation of products **1** and **2** (Scheme 1), although the K_T value of 0.06 for the **R1K ⇌ R1E** equilibrium suggests the predominance of the keto form (i.e. the **R1K** form) in aqueous media, it seems that this situation is reversed in basic media and the enolate form **R1E1(a)** predominates over the carbene form **R1K(a)** and the reaction proceeds by the nucleophilic attack of **R1E1(a)** on **R2** to first form compound **1** and then it proceeds via a second attack of **R1E1(a)** on **1** to form compound **2**. Further evidence to support this argument is the higher nucleophilicity, η; and the higher basicity (i.e. smaller pK_a value for deprotonation) of **R1E1(a)** compared to the **R1K1(a)** form (Tables 1 and 2) .

Table 1. Liquid phase PM3 calculated physical parameters of the studied molecules.

Compound	ΔH (cal mol⁻¹)	ΔS (cal mol⁻¹)	ΔG (kcal mol⁻¹)[a]	ΔH$_f$ (kcalmol⁻¹)	HOMO	LUMO	Nucleophilicity (η)[b]	Experimental Yield (%)
			T = 343 K (ε = 47.24)					
R1K	6249.087	86.069	-23.273	-105.766	-11.329	0.018	-11.347	
R2	5604.130	85.404	-23.689	-75.785	-10.857	0.718	-11.575	
1	9064.189	108.952	-28.306	-37.861	-10.065	-1.863	-8.202	59
2	12782.249	131.221	-32.227	-103.808	-9.921	-1.859	-8.062	15
3	11268.273	120.470	-30.053	-99.461	-9.936	-0.802	-9.134	57
4	15983.897	146.434	-34.243	-132.297	-9.834	-0.753	-9.081	16
R1K(a)	12604.066	98.677	-21.239	-185.011	-8.685	0.625	-9.310	
R1E1	13327.849	101.118	-21.356	-87.118	-9.904	0.017	-9.921	
R1E1(a)	12604.066	97.186	-20.731	-185.181	-8.804	-0.406	-8.398	
R3K	7242.087	93.873	-24.956	-69.146	-10.145	-0.739	-9.406	
R3K(a)	18143.301	120.397	-23.153	-147.226	-8.707	-0.105	-8.602	
R3E1	18129.246	119.193	-22.754	-47.677	-9.913	-0.538	-9.375	
R3E1(a)	18190.937	120.608	-23.178	-148.021	-8.847	0.098	-8.945	
R3E2	18222.994	119.722	-22.842	-47.937	-10.041	-0.155	-9.886	
R3E2(a)	18924.776	124.037	-23.620	-146.083	-8.685	-0.320	-8.365	
H₃O⁺	2750.472	47.158	-13.425	61.928	-15.994	1.652	-17.646	
H₂0	2730.416	46.135	-13.095	-61.414	-12.794	4.268	-17.062	
R4K	8118.436	97.785	-25.422	-111.147	-11.392	0.065	-11.457	
5	10389.545	114.701	-28.953	-142.383	-10.042	-0.481	-9.561	46
6	11016.198	115.088	-28.459	-148.209	-10.938	-0.143	-10.795	24
7	15999.285	145.441	-33.887	-220.448	-10.033	-0.509	-9.524	12
R4K(a)	18370.540	119.539	-22.631	-193.605	-8.797	0.436	-9.233	
R4E1	19259.580	122.297	-22.688	-92.314	-9.970	-0.437	-9.533	
R4E1(a)	18483.670	120.297	-22.823	-193.418	-8.779	0.444	-9.223	
R5K	6741.119	90.785	-24.398	-149.949	-11.482	0.049	-11.531	
8	10185.203	111.495	-28.058	-185.961	-11.056	-0.037	-11.019	55
9	10080.245	113.231	-28.768	-183.145	-10.103	-0.223	-9.880	48
10	14245.501	137.720	-32.992	-292.902	-9.958	-0.297	-9.661	10
R5K(a)	15761.846	122.368	-26.210	-229.112	-8.791	0.665	-9.456	
R5E1	16477.994	114.511	-22.799	-129.609	-10.005	-0.251	-9.754	
R5E1(a)	16726.542	117.887	-23.709	-228.808	-8.826	0.634	-9.460	
R5E2	16610.422	115.076	-22.861	-123.669	-9.608	-0.196	-9.412	
R5E2(a)	15770.958	112.325	-26.187	-229.079	-8.789	0.666	-9.455	
R6K	8091.277	100.368	-26.335	-195.638	-11.606	0.308	-11.914	
11	10618.015	114.735	-28.736	-230.841	-11.146	0.184	-11.330	57
12	10731.533	118.688	-29.978	-245.052	-10.955	0.144	-11.099	10
13	15969.012	148.524	-34.974	-423.969	-11.063	-0.061	-11.002	14
R6K(a)	17368.114	117.216	-22.837	-273.403	-8.799	0.867	-9.666	
R6E1	19569.412	126.417	-23.792	-168.694	-10.095	-0.201	-9.894	
R6E1(a)	17334.207	117.216	-22.871	-273.373	-8.792	0.870	-9.662	

