"Supporting Information"

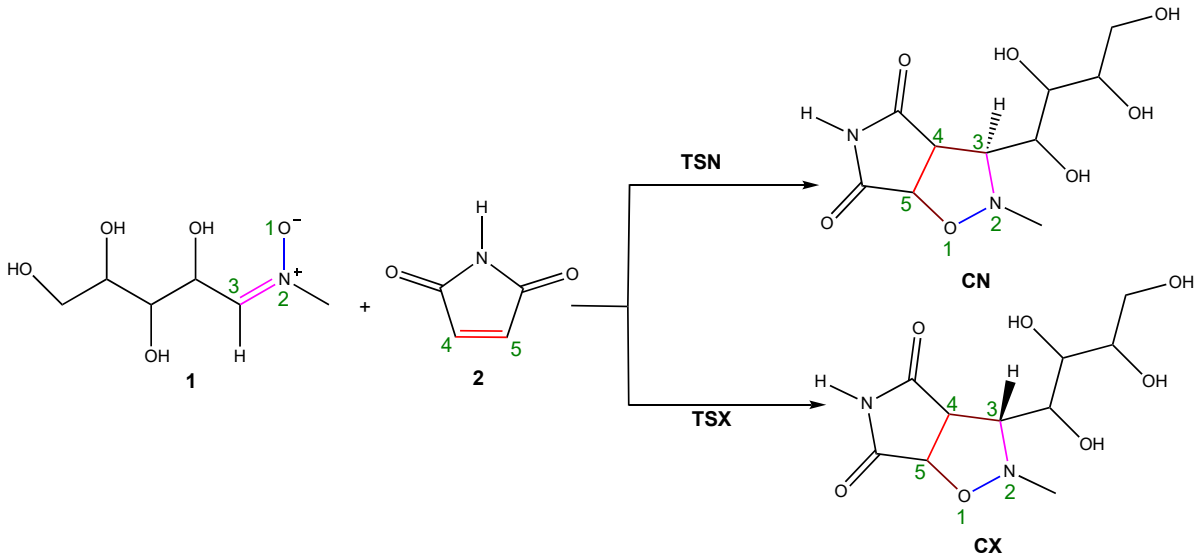
Mechanism and Stereoselectivity of a [3+2] Cycloaddition Involving a Glucosyl Nitrone: A MEDT Study

Mohamed Chellegui[a,b*], Simplice Koudjina[c,d], Ines Salhi[a], Sofiane Benmetir[e,f], Raad Nasrullah Salih[g], Haydar A. Mohammad-Salim[h,i], Guy Y.S. Atohoun[d] and Jesus Vicente de Julián-Ortiz[e]

[a]Laboratory of Organic Chemistry (LR17ES08), Faculty of Sciences, University of Sfax, 3038 Sfax, Tunisia.
[b]Namur Institute of Structured Matter, University of Namur, Rue de Bruxelles, 61, B-5000 Namur, Belgium.
[c]National High School of Applied Biosciences and Biotechnologies (ENSBBA), National University of Sciences, Technologies, Engineering and Mathematics (UNSTIM), BP 486 Abomey, Sogbo-Aliho, Benin.
[d]Laboratory of Chemical Physics-Materials and Molecular Modeling (LCP3M), University of Abomey-Calavi (UAC), 03 BP 3409 Cotonou, Benin.
[e]Department of Physical Chemistry, Faculty of Pharmacy, University of Valencia, Av. Vicente Andrés Estellés s/n, 46100 Valencia, Spain.
[f]Process and Environmental Engineering Laboratory (LIPE), Faculty of Chemistry, University of Science and Technology of Oran Mohamed BOUDIAF, P.O. Box 1503, El Mnaouer, 31000 Oran, Algeria.
[g]Nursing Department, Bardarash Technical Institute, Akre University for Applied science, Duhok 42001, Kurdistan Region, Iraq.
[h]Department of Chemistry, Faculty of Science, University of Zakho, Zakho 42002, Kurdistan Region, Iraq.
[i]TCCG Lab, Scientific Research Center, University of Zakho, Zakho 42002, Kurdistan Region, Iraq.

