An MEDT study of Diels-Alder reactions of a tetrahydroazulenone with maleimides: Mechanism, selectivity, and antimicrobial insights

Abdeljabbar Jaddi[a,b], Amine Rafik[a,c], Ouadia Hamlaoui[d], Mohammed Salah[d], Alberto García-Vela[b] and Khadija Marakchi[a]*

[a] *Laboratory of Spectroscopy, Molecular Modelling, Materials, Nanomaterials, Water and Environment, LS3MN2E/CERNE2D, Faculty of Sciences, Mohammed V University in Rabat, Rabat, Morocco.*

[b] *Instituto de Física Fundamental, Consejo Superior de Investigaciones Científicas, Serrano 123, 28006 Madrid, Spain.*

[c] *Departamento de Ciencias Integradas, Centro de Estudios Avanzados en Física, Matemática y Computación; Unidad Asociada GIFMAN, CSIC-UHU, Universidad de Huelva, Huelva, 21071, Spain.*

[d] *Molecular Modelling and Spectroscopy Research Team, Faculty of Science, Chouaïb Doukkali University, P.O. Box 20, 24000, El Jadida, Morocco.*

***Corresponding author: k.marakchi@um5r.ac.ma**

Table 1S. Local reactivity indices for the reaction of the dienes and the different dienophiles calculated at B3LYP/6-311++G(d,p) level of theory

	Atomic Site	P_k^+	P_k^-	ω_k	N_k
1a	C1	0.18	0.38	0.47	1.27
	C4	0.13	0.40	0.34	1.33
2a	C1	0.13	0.42	0.38	1.40
	C4	0.16	0.34	0.47	1.13
3a	C1	0.09	0.29	0.26	0.97
	C4	0.22	0.48	0.64	1.60
4a	C1	0.12	0.40	0.31	1.33
	C4	0.14	0.41	0.37	1.36
5a	C1	0.21	0.28	0.49	0.93
	C4	0.01	0.54	0.02	1.80
6a	C1	0.08	0.26	0.25	0.87
	C4	0.23	0.47	0.72	1.56
1b	C5	0.25	0.04	0.81	0.06
	C6	0.25	0.04	0.81	0.06
2b	C5	0.25	0.10	0.77	0.17
	C6	0.25	0.10	0.77	0.17
3b	C5	0.25	0.03	0.81	0.08
	C6	0.25	0.03	0.81	0.08
4b	C5	0.24	0.07	0.70	0.13
	C6	0.28	0.08	0.81	0.15
5b	C5	0.25	0.09	0.82	0.15
	C6	0.25	0.09	0.82	0.15
6b	C5	0.25	0.02	0.88	0.05
	C6	0.25	0.02	0.88	0.05

Table 2S. Relative energies **ΔE (kcal.mol^{-1})**, Gibbs free energies **ΔG (kcal.mol^{-1}),** relative enthalpies **ΔH (kcal.mol^{-1})**, and entropies **ΔS (cal.mol^{-1}.K^{-1})** of the TSs and products involved in the DA reactions of diene **1a** with different dienophiles at the B3LYP/6-311++g(d,p) in gas phase and in toluene solvent at a temperature of 383.15 K

		ΔE	ΔG	ΔH	ΔS
	TS1-*endo*	12.56	30.62	13.32	-45.15
	TS1-*exo*	15.14	32.96	15.75	-44.93
	TS2-*endo*	11.68	30.51	12.34	-47.40
	TS2-*exo*	16.32	34.63	16.91	-46.27
	TS3-*endo*	12.01	30.73	12.79	-46.84
	TS3-*exo*	15.09	32.60	15.66	-44.23
	TS4-*endo*	14.14	33.05	14.85	-47.51
	TS4-*exo*	16.96	35.54	17.60	-46.83
	TS5-*endo*	9.44	28.20	10.16	-47.09
	TS5-*exo*	16.28	34.49	16.85	-46.05
	TS6-*endo*	11.77	30.50	12.54	-46.86
Gas	**TS6-*exo***	14.60	32.02	15.16	-44.01
	P1-*endo*	-13.82	8.64	-10.65	-50.35