Table 1. Cont.

Compound	ΔH (cal mol⁻¹)	ΔS (cal mol⁻¹)	ΔG (kcal mol⁻¹)ᵃ	ΔH$_f$ (kcalmol⁻¹)	HOMO	LUMO	Nucleophilicity (η)ᵇ	Experimental Yield (%)
				T = 363 K (ε = 78.40)				
R7K	11364.453	114.981	-30.374	-185.028	-11.063	-0.041	-11.022	
R8	3563.453	59.771	-18.133	-17.071	-10.560	2.442	-13.002	
R9	3637.903	59.273	-17.878	15.501	-9.707	2.716	-12.423	
R10	6603.077	85.778	-24.534	42.036	-9.330	-0.082	-9.248	
14-OH	12074.647	118.843	-31.065	-142.197	-10.704	0.012	-10.716	91
14-NH₂	12606.540	121.978	-31.671	-115.892	-9.717	0.198	-9.915	91
14-NHPh	14384.721	131.234	-33.253	-84.046	-9.060	-0.157	-8.903	91
R7K(a)	24864.521	141.158	-26.376	-243.164	-8.464	0.652	-9.116	
R7E1	25643.604	143.758	-26.541	-151.205	-9.905	0.403	-10.308	
R7E1(a)	11364.453	139.490	-39.270	-243.571	-8.501	0.685	-9.186	
H₃O⁺	2919.050	47.636	-14.373	62.097	-15.994	1.642	-17.636	
H₂O	2891.295	46.591	-14.021	-61.254	-12.794	4.268	-17.062	
OH⁻	2524.759	42.407	-12.869	-142.332	-11.201	6.455	-17.656	
				T = 473 K (ε = 78.40)				
14-OH	20047.920	137.927	-45.192	-134.917	-10.704	0.012	-10.716	
14-NH₂	20884.456	141.853	-46.212	-107.621	-9.717	0.200	-9.917	
14-NHPh	24748.689	156.029	-24.120	-73.683	-9.060	-0.157	-8.903	
15	15544.809	116.427	-39.525	-81.917	-11.084	-0.640	-10.444	95
16	15831.565	117.270	-39.637	-59.973	-9.654	-0.446	-9.208	71
17	20574.229	136.912	-44.185	-25.753	-9.800	-0.461	-9.339	90
CH₃CH₂OH	6808.702	74.566	-28.461	-59.262	-11.102	3.295	-14.397	
				T = 373 K (ε = 25.30)				
R11	13085.134	123.690	-33.051	-228.325	-11.137	0.188	-11.325	
R12	5027.115	72.694	-22.088	-60.778	-9.847	0.931	-10.778	
R13	5120.630	73.307	-22.223	-6.014	-9.697	-0.457	-9.240	
18(a)	11732.778	114.256	-30.885	-243.788	-9.322	0.771	-10.093	96
18E	12135.123	116.007	-31.136	-137.535	-9.974	-0.335	-9.639	
20K	11753.872	113.663	-30.642	-147.469	-10.046	-0.109	-9.937	92
19(a)	11673.276	114.631	-31.084	-191.810	-9.579	-0.376	-9.203	94
19E	12750.364	120.777	-32.274	-79.395	-9.802	-0.788	-9.014	
21K	12047.588	116.145	-31.274	-86.109	-10.326	-1.368	-8.958	90
H₃O⁺	3004.184	47.867	-14.850	62.182	-15.994	1.642	-17.636	
H₂O	2791.943	46.591	-14.668	-62.254	-12.794	4.268	-17.062	

ᵃΔG = ΔH -TΔS, ᵇη = E$_{HOMO}$-E$_{LUMO}$

Table 2. Liquid phase PM3 calculated physical parameters of studied molecules.

