MALEAMIC ACIDS CYCLODEHYDRATION WITH ANHYDRIDES. DFT STUDY IN THE GAS PHASE AND SOLUTION

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Hybrid density functional B3LYP/6-31G(d,p) level of theory calculations in the gas phase and solution show that maleamic acids cyclodehydration to the corresponding maleimide and isomaleimide takes place in two stages, the first one leads to a mixed anhydride as a reaction intermediate. Isomaleimides are kinetically favored in the presence of acetic anhydride for Ph- substituent. Bu-substituent appears to make an exception, as long as maleimide formation is both thermodynamically and kinetically favored. If hydrogen atoms of acetic anhydride are replaced by fluorine, the activation barriers strongly decrease, recommending trifluoroacetic anhydride as a more effective dehydrating agent. Our computations reveal the favorable cyclic structure optimized transition-state for all the reaction pathways. Experimental data also confirm our theoretically results.

INTRODUCTION

N-Maleimide derivatives (**M**) have attracted great interest due to their potential applications in organic synthesis.[1] Recently, it has also been demonstrated that human hemoglobin chemically modified with maleimide-polyethylene glycol is a blood substitute and can be used on any blood type.[2] On the other hand, it has been shown that **M** have various applications in polymer chemistry.[3]

A standard method for **M** synthesis is the cyclic dehydration of the corresponding *N*-substituted maleamic acids (**MA**).[4,5] Simple heating or direct fusion of the corresponding anhydride and amine without isolation of the intermediate **MA** are also common methods. Various dehydrating agents have been used for cyclodehydration under mild conditions in order to avoid the decomposition or other undesired secondary reactions. Under certain conditions the reaction mixture has also been found to contain beside **M** isomer, *N*-substituted isomaleimide (**IM**) in different amounts. Acetic

anhydride without or with fused sodium acetate,[6-9] trifluoroacetic anhydride without an acid acceptor,[7] or in the presence of triethylamine,[10,11] acetyl chloride-triethylamine,[8] *N,N'*-dicyclohexylcarbodiimide,[6,10,12] etc. were mentioned as possible dehydration agents for **MA** cyclic dehydration. **IM** itself represents a potentially interesting class of compounds. They are used also as monomers in polymer synthesis.[13]

It becomes clear the importance of the study of cyclodehydration (CDH) mechanism in order to predict the best condition the reaction to **M** or **IM** formation to take place. Sauers reported that CDH of *N*-arylmaleamic acids in the presence of acetic anhydride alone has given mixtures of **IM** and **M**. *N*-arylmaleamic acids are supposed first to react with anhydride with a mixed anhydride formation, that can further undergo intramolecular cyclization yielding a mixture of **IM** and **M** (Scheme 1).[4] Some authors supposed that the cyclisation of mixed anhydride intermediate to the **M** occurs by acylation of the amide-nitrogen atom, whilst **IM** may be produced *via* the enol tautomer of the amide.[8,11]
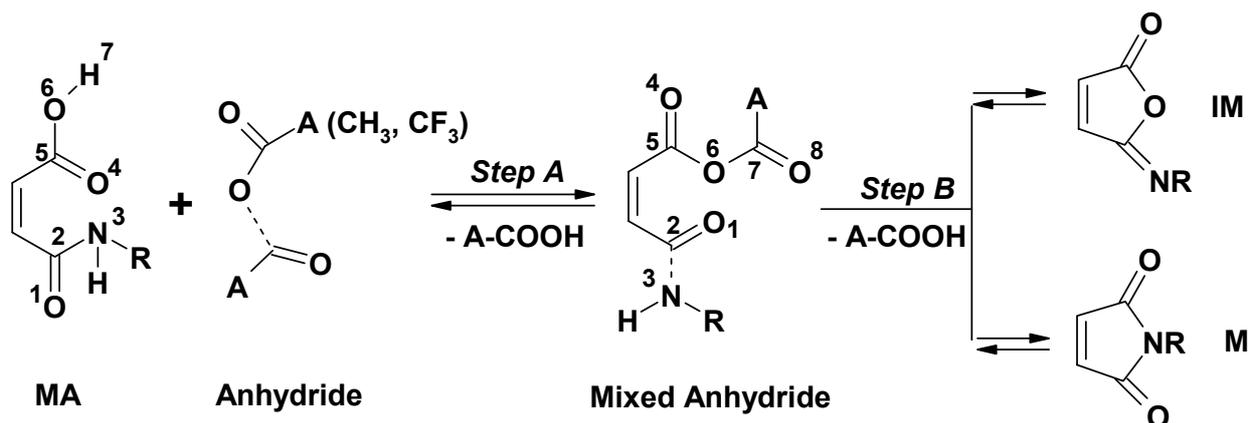
Scheme 1 – General reaction mechanism of cyclic dehydration of **MA** with anhydrides as dehydration agents.