1 General Aspects of Thermodynamics and Kinetics

In this work, DFT at the IEFPCM(toluene)/M06-2X-D3/6–311G(d,p) level of approximation is employed to describe the 32CA reaction between C-(D-glucoso)-N-methyl nitrone **1** and 1H-pyrrole-2,5-dione **2** (**Scheme S1**).



Scheme S1 32CA reactions stereoisomeric paths of C-(D-glucoso)-N-Methyl nitrone **1** with 1H-pyrrole-2,5-dione **2**. [**CN** = endo cycloadduct, **CX** = exo cycloadduct, **TSN** = TS-endo, and **TSX** = TS-exo].

The thermochemical state functions were calculated using the following expressions corresponding to the different reaction steps:

$\Delta X = X$ (product/TS) - [X (C-(D-glucoso)-N-Methyl nitrone) + X (1H-pyrrole-2,5-dione)].

With, X = E, H, G, and S.

2 Thermodynamic Data

The relative values of energy (E), enthalpy (H^0), entropy (S^0) and Gibbs enthalpy (G^0) of the reactants, products, and TSs are given in **Table S1**.

Table S1 Energies, enthalpies, entropies, and Gibbs enthalpies of reactants, transition states, and products calculated at the IEFPCM(toluene)/M06-2X-D3/6–311G(d,p) level of approximation (T = 383.15 K and P = 1 atm).

Systems	E (a.u.)	H^0 (a.u.)	S^0 (cal mol^{-1} K^{-1})	G^0 (a.u.)
1	-667.167799	-666.93619	129.482	-667.01525
2	-359.39309	-359.31449	80.971	-359.36393
CN	-1026.62570	-1026.30977	153.307	-1026.40337
CX	-1026.61991	-1026.30446	157.627	-1026.40071
TSN	-1026.55641	−1026.24508	160.387	-1026.35426
TSX	-1026.54871	-1026.23716	163.605	-1026.33705

3 Bond Evolution Theory (BET) analysis along the decomposition pathways

Table S2 Table Basin Populations (in e), IRC coordinates (RX, Bohr $AMU^{1/2}$), relative electronic energies (ΔE in kcal/mol) and C3-C4/O1-C5 bond lengths (in Å) along the **TSN** stereoisomeric channel of the 32CA reaction between C-(D-glucoso)-N-methyl nitrone **1** and 1H-pyrrole-2,5-dione **2**.

	SSD-I		**SSD-II**		**SSD-III**		**SSD-IV**		**SSD-V**		**SSD-VI**		**SSD-VII**	
Basins	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last
V(N2,C3)	3.75	3.98	3.16	3.16	3.03	3.03	2.66	2.42	2.35	2.35	2.27	2.19	2.13	1.83
V(C4,C5)	3.32	3.21	3.20	3.20	2.88	2.88	2.70	2.44	2.33	2.33	2.25	2.20	2.15	1.96
V(O1,N2)	1.45	1.29	1.25	1.25	1.24	1.24	1.20	1.15	1.12	1.12	1.09	1.08	1.07	0.96
V(O1)	6.01	5.82	5.78	5.78	5.80	5.80	5.80	5.80	6.02	6.02	5.29	5.25	5.24	5.05
V(N2)	---	---	0.88	0.88	1.09	1.09	1.25	1.57	1.70	1.70	1.82	1.92	2.01	2.35
V(C3)	---	---	---	---	---	---	0.32	0.40	---	---	---	---	---	---
V(C4)	---	---	---	---	0.35	0.35	0.45	0.63	---	---	---	---	---	---
V(C3,C4)	---	---	---	---	---	---	---	---	1.16	1.16	1.28	1.36	1.43	1.85
V(C5)	---	---	---	---	---	---	0.07	0.15	---	---	---	---	---	---
V'(O1)	---	---	---	---	---	---	---	---	---	---	0.75	0.82	---	---
V(O1,C5)	---	---	---	---	---	---	---	---	---	---	---	---	0.90	1.25
d(C3,C4)	2.867	2.293	2.250	2.250	2.206	2.206	2.165	2.075	2.027	2.027	1.979	1.938	1.880	1.508
d(O1,C5)	2.644	2.011	1.963	1.963	1.916	1.916	1.889	1.772	1.728	1.728	1.689	1.636	1.598	1.424
RX	-6.74	-0.67	-0.33	-0.33	0.00	0.00	0.32	0.99	1.33	1.33	1.67	2.01	2.35	6.71
E	24.75	33.23	33.65	33.65	33.83	33.83	33.56	31.44	29.39	29.39	26.71	23.50	19.96	0.00