Reaction	$\delta\Delta G_{(T)}$ [a]	pK_T [b]	K_T [c]	$\delta\Delta G_{(BH)}$ [d]	pK_a [e]
T = 343 K, (ε = 47.24)					
R1K ⇌ R1E	1.917	1.221	0.060	-	-
R1K ⇌ R1K(a)	-	-	-	1.703	1.085
R1E ⇌ R1E(a)	-	-	-	0.294	0.187
R3K ⇌ R3E1	2.202	1.403	0.040	-	-
R3K ⇌ R3E2	2.114	1.347	0.045	-	-
R3K ⇌ R3K(a)	-	-	-	1.472	0.938
R3E1 ⇌ R3E1(a)	-	-	-	-0.755	-0.481
R3E2 ⇌ R3E2(a)	-	-	-	-1.109	-0.706
R4K ⇌ R4E	2.734	1.742	0.018	-	-
R4K ⇌ R4K(a)	-	-	-	2.460	1.567
R4E ⇌ R4E(a)	-	-	-	-0.466	-0.297
R5K ⇌ R5E1	1.599	1.019	0.096	-	-
R5K ⇌ R5E2	1.537	0.979	0.105	-	-
R5K ⇌ R5K(a)	-	-	-	-2.143	-1.365
R5E1 ⇌ R5E1(a)	-	-	-	-1.241	-0.791
R5E2 ⇌ R5E2(a)	-	-	-	-3.657	-2.330
R6K ⇌ R6E	2.543	1.620	0.024	-	-
R6K ⇌ R6K(a)	-	-	-	3.167	2.017
R6E ⇌ R6E(a)	-	-	-	0.590	0.376
T = 363 K, (ε = 78.40)					
R7K ⇌ R7E	3.833	2.307	4.932E-3	-	-
R7K ⇌ R7K(a)	-	-	-	3.646	2.194
R7E ⇌ R7E(a)	-	-	-	-13.081	-7.875
T = 373 K, (ε = 25.30)					
20K ⇌ 18E	-0.494	-0.298	1.986	-	-
21K ⇌ 19E	-0.955	-0.560	3.631	-	-

[a] $\delta\Delta G_{(T)} = \Delta G_{(Enol)} - \Delta G_{(Keto)}$; [b] $pK_T = \delta\Delta G_{(T)} / 2.303RT$; [c] $pK_T = -\log K_T$; [d] $\delta\Delta G_{(BH)} = [\Delta G_{(B^-)} + \Delta G_{(H3O^+)}] - [\Delta G_{(BH)} + \Delta G_{(H2O)}]$; [e] $pK_a = \delta\Delta G_{(BH)} / 2.303RT$

For the formation of products **3** and **4** (Scheme 1), although K_T values of 0.04 and 0.05 for the **R3K ⇌ R3E1** and **R3K ⇌ R3E2** equilibria, respectively, suggest the predominance of the keto form (i.e. **R3K**) in aqueous media, it appears that in basic media a competition among two enolate ions and one carbene ion becomes inevitable. Although the respective nucleophilicity values are ranked in the increasing order **R3E1(a) < R3K(a) < R3E2(a)**, the magnitudes of the differences are not too large (Table 1). The same analogy exists within the pK_a values: the basicity increases (or acidity decreases)

in the order **R3K(a) < R3E1(a) < R3E2(a)** and again the magnitudes of the differences might allow for competition. It seems that in this case the competition was won by the **R3E1(a)** enolate ion which attacks **R2** to form compound **3** in 57 % yield. An attack of the second **R3E1(a)** enolate ion on compound **3** then afforded compound **4** in 16 % yield.