	P1-*exo*	-17.10	5.51	-13.92	-39.40
	P2-*endo*	-14.44	8.74	-11.32	-52.35
	P2-*exo*	-17.88	5.41	-14.73	-52.56
	P3-*endo*	-13.38	9.10	-10.27	-50.57
	P3-*exo*	-16.83	5.65	-13.70	-50.50
	P4-*endo*	-12.57	10.39	-9.44	-51.75
	P4-*exo*	-16.36	6.55	-13.18	-51.50
	P5-*endo*	-15.78	7.24	-12.63	-51.84
	P5-*exo*	-18.65	4.48	-15.49	-52.11
	P6-*endo*	-13.36	9.02	-10.28	-50.38
	P6-*exo*	-16.88	5.54	-13.77	-50.39
	TS1-*endo*	13.28	31.25	14.03	-44.95
	TS1-*exo*	15.37	32.81	15.96	-43.98
	TS2-*endo*	12.40	31.60	13.07	-48.35
	TS2-*exo*	16.80	35.25	17.40	-46.59
	TS3-*endo*	13.11	31.90	13.83	-47.16
	TS3-*exo*	15.31	33.26	15.89	-45.35
	TS4-*endo*	14.78	34.45	15.56	-49.29
	TS4-*exo*	17.54	35.92	18.16	-46.35
	TS5-*endo*	10.66	29.29	11.32	-46.88
	TS5-*exo*	16.43	34.45	16.98	-45.59
	TS6-*endo*	12.81	31.54	13.60	-46.82
Toluene	**TS6-*exo***	14.87	32.23	15.46	-43.76
	P1-*endo*	-12.74	9.65	-9.55	-50.11
	P1-*exo*	-16.26	6.21	-13.07	-50.30
	P2-*endo*	-13.38	10.08	-10.24	-53.02
	P2-*exo*	-17.03	6.55	-13.86	-53.26
	P3-*endo*	-12.32	10.28	-9.23	-50.91
	P3-*exo*	-16.05	6.57	-12.90	-50.81
	P4-*endo*	-11.55	11.56	-8.39	-52.06
	P4-*exo*	-15.43	7.82	-12.22	-52.30
	P5-*endo*	-14.62	8.48	-11.46	-52.04
	P5-*exo*	-17.87	5.23	-14.70	-52.03
	P6-*endo*	-12.32	9.84	-9.21	-49.70
	P6-*exo*	-16.09	6.40	-12.94	-50.48

Table 3S. Relative energies **ΔE (kcal.mol^{-1})**, Gibbs free energies **ΔG (kcal.mol^{-1}),** relative enthalpies **ΔH (kcal.mol^{-1})**, and entropies **ΔS (cal.mol^{-1}.K^{-1})** of the TSs and products involved in the DA reactions of diene **1a** with different dienophiles at the B3LYP/6-311++g(d,p) in gas phase and in toluene solvent at a temperature of 298.15 K

	ΔE	**ΔG**	**ΔH**	**ΔS**
TS1-*endo*	11.69	26.37	12.39	-46.88
TS1-*exo*	16.53	31.01	17.08	-46.69
TS2-*endo*	14.12	28.41	14.71	-45.95
TS2-*exo*	14.90	29.29	15.40	-46.59
TS3-*endo*	11.75	26.95	12.45	-48.63

	TS3-*exo*	16.56	30.75	17.05	-45.93
	TS4-*endo*	14.14	29.01	14.77	-47.75
	TS4-*exo*	16.96	31.55	17.52	-47.07
	TS5-*endo*	11.80	26.32	12.44	-46.53
	TS5-*exo*	14.87	29.04	15.32	-46.02
	TS6-*endo*	11.77	26.51	12.48	-47.05
Gas	**TS6-*exo***	14.60	28.27	15.07	-44.25
	P1-*endo*	-13.82	4.78	-10.59	-51.54
	P1-*exo*	-17.10	1.61	-13.85	-51.87
	P2-*endo*	-14.44	4.19	-11.27	-51.86
	P2-*exo*	-17.88	0.84	-14.68	-52.05
	P3-*endo*	-13.38	5.21	-10.23	-51.80
	P3-*exo*	-16.83	1.78	-13.65	-51.72
	P4-*endo*	-12.57	6.00	-9.39	-51.62
	P4-*exo*	-16.36	2.18	-13.13	-51.35
	P5-*endo*	-15.78	2.84	-12.58	-51.71
	P5-*exo*	-18.65	0.06	-15.44	-51.97
	P6-*endo*	-13.36	4.74	-10.24	-50.243
	P6-*exo*	-16.88	1.26	-13.72	-50.242
	TS1-*endo*	12.48	27.22	13.18	-47.11
	TS1-*exo*	16.82	31.10	17.38	-46.01
	TS2-*endo*	14.88	29.39	15.49	-46.62
	TS2-*exo*	15.22	29.74	15.72	-47.01
	TS3-*endo*	12.81	28.12	13.50	-49.04
	TS3-*exo*	16.79	30.83	17.31	-45.36
	TS4-*endo*	14.82	29.68	15.48	-47.63
	TS4-*exo*	17.52	31.91	18.08	-46.41
	TS5-*endo*	13.18	27.61	13.80	-46.32
	TS5-*exo*	14.64	28.77	15.12	-45.81
	TS6-*endo*	13.14	27.98	13.92	-47.17
Toluene	**TS6-*exo***	15.20	28.92	15.76	-44.15
	P1-*endo*	-12.75	5.814	-9.50	-51.36
	P1-*exo*	-16.27	2.427	-13.00	-51.73
	P2-*endo*	-13.41	5.474	-10.20	-52.59
	P2-*exo*	-17.04	1.851	-13.81	-52.52
	P3-*endo*	-12.37	5.961	-9.22	-50.91
	P3-*exo*	-16.10	2.442	-12.87	-51.35
	P4-*endo*	-11.54	7.065	-8.33	-51.63
	P4-*exo*	-15.39	3.124	-12.13	-51.16
	P5-*endo*	-9.02	9.693	-5.67	-51.52
	P5-*exo*	-11.89	6.913	-8.53	-51.78
	P6-*endo*	-11.99	6.04	-8.78	-49.72
	P6-*exo*	-15.76	2.53	-12.52	-50.47