Table S3 Table Basin Populations (in e), IRC coordinates (RX, Bohr AMU$^{1/2}$), relative electronic energies (ΔE in kcal/mol) and C3-C4/O1-C5 bond lengths (in Å) along the **TSX** stereoisomeric channel of the 32CA reaction between between C-(D-glucoso)-N-methyl nitrone **1** and 1H-pyrrole-2,5-dione **2**.

	SSD-I		**SSD-II**		**SSD-III**		**SSD-IV**		**SSD-V**		**SSD-VI**		**SSD-VII**	
Basins	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last
V(N2,C3)	3.70	3.88	3.63	3.70	2.81	2.57	2.47	2.39	2.32	2.20	2.14	2.09	2.03	1.84
V(C4,C5)	3.31	3.20	3.19	3.14	2.89	2.76	2.55	2.44	2.35	2.22	2.17	2.13	2.09	1.97
V(O1,N2)	1.52	1.39	1.36	1.33	1.31	1.23	1.20	1.15	1.14	1.09	1.09	1.05	1.03	0.96
V(O1)	5.88	5.86	5.82	5.76	5.78	5.73	5.72	5.73	5.76	6.04	5.37	5.28	5.24	5.09
V(N2)	---	---	---	---	0.95	1.33	1.45	1.58	1.69	1.87	1.96	2.02	2.07	2.31
V(C3)	---	---	0.30	0.36	0.39	0.47	0.52	0.53	---	---	---	---	---	---
V(C4)	---	---	---	---	0.27	0.45	0.53	0.62	---	---	---	---	---	---
V(C3,C4)	---	---	---	---	---	---	---	---	1.25	1.43	1.50	1.57	1.61	1.89
V(C5)	---	---	---	---	---	---	0.16	0.21	0.21	0.20	---	---	---	---
V'(O1)	---	---	---	---	---	---	---	---	---	---	0.73	0.82	---	---
V(O1,C5)	---	---	---	---	---	---	---	---	---	---	---	---	0.92	1.25
d(C3,C4)	3.212	2.368	2.322	2.229	2.183	2.088	2.041	1.933	1.946	1.856	1.812	1.770	1.728	1.547
d(O1,C5)	2.720	2.163	2.124	2.045	2.005	1.929	1.890	1.833	1.814	1.734	1.693	1.651	1.609	1.426
RX	7.54	1.21	0.90	0.30	0.00	-0.60	-0.91	-1.21	-1.51	-2.11	-2.41	-2.72	-3.02	-7.53
E	26.60	37.68	38.68	38.81	39.99	39.09	37.85	36.01	27.14	27.13	23.33	19.33	15.34	0.00

4 Drug-likeness assessment and ADMET predictions

Table S4 Main features of the five druglikeness rules evaluated for **CN** and **CX** compounds.

Lipinski	Ghose	Veber	Egan	Muegge
MW ≤ 500 Da	160 Da ≤ MW ≤ 480 Da	#Rotatable bonds ≤ 10	WLOGP ≤ 5.88	200 Da ≤ MW ≤ 600 Da
MLOGP ≤ 4.15	WLOGP <-0.4	TPSA ≤ 140 Å^2	TPSA > 131.6 Å^2	XLOGP3<-2
#H-bond donors ≤ 5	40 ≤ MR ≤ 130			TPSA ≤ 150 Å^2
#H-bond acceptors ≤ 10	20 ≤ #atoms ≤ 70			#Rings ≤ 7
				#Carbons > 4
				#Heteroatoms > 1
				#Rotatable bonds ≤ 15
				#H-bond donors ≤ 5
				#H-bond acceptors ≤ 10

Table S5 Compounds **CN** and **CX** distribution and exertion SwissADME-Computed Drug-Likeness Predictions.