For the formation of products **5-7** (Scheme 2) a K_T value of 0.02 for the **R4K** ⇌ **R4E** equilibrium suggests the predominance of the keto form (i.e. **R4K**) in aqueous media, but again in basic media it would seem that a competition exists between the enolate ion **R4E(a)**, formed by deprotonation of the enol form **R4E**, and the carbene ion **R4K(a)**, which forms by deprotonation of the keto form **R4K**. Since the yield of compound **5** (46%) is the highest, that implies that the **R4E(a)** enolate ion attacks **R2** to form compound this compound. A further attack of enolate **R4E(a)** ion on compound **5** affords compound **7** in 12 % yield. Alternatively, when carbene ion **R4K(a)** attacks **R2** then compound **6** is formed (in 24 % yield) by an intramolecular ring closure reaction as follows:

The slightly higher nucleophilicity and stronger basic strength of **R4E(a)** compared to **R4K(a)** are indicative of a high yield for compound **5** than that of compound **6** (Tables 1 and 2). For the formation of compounds **8-10** (Scheme 3) K_T values of 0.10 and 0.11 for the **R5K** ⇌ **R5E1** and **R5K** ⇌ **R5E2** equilibria indicate the favorability of the keto form **R5K** over the enol forms **R5E1** and **R5E2** (Table 2). However, in basic media there seems to be a competition among the enolate ions and carbene ion. When we consider the higher yield of compound **8** it seems that this time the enolate ion **R5K(a)** is favored and this ion attacked **R2** to afford compound **8** in 55 % yield. A competitive reaction is the attack of enolate ion **R5E1(a)** on **R2** to afford compound **9** in a yield of 49 %. Attack of the same enolate ion **R5E1(a)** on compound **9** affords the molecule **10** in 10 % yield. The nucleophilicity of those three species were found to be in the increasing order: **R5E1(a) < R5K(a) < R5E2(a),** which accounts for the higher yield of the **R5E2(a)** enolate initiated reaction giving compounds **9** and **10** (total yield is 59 %) (Table 1). The basicity order is found be be in the increasing order **R5E1(a) < R5K < R5E2(a)** (Table 2). The higher basicity (or lower acidity) of **R5E2(a)** is further evidence for the higher yield of compounds **9** and **10**.

For the formation of compounds **11-13** (Scheme 3) a K_T value of 0.02 for the **R6K $\rightleftharpoons$ R6E** equilibrium suggests the ketone form **R6K** is favored (Table 2). When we take into account the percent yield and the structures of the products **11-13** it seems that only the carbene ion **R6K(a)**, formed by deprotonation of **R6K** in basic media, acts as nucleophile to attack **R2** and give compound **12** in 10 % yield and a subsequent intramolecular rearrangement of compound **12** in basic media produces compound **11** in a 57 % yield. Alternatively, attack of the carbene ion on **12** produces compound **13** in 14 % yield. The nucleophilicities of enolate and carbene ions are almost the same (Table 1) but the basicity of the carbene ion is greater than that of the enolate ions (Table 2) which explains why the enolate ion is inactive in this reaction. For the formation of compounds **14-OH, 14-NH₂** and **14-NHPh** (Scheme 4) the K_T value of 0.01 for the **R7K $\rightleftharpoons$ R7E** equilibrium suggests the keto form **R7K** is favored (Table 2). It seems that the formation of compounds **14-OH, 14-NH₂** and **14-NHPh** occurs by nucleophilic attack of **R8**, **R9** and **R10** on **R7K,** which is more electropositive compared to **R7E**. These products were found to produced in about 91 % yield. These products rearrange into compounds **15**, **16** and **17** respectively. The overall mechanism can be summarized as follows:
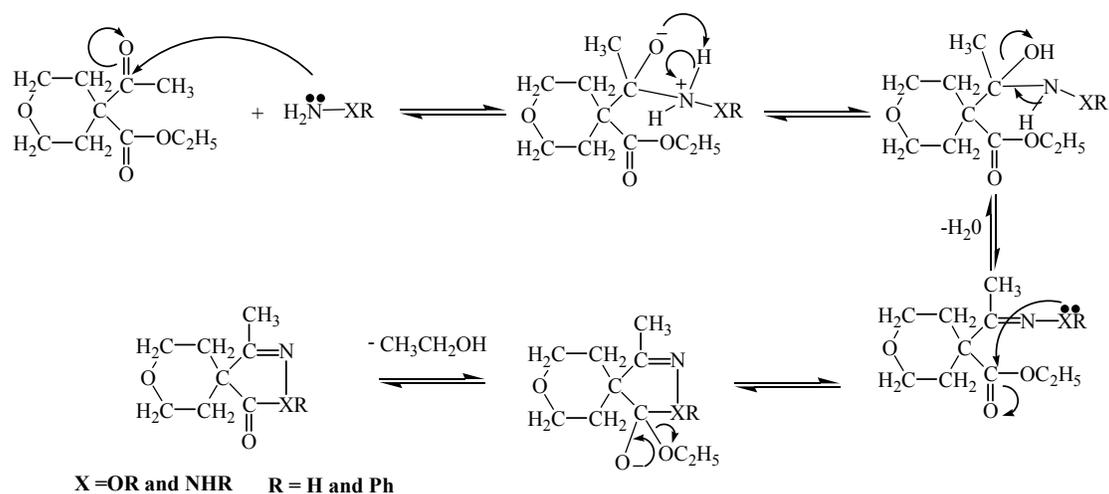
The tautomeric equilibrium constants of 1.99 and 3.63 for **20K $\rightleftharpoons$ 18E** and **21K $\rightleftharpoons$ 19E** (Table 2) indicate the predominance of enol forms **18E** and **19E** over **20K** and **21K** respectively (Scheme 5). The bigger nucleophilicity of 18E and 19E well explains the high yields of those compounds (Table 1).