Following the experimental studies, a fundamental interest appeared in understanding the parameters that influence the selectivity of these reactions. Our previous study of **MA** cyclic dehydration to **M** and **IM** with acetic anhydride in the presence of acetate anion or triethylamine indicated as most probable an ionic reaction mechanism.[14] An ionic mechanism is also supported elsewhere.[15] The presence of tertiary base leads experimentally to the darkness of the reaction mixture, suggesting that also undesired reactions occurred.

There are a lot of examples describing the reactions that proceed by different mechanisms in different work conditions. In order to extend our study, we report here a theoretical investigation at DFT (B3LYP) level of theory in the gas phase and solution of the possible mechanisms of CDH reaction in the presence of acetic anhydride, and trifluoroacetic anhydride, in the absence of acetate anion or tertiary base. The most important part of the reaction mechanism represents the transition state structure that explains chemical transformations as well as the reaction conditions required to enforce the transformations.[16]

METHODS AND THEORETICAL BACKGROUND

DFT computations were performed using GAUSSIAN 98[17] at B3LYP/6-31G(d) level of theory. A proper SCRF model for the calculation of the stationary points on the energy hypersurface, minima as well as transition structures, is the Onsager reaction field model.[18] Dimethylsulfoxide was the proper solvent for both theoretical and experimental investigations of the reaction mechanisms.

The energy was considered as the sum of electronic correction in solvent and thermal free energies, at 298 K and 1 atm and was further assimilated as energetic criteria for the reaction evolution. As long as the transition states involve both formation and breaking of chemical bond, electron correlation effects were predicted to be important. Hessian matrices were computed for all stationary points (minima and transition states) at the same level as that used for the optimizations. The absence of negative eigenvalues confirmed a stationary point as a minimum, while the presence of a single negative eigenvalue established the stationary point as a transition state. In addition, for transition states intrinsic reaction coordinate (IRC) calculations were performed.

In the early stage of reactivity theory, Pearson pointed out that the HOMO-LUMO gap represents the chemical hardness of a molecule and it is used as a direct indicator of the chemical reactivity. A large HOMO-LUMO gap implies low chemical reactivity because it is energetically unfavorable to add electrons to a high-lying LUMO or to extract electrons from a low-lying HOMO.[19]

RESULTS AND DISCUSSION

In the initially step, the energy differences between the last occupied orbital and the first unoccupied orbital for the reacting molecules were estimated. As the energies of frontier orbitals HOMO-LUMO gap were found to be lower than 6 eV, the reactions were theoretically considered to proceed under orbital control, according to the Parson's rules.[20] On the other side, as the charges calculated for all the optimized reacting molecules are highly enough to be neglected, the reactions

were not considered to be under charge control, but under charge influence.