Property	CN	CX	Comment
BBB Permeability	0.284	0.303	Blood Brain penetration. Category 1: BBB+; Category 0: BBB-; The output value is probably being BBB+
PPB	11.77%	14.65%	Plasma Protein Binding Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
CL (Clearance)	1.517	1.508	The unit of predicted CL plasma penetration is ml/min/kg. >15 ml/min/kg: high clearance 5-15 ml/min/kg: moderate clearance >5 ml/min/kg: low clearance

Table S6 SwissADME-Computed Drug-Likeness and Metabolism Predictions for **CN** and **CX** Compounds.

Property	CN	CX
CYP1A2	inhibitor(substrate)	
	0.013(0.063)	0.017(0.063)
CYP2C19	inhibitor(substrate)	
	0.025(0.243)	0.021(0.248)
CYP2C9	inhibitor(substrate)	
	0.001(0.077)	0.001(0.103)
CYP2D6	inhibitor(substrate)	
	0.004(0.127)	0.005(0.138)
CYP3A4	inhibitor(substrate)	
	0.006(0.022)	0.005(0.02)

5 Molecular Docking against 1CIN

Table S7 Binding affinity (kcal/mol) and nonbonding interactions of 1CIN and its products, **CN** and **CX**.

Complex	Amino acid	Bond Type	Distance (A°)
CN	HIS A64	Hydrogen bond	2.6
	LYS A170	Hydrogen bond	2.8
	TRP A5	Hydrogen bond	2.0
	GLU A236	Weak Hydrogen bond	2.8
	PHE A231	Hydrophobic bond	2.9
	GLY A63	Hydrogen bond	1.9
	HOH A366	Hydrogen bond	2.4
	HOH A366	Hydrogen bond	1.9
	HOH A366	Hydrogen bond	2.1
	HOH A366	Hydrogen bond	2.2
CX	SER A71	Hydrogen bond	2.5
	ASP A59	Hydrogen bond	2.1
	HOH A169	Weak Hydrogen bond	2.3
	HOH A173	Weak Hydrogen bond	2.0
	VAL A61	Weak Hydrogen bond	1.9
	HOH A178	Hydrogen bond	1.5
	ALA A69	Hydrogen bond	1.9
	HOH A202	Weak Hydrogen bond	2.4
	HOH A154	Weak Hydrogen bond	3.0

6 Cartesian Coordinates of all the Stationary Points as Computed at the IEFPCM(toluene)/M06-2X-D3/6–311G(d,p) level of approximation

C-(D-glucoso)-N-methyl nitrone **1**

C	3.33963600	0.08465600	0.13162200
H	3.37006500	0.42993100	1.17069800
H	4.12814600	0.59734100	-0.43164100
C	1.97992900	0.45890100	-0.44952200
H	1.92709100	0.13113200	-1.49678900
C	0.83361900	-0.25328200	0.28065000
H	0.97573700	-0.16394500	1.36636300
C	-0.52384200	0.38298100	-0.03616400
H	-0.50029300	0.80473000	-1.05349700
C	-1.63665400	-0.62816000	0.00308700
H	-1.47306100	-1.68766500	0.11784300
N	-2.84675800	-0.19290000	-0.11098600
O	-3.14638700	1.04762300	-0.26544900
C	-4.00130600	-1.09950200	-0.06411600
H	-4.62454400	-0.78322400	0.76984400
H	-4.54831100	-0.96690200	-0.99532500
H	-3.67314200	-2.12873600	0.05698500
O	-0.75276200	1.40216900	0.91074100
H	-1.62304200	1.76061300	0.67378400
O	0.80015200	-1.61149400	-0.12002000
H	1.70197700	-1.94715100	-0.03231100
O	1.80836400	1.85614900	-0.33825000
H	2.36347200	2.28125100	-0.99668700
O	3.50048000	-1.32719400	0.04854900
H	4.27614900	-1.58865900	0.54973500