Conclusions

It seems that theoretical calculations can give some clues about the mechanism and the possible yields of some synthetic reactions. However, to be more conclusive further work should be done using other calculation methods and different basis sets which might give better correlation with experimental values.

Experimental

General

The ^{1}H-NMR spectra were recorded using a JEOL C-90 MHz spectrometer at room temperature. Elemental analysis were done using a Carlo Erba EA 1108 type instrument.

Syntheses; general method for the alkylation reactions of β-carbonyl derivatives with 2-chloro-1-(2-chloroethoxy)ethane

The appropriate β-dicarbonyl compound (1 mole) was added to a mixture of 2-chloro-1-(2-chloroethoxy)ethane (1.2 mole) and K_2CO_3 (2.5 mole) in DMSO (400 mL) and stirred vigorously at 70°C for 20h. The reaction mixture was then cooled down and water was added until all the K_2CO_3 was dissolved. The solution was then extracted with ether a few times. The combined ether extracts were washed with water till neutral and dried over anhydrous Na_2SO_4. After filtration and evaporation of the ether the residue was distilled under vacuum to separate the products.

Alkylation of acetylacetone: Acetylacetone (0.5 mole), 2-chloro-1-(2-chloroethoxy)ethane (0.6 mole), K_2CO_3 (1.25 mole) and DMSO (200 mL) afforded the following compounds:

4-[2-(2-chloroethoxy)ethoxy]pent-3-en-2-one (**1**): c.a. 60.9 g (59 % yield); b.p. 104-105°C (1 mm Hg); n_D^{20}:1.1258; d_4^{20}: 1.4964; ^{1}H-NMR (CCl$_4$): δ(ppm) = 1.94 (s, 3H), 2.12 (s, 3H), 3.37-3.87 (m, 8H), 5.36 (s, 1H); Anal. Calc. for $C_9H_{15}ClO_3$: C, 52.30; H, 7.26; Cl, 17.19 %, found: C, 52.33; H, 7.28; Cl, 17.17 %.

4-{2-[2(1-methyl-3-oxobut-1-enyloxy)ethoxy}pent-3-en-2-one (**2**): c.a. 20.8 g (45 % yield); b.p. 160-161 ^{o}C (1 mm Hg); n_D^{20}:1.4997; d_4^{20}:1.0935; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.96 (s, 6H), 2.11 (s, 6H), 3.73 (m, 8H), 5.36 (s, 2H); Anal. Calc. for $C_{14}H_{22}O_5$: C, 62.61; H, 8.17 %, found: C, 62.22; H, 8.15 %.

Alkylation of benzoylacetone: Benzoylacetone (0.2 mole), 2-chloro-1-(2-chloroethoxy)ethane (0.24 mole), K_2CO_3 (0.5 mole) and DMSO (100 mL) afforded the following compounds:

3-[2-(2-chloroethoxy)ethoxy]-1-phenylbut-2-en-1-one (**3**): c.a. 30.7 g (57.2 % yield); b.p. 111-113 ^{o}C (1 mm Hg); n_D^{20}:1.5305; d_4^{20}:1.1722; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.92 (s, 3H), 3.39-3.88 (m, 8H), 7.36-7.96 (m, 5H); Anal. Calc. for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.33; Cl, 13.22 %, found: C, 62.55; H, 6.32; Cl, 13.24 %.