Step A. All attempts to transfer the carboxylic hydrogen from **MA** to one of the carbonyl oxygen from anhydride were unsuccessful, indicating that the ionic reaction mechanism is no more proper to this reacting system. Moreover, our computations revealed, that the atomic charges and molecular geometries corresponding to the first step favor two cyclic transition states formation, in six and eight centers, **TS16** and **TS18**, respectively (Fig. 1).
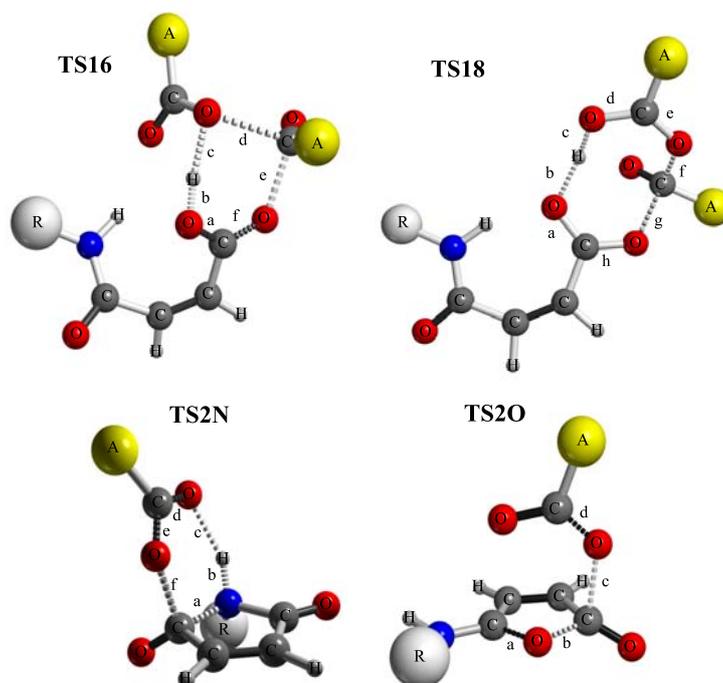

Fig. 1 – Geometries of transition states corresponding to the Step 1 (**TS16** and **TS18**) and to the Step 2 (**TS2N** and **TS2O**).

The centers that are most probable to interact are H7 from **MA** over C–O–C anhydride oxygen, and O4 from **MA** over carbonyl carbon from anhydride (Scheme 1, *Step A*). These centers corresponded to the highest opposite values, according to the hypothesis of stereoelectronic control for this reaction. In **TS16 b** and **d** bonds were breaking, **c** and **e** were forming, **a** became a double bond and **f** became a simple bond (Figure 1). **TS16** was not found aromatic, although 6 electrons were involved, as CO–A group was out of plane. If considering **TS18**, **b** and **f** bonds were breaking, **c** and **g** bonds were forming, **d** and **h** double bonds became simple bonds, **a** and **e** simple bonds became double bonds. Also, the aromaticity was not suitable for **TS18**, because of CO–A group out-of-plane position. The free energies and imaginary frequences corresponding to the *step A* transition states are given in Table 1.

Table 1

Free energies (a.u.) and imaginary frequencies (cm^{-1}) in **TS16** and **TS18**, in solvent and in the gas phase (given in parentheses):

R	A	TS16		TS18	
		Energies	ν	**Energies**	ν
Bu	**CH$_3$**	-974.560118	-432.3	-974.577553	-311.4
		(-974.557122)	(-408.3)	(-974.571305)	(-471.4)
	CF$_3$	-1570.010864	-253.7	-1570.027893	-261.5
		(-1570.00997)	(-250.3)	(-1570.02427)	(-463.9)
Ph	**CH$_3$**	-1048.392431	-487.1	-1048.408503	-272.5
		(-1048.38887)	(806.8)	(-1048.40259)	(442.3)
	CF$_3$	-1643.841740	-320.5	-1643.858182	-192.7
		(-1643.84057)	(-341.7)	(-1643.85115)	(-424.6)

