Experimental and Computational Studies Addressed to 1,3-Dipolar Cycloadditions of D-Erythrose 1,3-Dioxane 1,5-Lactone with *Regio*- and *Stereo*-selectivity.

Biomolecular SIMulations Research Group

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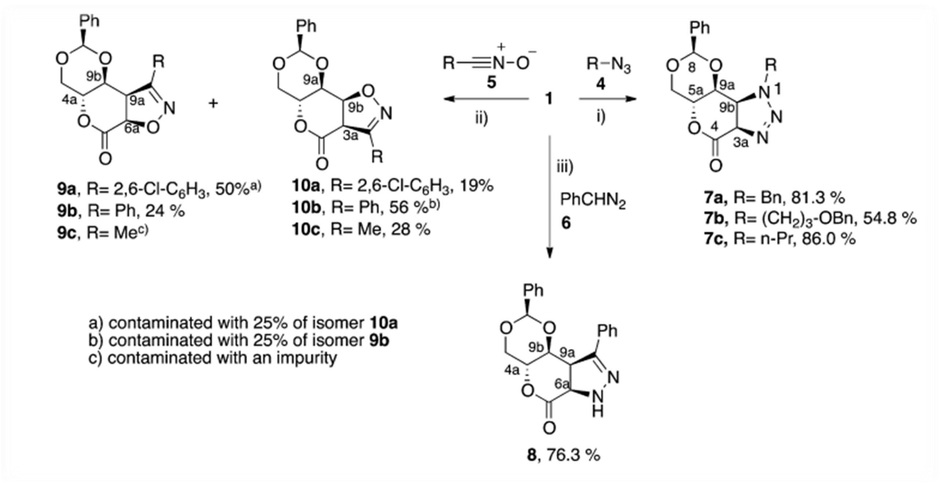
Introduction

A new D-erythrose 1,3-dioxane 1,5-lactone derivative **1** was synthetized and found to be a highly stereo-selective template as dipolarophile in 1,3-dipolar cycloadditions, and in this context interesting versatile fragments, useful in the synthesis of iminosugars of several types.[1]

In order to understand the mechanism of the [3π + 2π] cycloadditions with three types of 1,3-dipoles: alkyl azides (**4**), nitrile oxides (**5**), and a diazo compound (**6**), the free energy profile of these reactions was studied by theoretical and computational means.



Scheme 1: 1,3-Dipolar Cycloaddition of Lactone **1** to Azides, Nitrile Oxides, and Phenyldiazomethane

Methodology

All geometry optimizations: B3LYP/ 6-31G(d). Single points energy calculations with IEF-PCM, M06-2X/6-311++G(3df,2pd), with a dielectric constant of 2.4, 4.0, 33.0 to simulate the toluene, diethyl ether, and methanol solvent, respectively.

Conclusions

The computational results showed that all the studied cycloadditions are concerted processes, involving exoenergonic free activation energies. The *stereo-selectivity* of the reactions is due to a combination of the steric effect endorsed by hydrogen H-8 and the hyper conjugative effect of the incoming 1,3-dipole with the lactone. The *regio-selectivity* observed in alkyl azides and phenyldiazomethane is mostly dependent on the distortion effect during the cycloaddition process.

Results

A. *Stereo-specificity*

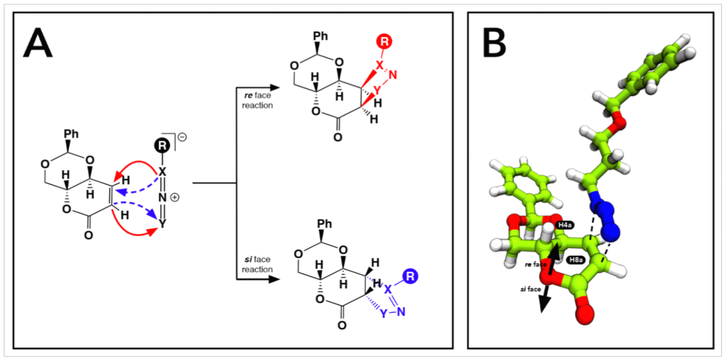
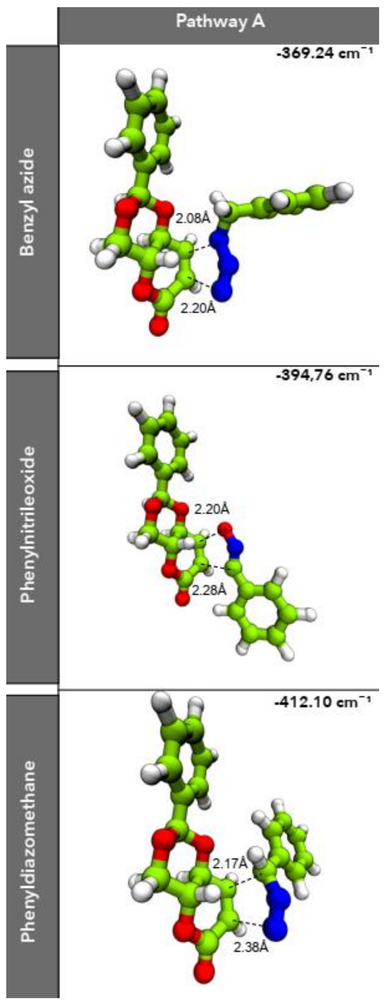


Figure 1: (**A**) Stereoselectivity of the reactions of the lactone 1 with 1,3-dipole compounds. (**B**) Transition state structure obtained from cycloaddition of an azide compound at the re face of the lactone.