3-{2-[2(1-methyl-3-oxo-3-phenylprop-1-enyloxy)ethoxy]ethoxy}1-phenylbut-2-en-1-one (**4**): c.a. 12.6 g (16 % yield); b.p. 154-157°C (1 mm Hg); n_D^{20}:1.5305; d_4^{20}:1.1580; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.95 (s, 6H), 7.34-7.97 (m, 10H); Anal. Calc. for $C_{24}H_{26}O_5$: C, 73.10; H, 6.60 %, found: C, 73.12; H, 6.58 %.

Alkylation of dimedone: Dimedone (0.43 mole), 2-chloro-1-(2-chloroethoxy)ethane (0.6 mole), K_2CO_3 (1.25 mole) and DMSO (400 mL) afforded the following compounds:

3-[2-(2-Chloroethoxy)ethoxy]-5,5-dimethylcyclohex-2-en-1-one (**5**): c.a. 32 g, (46.3 % yield); b.p. 165-166 ^{o}C (1 mm Hg); n_D^{20}:1.5130; d_4^{20}:1.2554; ^{1}H-NMR (CCl$_4$): δ (ppm) = 0.98 (s, 6H), 2.00 (s, 2H), 3.85 (t, 2H), 5.15 (s, 1H); Anal. Calc. for $C_{12}H_{19}ClO_3$: C, 58.42; H, 7.71; Cl, 14.40 %. Found: C, 58.41; H, 7.33; Cl, 14.38 %.

3,3-Dimethyl-9-oxaspiro[5.5]undacane-1,5-dione (**6**) : c.a. 25 g (28.3 % yield); b.p. 157-158°C (1 mm Hg); ^{1}H-NMR (CCl$_4$): δ (ppm) = 0.60 (s, 6H), 1.81 (t, 4H), 2.48 (s, 4H), 3.55 (m, 8H), 5.14 (s, 2H); Anal. Calc. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57 %, found: C, 68.56; H, 8.58 %.

3-{2-[2-(5,5-Dimethyl-3-oxocyclohex-1-enyloxy)ethoxy]ethyl}-5,5-dimethlycyclohex-2-en-1-one (**7**): c.a. 21.6 g (12.3 % yield); b.p. 222-230°C (1 mm Hg); ^{1}H-NMR (CCl$_4$): δ (ppm) = 0.95 (s, 12H), 2.05 (s, 4H), 2.27 (s, 4H), 3.69 (m, 8H), 5.14 (s, 2H); Anal. Calc. for $C_{20}H_{30}O_5$: C, 68.52; H, 8.57 %, found: C, 68.80; H, 8.62 %.

Alkylation of acetyl acetate: Acetyl acetate (1 mole), 2-chloro-1-(2-chloroethoxy)ethane (1.2 mole), K_2CO_3 (2.5 mole) and DMSO (400 mL) afforded the following compounds:

1-(4-Acetylperhydro-2H-pyran-4-yl)ethan-1-one (**8**): c.a. 110 g (55 % yield); b.p. 78-79°C (1 mm Hg); n_D^{20}:1.4648; d_4^{20}:1.1065; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.25 (s, 3H), 2.06 (m, 4H), 4.12 (q, 2H); Anal. Calc. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00 %, found: C, 60.07; H, 8.05 %.

Ethyl 3-[2-(2-chloroethoxy)ethoxy]but-2-enoate (**9**): c.a. 48 g (48 % yield); b.p. 114-116°C (1mm Hg); n_D^{20}:1.4755; d_4^{20}:1.1342; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.25 (s, 3H), 2.55 (s, 3H), 3.37-4.85 (m, 10H), 4.88 (s, 1H); Anal. Calc. for $C_{10}H_{14}ClO_4$: C, 50.84; H, 7.19; Cl, 15.01, found: C, 50.72; H, 7.21; Cl, 14.99 %.