Computations are able to provide the total energy of any molecule (reactants, intermediates, and products), the energy of transition states, and can eliminate the pathways that are not possible. This information could not be experimentally determined. The energy profile including activation energies (Ea) computed in solvent for CDH of Bu-substituted **MA** to the **IM** and **M** mixture using acetic anhydride as dehydrating agent is given in Figure 2 and the values of relative free energies are presented in Table 2.
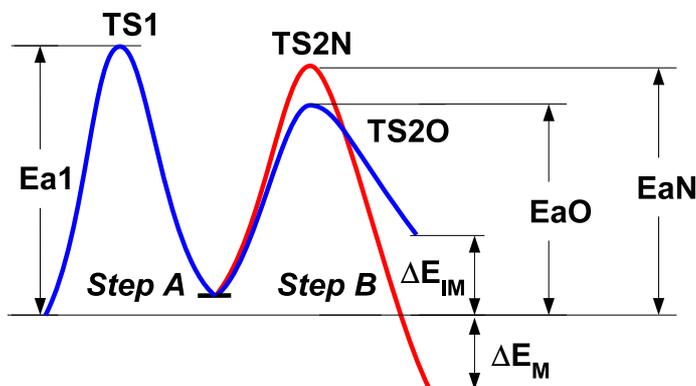

Fig. 2 – The relative free energy profile related to the initial state for reactions of Bu-substituted **MA** with acetic anhydride as dehydrating agent.

Table 2

Global free activation energies (Ea, kcal/mol) and global free reaction energies (ΔE, kcal/mol) at B3LYP/6-31G(d) level of theory in solvent and in the gas phase (given in parentheses):

R	A	Ea_{16}	Ea_{18}	ΔE Mix Anh	Ea_N	Ea_O	ΔE_M	ΔE_{IM}
Bu	CH_3	*35.7* *(34.3)*	24.8 (25.4)		30.6 (31.8)	31.44 (35.3)	-9.8 (-4.0)	4.3 (10.5)
				8.83 (4.26)				
	CF_3	*34.2* *(33.1)*	23.5 (24.2)		21.22 (21.5)	14.7 (20.1)	-20.1 (-19.5)	-6.0 (-4.9)
				3.26 (-0.82)				
Ph	CH_3	*24.8* *(28.7)*	17.9 (20.8)		24.8 (32.2)	22.9 (33.9)	-12.1 (-0.6)	-6.6 (5.2)
				0.05 (0.56)				
	CF_3	*23.6* *(28.1)*	13.3 (21.6)		14.6 (20.4)	5.7 (17.8)	-22.4 (-16.1)	-16.8 (-10.2)
				-1.22 (-2.05)				

Molecules, at room temperature, have enough thermal and kinetic energy to favor the processes requiring less than 22-24 kcal/mol. If consider the global free activation energies and global free reaction energies (Tab. 2) one can concluded that also theoretically **MA** cyclodehydration takes place at room temperature. For the first step of reaction it is obvious that **TS18 i**s energetically favored, perhaps due to the lower strains in the 8-membered cycle (Tab. 2).

Step B. into the next step, we focused our attention on finding the most probable pathways for the internal cyclization of mixed anhydride to the final products, **M** and **IM**. According to charges values, the most probable chemical interactions consisted in nucleophylic attack of either N3 or O1 from amide group (Scheme 1). The amide nitrogen interaction with C5 carbonyl carbon leaded to **M** formation through **TS2N** in which **a** and **c** bonds were forming and **b** and **f** bonds were breaking (Figure 1). The corresponding transition state **TS2N** had a six-membered cyclic structure but no aromaticity probably because N-H bond modification from

1.08 Å in transition state if compared with 1.02 Å in mixed anhydride.

Another theoretical possibility consisted in the attack of carbonyl oxygen from amide group O1 over C5 carbonyl carbon that leaded to the cyclic transition state **TS2O** (Figure 1), and finally to **IM** formation. In **TS2O b** bond was forming while **c** bond was breaking. Our computations indicated that **a** and **b** bonds from the forming cycle and **c** and **d** bonds, were situated in orthogonal planes

respectively. The molecular complex stabilizes by ejecting the acyl group, immediately after transition state is achieved. Theoretically, it could also be possible O1 attack over C7, but the activating barrier was found to be too high to support a reaction that took place experimentally at room temperature. The energy corresponding to **TS2O** was lower than that of **TS2N** (excluding the case of BuMA and acetic anhydride), supporting the non-aromaticity of **TS2N** (Tab. 2, 3).