Table 4S. Calculated bond lengths (Å) and l index of bond formation for the reaction of the diene **1a** with the various dienophiles

Structures	**r (Å)**	***l***	**r (Å)**	***l***
	C1-C5		**C4-C6**	
P1-*endo*	1.587	0.430	1.548	0.694
TS1-*endo*	2.491		2.022	
P1-*exo*	1.580	0.400	1.556	0.686
TS1-*exo*	2.527		2.045	
P2-*endo*	1.587	0.451	1.548	0.675
TS2-*endo*	2.458		2.051	
P2-*exo*	1.580	0.383	1.556	0.682
TS2-*exo*	2.554		2.051	
P3-*endo*	1.588	0.465	1.549	0.675
TS3-*endo*	2.437		2.052	
P3-*exo*	1.581	0.400	1.556	0.688
TS3-*exo*	2.530		2.042	
P4-*endo*	1.589	0.436	1.551	0.689
TS4-*endo*	2.484		2.032	
P4-*exo*	1.583	0.389	1.557	0.684
TS4-*exo*	2.550		2.048	
P5-*endo*	1.588	0.437	1.548	0.677
TS5-*endo*	2.482		2.047	
P5-*exo*	1.580	0.386	1.555	0.672
TS5-*exo*	2.550		2.065	
P6-*endo*	1.588	0.462	1.549	0.677
TS6-*endo*	2.443		2.049	
P6-*exo*	1.582	0.391	1.556	0.690
TS6-*exo*	2.544		2.038	

Table 5S. Predicted ADMET properties and rules of five of the compounds

Properties	P1- *endo/exo*	P2- *endo/exo*	P3- *endo/exo*	P4- *endo/exo*	P5- *endo/exo*	P6- *endo/exo*	Unit
Absorption							
Water solubility	-3.01	-3.279	-4.481	-4.136	-3.275	-5.012	Numeric (log mol/L)
Caco2 permeability	0.643	1.235	1.353	1.381	0.101	1.324	Numeric (log Papp in 10-6 cm/s)
Intestinal absorption (human)	96.769	96.559	98.449	96.326	99.944	96.899	Numeric (% Absorbed)
Skin Permeability	-3.529	-3.451	-3.092	-3.265	-3.352	-3.181	Numeric (log Kp)
P-glycoprotein substrate	No	No	No	Yes	No	No	Categorical (Yes/No)
P-glycoprotein I inhibitor	No	No	Yes	Yes	No	Yes	Categorical (Yes/No)
P-glycoprotein II inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
Distribution							
VDss (human)	0.196	0.235	0.486	0.214	0.325	0.474	Numeric (log L/kg)
Fraction unbound (human)	0.409	0.382	0.024	0.154	0.379	0.017	Numeric (Fu)
BBB permeability	-0.122	0.245	0.178	0.167	0.294	0.14	Numeric (log BB)
CNS permeability	-2.953	-2.927	-1.88	-1.824	-2.84	-1.641	Numeric (log PS)
Metabolism							
CYP2D6 substrate	No	No	No	No	No	No	Categorical (Yes/No)
CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
CYP1A2 inhibitior	No	No	No	No	No	No	Categorical (Yes/No)
CYP2C19 inhibitior	No	No	Yes	No	No	Yes	Categorical (Yes/No)
CYP2C9 inhibitior	No	No	No	No	No	No	Categorical (Yes/No)
CYP2D6 inhibitior	No	No	No	No	No	No	Categorical (Yes/No)
CYP3A4 inhibitior	No	No	No	No	No	No	Categorical (Yes/No)
Excretion							
Total Clearance	-0.212	-0.115	0.008	0.911	-0.242	0.023	Numeric (log ml/min/kg)

Renal OCT2 substrate	No	No	No	Yes	No	No	Categorical (Yes/No)
Lipinski's rule of 5							
MW	259.3	273.33	335.4	315.41	289.33	369.84	Numeric (g/mol)
NRBs	0	0	1	1	1	1	-
NHBDs	1	0	0	0	0	0	-
NHBAs	4	4	4	4	5	4	-
TPSA (A°2)	63.24	54.45	54.45	54.45	63.68	54.45	-

Table 6S. The toxicity prediction of the compounds

	Predicted LD50	Predicted toxicity class	Average similarity	Prediction accuracy
P1-*endo/exo*	1000mg/kg	Class 4	88.79%	70.97%
P2-*endo/exo*	1000mg/kg	Class 4	88.79%	70.97%
P3-*endo/exo*	1000mg/kg	Class 4	70.6%	69.26%
P4-*endo/exo*	1000mg/kg	Class 4	88.79%	70.97%
P5-*endo/exo*	1000mg/kg	Class 4	71.32%	69.26%
P6-*endo/exo*	7000mg/kg	Class 6	66.83%	68.07%