Ethyl 3-(2-{2-[(2-(ethoxycarbonyl)-1-methylvinyloxy]ethoxy}ethoxy)but-2-enoate (**10**): c.a. 33 g (10 % yield); b.p. 179-181°C (1 mm Hg); ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.14 (t, 6H), 2.19 (s, 6H), 3.71 (m, 8H), 3.95 (q, 4H);4.81 (s, 2H); Anal. Calc. for $C_{16}H_{26}O_7$: C, 58.18; H, 7.88, found: C, 56.16; H, 7.89 %.

Alkylation of malonic ester: Malonic ester (1 mole), 2-chloro-1-(2-chloroethoxy)ethane (1.2 mole), K_2CO_3 (2.5 mole) and DMSO (400 mL) afforded the following compounds:

Ethyl 4-(ethoxycarbonyl)perhydro-2H-pyran-4-carboxylate (**11**): c.a. 130 g (56.5 % yield); b.p. 179-181°C (1 mm Hg); n_D^{20}:1.4554; d_4^{20}:1.1081; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.12 (t, 6H), 1.84 (m, 4H), 4.12 (q, 4H); Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83, found: C, 57.37; H, 7.81 %.

Diethyl 2-[2-(2-chloroethoxy)ethyl]propane-1,3-dioate (**12**): c.a. 27 g (10.1 % yield); b.p. 116-118$^\text{o}$C (1 mm Hg); n_D^{20}:1.4542; d_4^{20}:1.1346; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.30 (t, 6H), 2.00 (m, 2H), 3.50 (m, 7H), 4.12 (q, 4H); Anal. Calc. for C$_{11}$H$_{19}$ClO$_5$: C, 49.53; H, 7.13; Cl, 13.32, found: C, 49.51; H, 7.11; Cl, 13.30 %.

Diethyl 2-{2-[3,3-bis(ethoxycarbonyl)propoxy]ethyl}propane-1,3-dioate (**13**): c.a. 54 g (13.8 % yield); b.p. 186-188$^\text{o}$C (1 mm Hg); n_D^{20}:1.4552; d_4^{20}:1.1175; ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.12 (t, 12H), 1.87 (m, 4H), 3.36 (m, 6H) 4.00 (q, 8H); Anal. Calc. for C$_{18}$H$_{30}$O$_9$: C, 55.39; H, 7.69, found: C, 57.37; H, 7.70 %.

Synthesis of 1,2-azolones

Ketoester **8** (0.10 mol), the hydrochloride salts of hydroxylamine, hydrazine or phenyl hydrazine (0.11 mol) and sodium acetate (10 %, 0.12 mol) solutions were mixed and stirred at 90$^\text{o}$C for 6 h. The precipitate was filtered off, washed with water, dried and recrystallized. If a liquid product was obtained the reaction mixture was extracted with ether two or three times. The ether extracts were mixed and washed with water, then dried over Na$_2$SO$_4$. After evaporating the ether the residue was distilled under vacuum to separate the product.

Ethyl 4-((hydroxyamino)ethyl)perhydro-2H-pyran-4-carboxylate (**14**): Ketoester **8** (0.05 mole) and hydroxylamine hydrochloride (0.05 mole) mixture afforded 9.8 g of the product (90.8 % yield), b.p. 116-117$^\text{o}$C (1 mm Hg); ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.25 (t, 3H), 1.76 (m, 4H), 2.00 (s, 3H), 3.25-3.87 (m, 4H), 4.12 (q, 2H), 9.25 (s, 1H); Anal. Calc. for C$_{10}$H$_{17}$NO$_4$: C, 55.81; H, 7.91; N, 6.51, found: C, 55.78; H, 7.82; N, 6.49 %.

3-Aza-4-methyl-2,8-dioxaspiro[4.5]dec-3-en-1-one (**15**): Heating of oxime **14** (0.045 mole) at 180-200$^\text{o}$C afforded product **15,** c.a. 8 g (95 % yield), b.p. 98-99 $^\text{o}$C (1 mm Hg); ^{1}H-NMR (CCl$_4$): δ (ppm) = 1.75 (m, 4H), 2.00 (s, 3H), 3.75 (m, 4H); Anal. Calc. for C$_8$H$_1$NO$_3$: C, 56.81; H, 6.51; N, 8.28, found: C, 56.78; H, 6.50; N, 8.29 %.