Table 3

Free energies (a.u.) and imaginary frequencies (cm^{-1}) in **TS2N and TS2O**,
in solvent and in the gas phase (given in parentheses):

R	A	TS2N		TS2O	
		Energies	**ν**	**Energies**	**ν**
Bu	**CH$_3$**	-745.524144	-146.2	-745.522750	-141.0
		(-745.523951)	(-133.2)	(-745.518409)	(-154.7)
	CF$_3$	-1043.254957	-163.9	-1043.254957	-163.9
		(-1043.25364)	(-120.8)	(-1043.25586)	(-183.3)
Ph	**CH$_3$**	-819.302326	-226.3	-819.347371	-226.3
		(-819.346073)	(-216.6)	(-819.343467)	(-146.5)
	CF$_3$	-1117.079467	-218.6	-1117.079467	-218.6
		(-1117.07814)	(-202.8)	(-1117.08229)	(-177.1)

As long as the relative free energy of the reaction corresponding to **PhMA** was lower than that of **BuMA**, for both in solvent and gas phase (Fig. 2 and Tab. 2), one could conclude the easier cyclodehydration of **PhMA** compared to **BuMA**. Moreover, when the **R** electron-withdrawing strength increased, **M** product was favored. If one compared the cyclization barriers (Tab. 2), it was found that **Ea$_N$** > **Ea$_O$**, suggesting that **IM** formation was kinetically favored, both for **BuMA** and **PhMA**. The global free reaction energies for **IM** were higher than that for **M**, so that the cyclization to **M** was thermodynamically favored. An exception was provided by **BuMA** in the presence of acetic anhydride when **M** formation was both thermodynamically and kinetically favored. The computed energies in solvent were generally slightly higher than those in gas phase, but supported the same mechanism.

Trifluoroacetic anhydride A represents a particular case for the barriers corresponding to **Ea$_{18}$**, **Ea$_N$** and **Ea$_O$** were steadily lower, hence the cyclization reactions was favored in the presence of this dehydrating agent.

EXPERIMENTAL

In order to test our theoretical assumptions, we made an experimental study over the CDH of Bu- and Ph-maleamic

acids with acetic and trifluoroacetic anhydride as dehydration agents. The corresponding **MA** were synthesized and purified by known methods.[21] We followed and monitored the reaction progress using the signals corresponding to the *cis*-vinyl protons from ^{1}H-NMR spectra recorded on a Brüker 400 MHz instrument in DMSO-d$_6$ as solvent. All experiments were carried out at room temperature.

When stoiechiometric amounts of **MA** and dehydrating agent were used, initially moment vinyl protons appeared as a broad peak, corresponding to a mixture of states. The signals split in time into the spin-spin coupled sharp doublets, with system stabilization. It is to be mentioned that the reaction has been found stable even after 96 hours.

Trifluoroacetic anhydride A represents a particular case (Fig. 3). In the presence of Bu-maleamic acid, vinyl protons appeared at start as broad peaks. In a short time, two sharp doublets (at 6.44, 6.41, and 6.24, 6.21 ppm corresponding to the vinyl protons from maleamic acid and at 6.32, 6.29, and 6.15, 6.12 ppm assigned to the vinyl protons from mixed anhydride) could be seen. After several minutes the doublets corresponding to the vinyl protons from unreacted maleamic acid disappeared. This behavior was determined by analyzing the different vicinities of vinyl protons for fluorine substituent.