1H-pyrrole-2,5-dione 2

C	0.00045500	-0.16052300	1.14996800
C	-0.00139600	1.26494100	0.66403000
C	-0.00139600	1.26494100	-0.66403000
C	0.00045500	-0.16052300	-1.14996800
H	-0.00248200	2.09827700	1.35069200
H	-0.00248200	2.09827700	-1.35069200
O	0.00045500	-0.55666800	2.28163400
O	0.00045500	-0.55666800	-2.28163400
N	0.00103600	-0.94169800	0.00000000
H	0.00172300	-1.95100300	0.00000000

CN

C	-2.19032900	1.40956400	-0.27502000
C	-1.61377900	0.63370900	0.89962000
C	-2.57620800	-0.53198600	1.12193600
C	-3.63924300	-0.38911000	0.01938100
H	-1.52979400	1.31711900	1.74352000
H	-3.07408700	-0.55264500	2.09070000
O	-1.72224900	2.39453500	-0.79418700
O	-4.53547500	-1.13952600	-0.23057700
N	-3.36710400	0.80079600	-0.65553600
H	-3.91406700	1.12121500	-1.44564200
C	4.27517700	-0.53259700	0.60046100
H	3.92371600	-1.40754200	1.15928400
H	5.06278000	-0.03800300	1.17639800
C	3.10832000	0.42598700	0.43501300
H	3.45347600	1.34465200	-0.05264800
C	2.00757500	-0.17014100	-0.45896300
H	1.83753700	-1.21252800	-0.15179800
C	0.68026000	0.59076700	-0.32885200
H	0.24033600	0.61833300	-1.32939500

C	-0.26881200	-0.10125700	0.65051200
H	0.23576200	-0.18291300	1.61629800
N	-0.64276900	-1.46423100	0.25083600
O	-1.81277000	-1.72960700	1.01648300
C	-0.93669600	-1.65798300	-1.16897600
H	-1.36522400	-2.65231200	-1.27848800
H	-1.62483700	-0.92208600	-1.60387700
H	0.00469200	-1.61802900	-1.72041000
O	0.91470200	1.92179600	0.11221200
H	0.17297200	2.46074500	-0.19562100
O	2.37893000	-0.11027100	-1.82360700
H	3.26357500	-0.49476000	-1.88092700
O	2.64635100	0.68351800	1.74761500
H	2.05709400	1.44380600	1.67315900
O	4.73689200	-0.90165200	-0.69417500
H	5.39653900	-1.59307400	-0.60842500

CX

C	2.65738100	0.80364700	-0.76814500
C	1.17777000	0.46805800	-0.64809200
C	1.12552000	-1.01618200	-0.31240000
C	2.58699100	-1.48759900	-0.33527000
H	0.69938200	0.73761500	-1.58532600
H	0.52026000	-1.61448700	-0.99096700
O	3.14314700	1.89126700	-0.92062200
O	2.99987200	-2.58791300	-0.10443300
N	3.36510400	-0.38563400	-0.67137300
H	4.37613100	-0.42188800	-0.71136400
C	-3.11780700	-1.52653000	-0.68507400
H	-2.31431100	-2.20254000	-0.36813200
H	-3.53106600	-1.88310500	-1.63318400

C	-2.51779800	-0.14504600	-0.88257900
H	-3.28533700	0.53832300	-1.26290900
C	-2.04075500	0.43560700	0.46202300
H	-1.63245400	-0.36537500	1.08344800
C	-0.98681100	1.54258500	0.33849900
H	-1.23018600	2.22867400	1.15465500
C	0.49056300	1.13071800	0.55715200
H	1.04074700	2.03157100	0.84258600
N	0.59868300	0.14998200	1.64090700
O	0.54071400	-1.11979100	0.98762500
C	1.83522100	0.23470800	2.41410600
H	1.86293200	-0.61210400	3.09739200
H	2.74844300	0.23548400	1.80674700
H	1.79786800	1.15510600	2.99735300
O	-1.13944300	2.20733200	-0.91268000
H	-0.83348900	3.11424400	-0.83319000
O	-3.15432100	1.03182300	1.11571700
H	-3.81634600	0.33353900	1.19267800
O	-1.48299400	-0.31335700	-1.83610400
H	-1.27865700	0.57378800	-2.15168800
O	-4.12571200	-1.42585800	0.31316300
H	-4.38217600	-2.30709500	0.59252900