2,3-Diaza-4-methyl-8-oxaspiro[4.5]dec-3-en-1-one (**16**): Reaction of ketoester **8** (0.1 mole), hydrazine hydrochloride (0.1 mole) and sodium acetate (1.2 mole) in water (90 mL) afforded the product **16,** c.a. 12 g (71.14 % yield), m.p. 169-171$^\text{o}$C (from ethyl alcohol); ^{1}H-NMR (DMSO-d$_6$): δ (ppm) = 1.72-2.19 (m, 4H), 2.28 (s, 3H), 3.84-4.46 (m, 4H), 11.20 (s, 1H broad); Anal. Calc. for C$_8$H$_{12}$N$_2$O$_2$: C, 57.14; H, 7.14; N, 16.67, found: C, 57.12; H, 7.13; N, 66.69 %.

2,3-Diaza-4-methyl-8-oxa-2-phenylspiro[4.5]dec-3-en-1-one (**17**): A mixture of ketoester **8** (0.1 mole) phenylhydrazine hydrochloride (0.11 mole) and sodium acetate (0.27 mole) in water (90 mL) afforded the product **17**, c.a. 22 g (90 % yield), m.p. 94-96$^\text{o}$C (from ethyl alcohol); ^{1}H-NMR (DMSO-d$_6$):

δ (ppm) = 1.84-2.26 (m, 4H), 2.39 (s, 3H), 3.81-4.46 (m, 4H); Anal. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.44; found: C, 68.78; H, 7.88; N, 11.40 %.

General method for the preparation of barbituric acids.

A mixture of diester **11** (0.05 mol), metallic sodium (0.05 mol) and carbamide or thiocarbamide in absolute ethanol (50 mL) was mixed for 7 h at 100°C. The precipitated sodium salt was filtered, washed with absolute ethanol and dissolved in water. The solution was acidified with HCl. The precipitate was filtered and recrystallized from water.

2,4-Diaza-3-hydroxy-9-oxaspiro[4.5]undec-2-ene-1,5-dione sodium salt (**18**): A mixture of diester **11** (0.05 mole), sodium metal (0.05 mole) and carbamide (0.05 mole) afforded the product **18,** c.a. 10.6 g (96 % yield).

2,4-Diaza-9-oxaspiro[4.5]undecane-1,3,5-trione (**20**): The salt **18** (0.048 mole) afforded the acid **20**, c.a. 9.1 g (92 % yield) m.p. 166-167°C;. ¹H-NMR (DMSO-d₆): δ (ppm) = 2.25 (m, 4H), 3.83 (m, 4H), 13.08 (s, 2H broad); Anal. Calc. for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.05; N, 14.14, found: C, 48.49; H, 5.04; N, 14.10 %.

2,4-Diaza-9-oxa-3-sulfanylspiro[4.5]undec-2-ene-1,5-dione sodium salt (**19**): A mixture of diester **11** (0.05 mole), sodium metal (0.05 mole) and thiocarbamide (0.05 mole) afforded the product **19**, c.a. 11.0 g, (94 % yield).

2,4-Diaza-9-oxa-3-thioxospiro[4.5]undecane-1,5-dione (**21**): The salt **19** (0.046 mole) afforded the acid **21,** c.a. 9.6 g (90 % yield), m.p. 191-193°C; ¹H-NMR (DMSO-d₆): δ (ppm)=2.48 (m, 4H), 3.92 (m, 4H), 7.37; 9.80 and 10.72 (s, 2H broad); Anal. Calc. for $C_8H_{10}N_2O_3S$: C, 44.87; H, 4.67; N, 13.08; S, 14.95, found: C, 44.87; H, 4.19; N, 13.02; S, 15.99 %.

Computational Details

Theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) using PM3 semi empirical SCF-MO method in the MOPAC 7.0 program [24], implemented on an Intel Pentium4 400 MHz computer. All the structures were optimized to a gradient norm of <0.1 in the liquid phase. The initial estimates of the geometry of all structures were obtained by a molecular mechanics program of CS ChemOffice Pro for Windows [25], followed by full optimized of all geometrical variables (bond lengths, band angles and dihedral angles), without any symmetry constraint, using semi empirical PM3 quantum chemical methods in the MOPAC 7.0 program.

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