On contrary, Ph-maleamic acid gave at start two sharp doublets corresponding to the vinyl protons from **MA** and mixed anhydride, and in a shorter time than that required to perform the spectrometer calibration, the peaks became much broader. In a short time after that only the sharp peaks corresponding to **MA** remained. Our computations found for this case very law values corresponding to **Ea$_{18}$**, indicating an enhanced rate of mixed anhydride formation (Table 2).
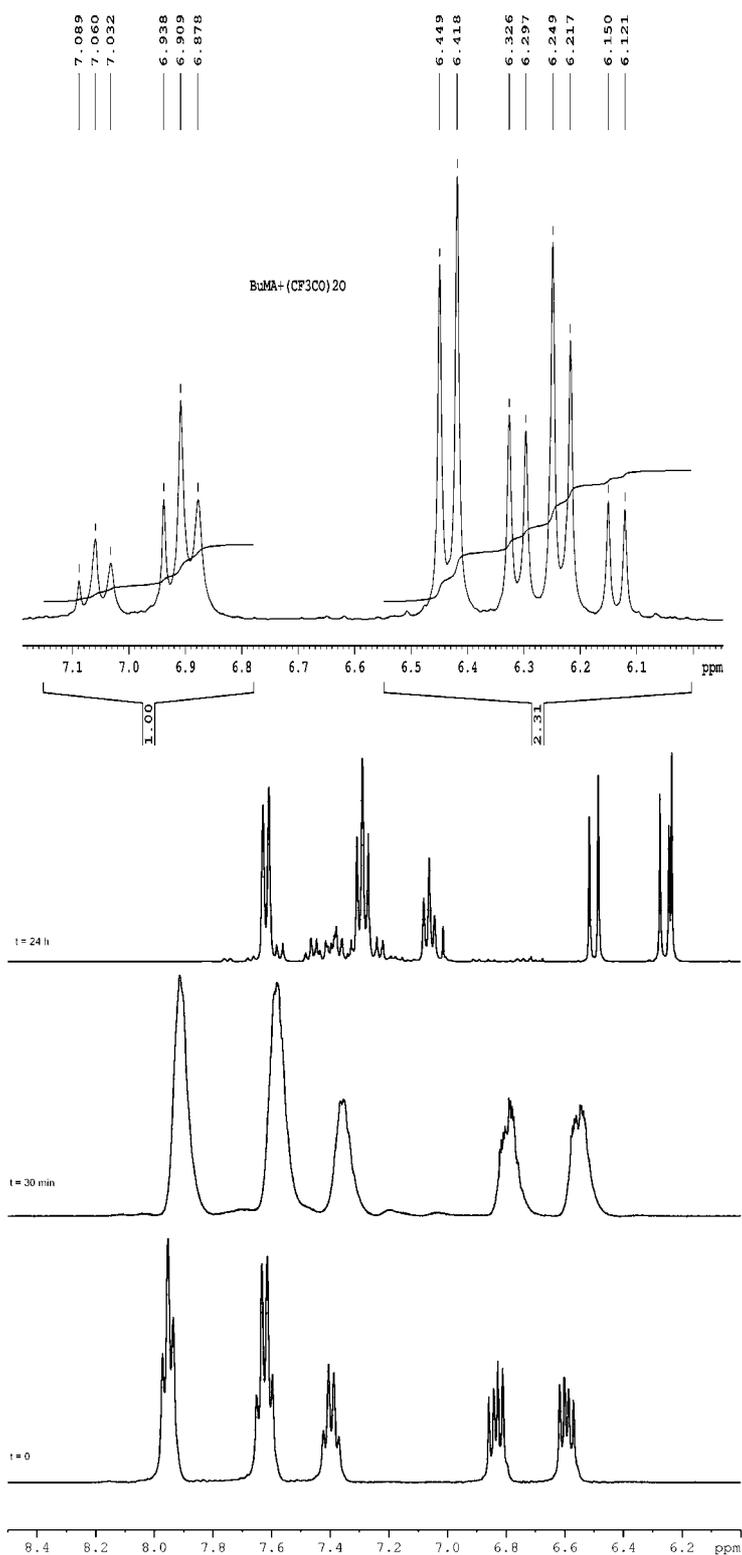
Fig. 3 – ^{1}H NMR spectra for stoiechiometric amounts of **MA** (BuMA left, PhMA right) and trifluoroacetic anhydride.

CONCLUSIONS

In summary, our theoretical study found **MA** cyclic dehydration to be under both charge and sterical control. The calculated results have demonstrated interesting substituent effects from **MA** and anhydride on the optimized transition-state geometries, transition-state stabilization, and

free energy barriers. Further cyclization of mixed anhydride intermediate over amide O or N gives kinetically favored **IM** or thermodynamically favored **M**, respectively. Trifluoroacetic anhydride as dehydrating agent is found to be the most effective.

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