The *stereo-selectivity* of the reactions is due to a combination of the steric effect endorsed by hydrogen H-8 and the hyper conjugative effect of the incoming 1,3-dipole with the lactone.

B. *Regio-specificity*



Transition state structures

Table 1: Profile energetic

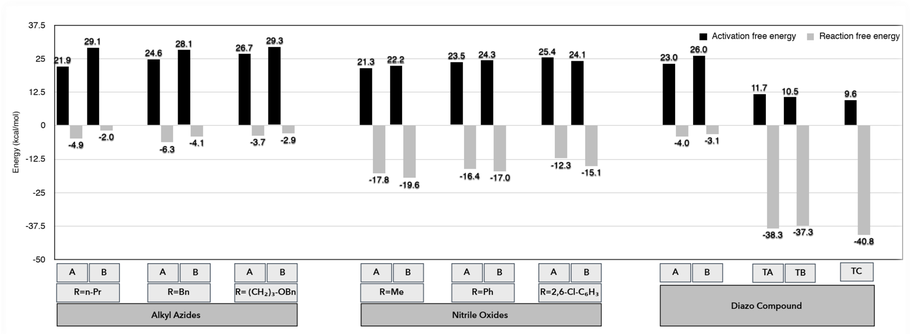
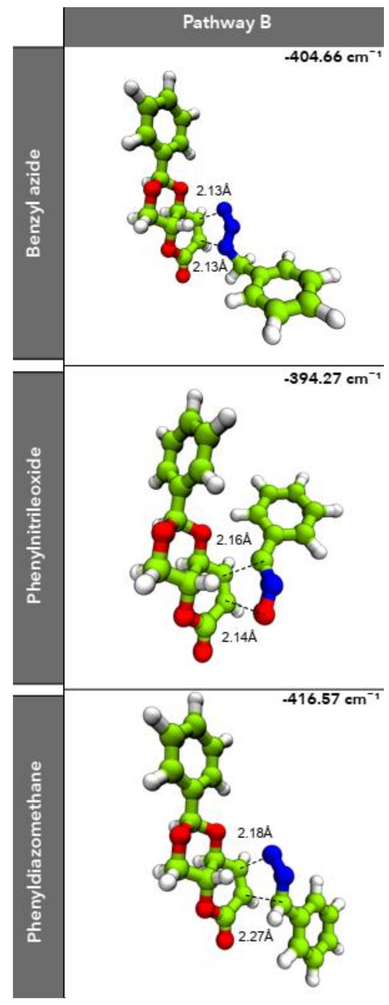


Table 2: Decomposition of the activation energies

1,3-Dipole Molecule		Pathway	Decomposition of the activation energies (kcal/mol)			
			Distortion	Entropic	Interaction	Solvent
Alkyl Azide	R=n-Pr	A	26.8	4.4	-8.0	-5.8
		B	30.7	5.3	-5.6	-6.6
	R= Bn	A	30.1	3.0	-7.6	-3.9
		B	30.3	4.3	-4.9	-5.9
	R= $(CH_2)_3$-OBn	A	28.5	4.2	-5.3	-4.9
		B	31.7	4.7	-6.5	-5.2
Nitrile Oxides	R=Me	A	23.9	3.1	-5.4	-3.3
		B	23.7	2.9	-3.7	-3.5
	R=Ph	A	26.8	2.9	-6.2	-2.8
		B	25.6	3.7	-4.4	-4.2
	R=2,6-Cl-C_6H_3	A	26.7	4.3	-5.9	-4.0
		B	25.2	4.4	-4.5	-5.4
Diazo compound		A	25.6	5.1	-7.1	-5.5
		B	27.9	4.6	-5.8	-5.2
		TA	16.1	1.57	-5.9	-1.7
		TB	13.4	3.15	-6.5	-2.8
		TC	15.9	0.43	-6.8	-0.5



Transition state structures

In the nitrile oxides cases, pathways A and B are competitive and both isomers are obtained. In the cases of the alkyl azides and diazo compounds only one isomer is favored from kinetic and thermodynamic points of view. The pathway A is favored because it requires a lower distortion of the 1,3-dipole molecules during the reaction.

References: 1)*Sousa, C. E. A.; Mendes, R. R.; Costa, F. T.; Duarte, V. C. M.; Fortes, A. G.; Alves, M. J. Curr. Org. Synth. 2014, 11, 182-203 and references cited herein. 2) Sousa, C.E.A.; Ribeiro, A. M. P.; Gil Fortes, A.; N. M. F. S. A. Cerqueira; Alves, M. J. J. Org. Chem., 2017, 82 (2), pp 982–991.*

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