TSN

C	-2.19595400	1.42516600	-0.42227600
C	-2.13314600	0.93512800	0.96633600
C	-3.05907300	-0.09942800	1.10430100
C	-3.80864500	-0.21282400	-0.19580300
H	-1.74823800	1.56848100	1.75002200
H	-3.55314400	-0.39762400	2.01584500
O	-1.51211400	2.27713500	-0.95976500

O	-4.74707800	-0.90469900	-0.47309700
N	-3.17293200	0.67939400	-1.06796800
H	-3.42774900	0.80167700	-2.03742000
C	4.65261700	-0.13617000	-0.04115600
H	4.81525300	-0.23882700	1.03796600
H	5.42971400	0.51258700	-0.45380800
C	3.30980000	0.54389000	-0.27275100
H	3.10204800	0.54470400	-1.35376900
C	2.16058400	-0.18831200	0.44025500
H	2.33079600	-0.09484300	1.52381200
C	0.79459300	0.42932600	0.11063000
H	0.64489100	0.36196100	-0.97335000
C	-0.30933000	-0.30035900	0.84062900
H	-0.29810600	-0.24768300	1.92196900
N	-0.95465500	-1.34158400	0.33560500
O	-2.01705900	-1.70268200	0.98718100
C	-0.86136300	-1.75450000	-1.07195900
H	-1.49375900	-2.63244500	-1.16867500
H	-1.21482700	-0.96637800	-1.73734300
H	0.17558100	-1.99987900	-1.28715000
O	0.79786900	1.78330300	0.52811300
H	0.07361200	2.23447100	0.05931900
O	2.06003300	-1.54200200	0.05056400
H	2.94584400	-1.86128300	-0.17566500
O	3.48710700	1.84833100	0.22998400
H	2.60773400	2.23321800	0.34239400
O	4.64735200	-1.40653000	-0.68658000
H	5.47407100	-1.85715800	-0.49805900

TSX

C	2.66753300	1.24015900	-0.33339700
C	1.29296400	0.85614200	-0.75386100
C	1.34456400	-0.42761900	-1.28013500
C	2.76784200	-0.89331800	-1.23376200
H	0.56082800	1.61469500	-0.98226200
H	0.65838600	-0.87102200	-1.98459000
O	3.06362700	2.28118300	0.12802300
O	3.25599200	-1.89985700	-1.67254800
N	3.45797300	0.10745000	-0.54572400
H	4.45645400	0.09156300	-0.39560200
C	-3.97864900	-0.41870400	-1.00336600
H	-3.40895400	-0.83502600	-1.84259100
H	-4.83036300	0.13910600	-1.40220200
C	-3.08601100	0.57039600	-0.26296500
H	-3.63241300	0.96528100	0.60526300
C	-1.78074000	-0.08768400	0.21770200
H	-1.23755000	-0.41099700	-0.67822000
C	-0.91235800	0.85747400	1.05674000
H	-1.35940500	0.82434900	2.05952700
C	0.54146100	0.44194600	1.25376900
H	1.06232400	1.07375300	1.97121700
N	0.98336400	-0.81542200	1.24485300
O	0.68691500	-1.55595900	0.24160300
C	2.12938400	-1.24395000	2.05947700
H	2.80080300	-1.81069400	1.41846000
H	2.63725800	-0.37695400	2.47904800
H	1.76205100	-1.88361600	2.86180600
O	-0.98272100	2.18776700	0.56522500
H	-0.59010100	2.79397200	1.20038800
O	-2.02210300	-1.16378700	1.09910800
H	-2.77095000	-1.66919700	0.75703700
O	-2.83456300	1.56996100	-1.22946700

H	-2.25992900	2.22169400	-0.81340700
O	-4.40821900	-1.44383600	-0.11440500
H	-4.92516500	-2.08394000	-0.60928900