Theoretical Study of Diels-Alder reactions : Correlation Analysis of The Three Electron Demand Types

Abdulkhalik S. Alkazzaz
E-mail:a_kh_shihab@yahoo.com

Department of Chemistry , College of Science , Mosul University

(NJC)

(Received on 4/6/2013) **(Accepted for publication 25/11/2013)**

Abstract

Semiemperical calculations were performed on some compounds of the three types of Diels-Alder reactions,normal,neutral and inverse electron demand reactions. Bivariate and partial correlation matrices ,and multivariant correlation between log k(k,rate constant collected from literature) and the calculated quantum descriptors. Also the data were subjected to ridge regression to obtain models with better predictive power and to reduce correlation among predicator variables.

الخلاصة

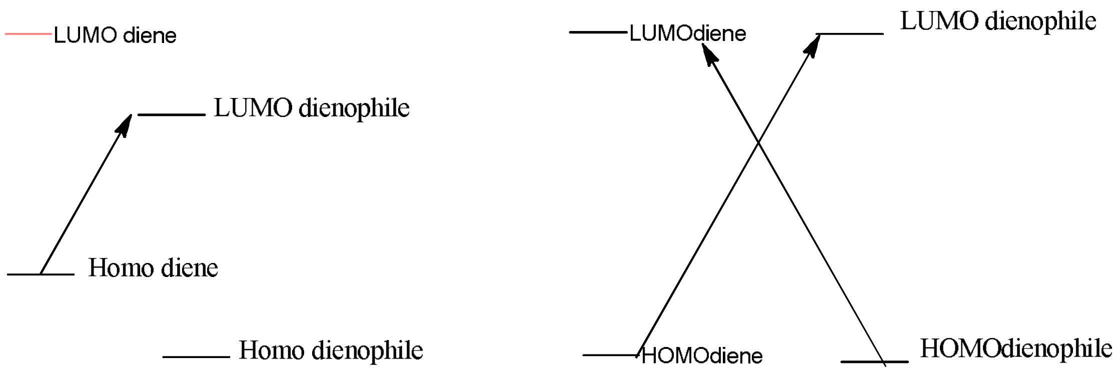
اجريت الحسابات شبه التجريبية لبعض المركبات التي تعاني من تفاعلات ديلز-الدير ومن الأنواع الثلاثة الاعتيادية والمتعادلة والعكسية. وتم حساب مصفوفة العلاقة الجزئية الثنائية لغرض إيجاد علاقة خطية متعددة المتغيرات بين لوغارتم ثابت سرعة التفاعل (المقتبس من الادبيات) والمتغيرات الكمية المحسوبة، بواسطة التحليل الانحداري المتعدد. ثم عرضت المعطيات الناتجة لتحليل ريج الانحداري لغرض تصحيح المعاملات وجعل العلاقات اكثر تحقيقا مع المتغير العملي (لوغارتم ثابت سرعة التفاعل).

مفاتيح الكلمات: تفاعلات ديلز-الدير، حسابات كمية شبة تجريبية، حسابات التحليل الانحداري المتعدد، الانحداري.Ridgeتحليل

Introduction

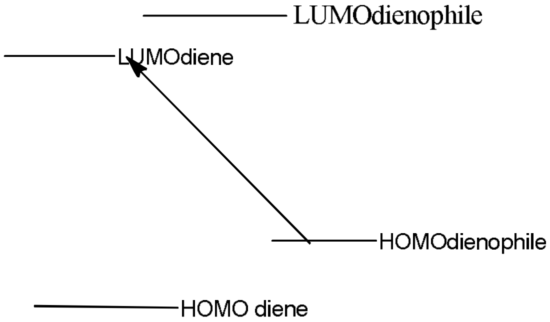
Diels-Alder (DA) reactions are synthetically important reactions, used routinely by organic chemists[1]. They have been used as highly regio- and stereospecfic reactions for the construction of six- membered ring compounds of up to four stereogenic centers. The classic DA reaction is a cycloaddition between a conjugated diene and a second component, called the dienophile which has at least a π bond.[2] Frontier molecular orbital (FMO) theory dictates the DA reaction between HOMO-LUMO molecular orbitals in the two partners closest in energy. According to Woodward-Hoffmann's rules, the concept of Orbital symmetry conservation. DA cycloadditions are thermally allowed $\pi 4s+\pi 2s$ reaction types.[3]

DA reactions had been classified into three types[4] (Scheme I) following the molecular electronic theory of Fukui [4]. In type I (normal electron demand) the dominant FMOs interactions are of the HOMO$_{\text{diene}}$ with LUMO$_{\text{dienophile}}$. For type II (neutral electron demand) DA reactions, the similarity of the FMO in the diene and the dienophile energies implies that both HOMO-LUMO interactions of the diene and the dienophile are involved .Where this type can be regarded as transition between type I and type III. In type III (inverse electron demand) the dominated interactions are that of the LUMO of the diene and the HOMO of the dienophile.



type I (normal) electron demand

type II(neutral electron demand)



typeIII(inverse electron demand)

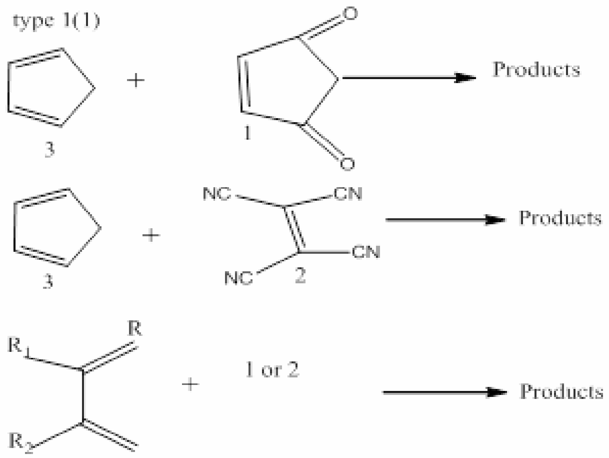
Scheme I

Normal electron demand DA reactions are promoted by electron –donating (ED) substituent in the diene and electron –withdrawing(EW) substituent in the dienophile. The opposite situation applies for inverse electron demand reactions. Neutral DA reactions are insensitive to ED and EW substituent.

In the present work we try to find linear correlations for the reactivity of the three types of reactions with some of their quantum descriptors. In this context, correlations between log k and ground state HOMO $_{diene}$, LUMO $_{diene}$, HOMO$_{dienophile}$, and LUMO $_{dienophile}$, and the transition state descriptors the energy differences ΔE HOMO $_{diene}$ – LUMO $_{dienophile}$ (HOMO $_{diene}$-controlled reaction (HOC))and , ΔE HOMO $_{dienophile}$ –LUMO $_{diene}$(LUMO $_{diene}$-controlled reaction (LUC)) were sought .

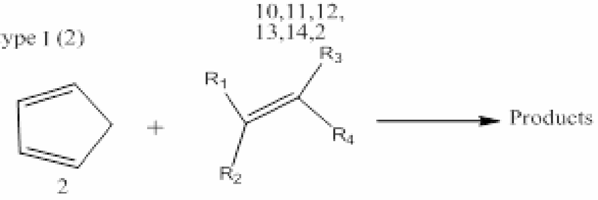
Although there are few examples of kinetic studies of DA reactions, rate constant for the three types of reactions were collected from the old and recent literature[4,6] to insure diversity.

type 1(1)



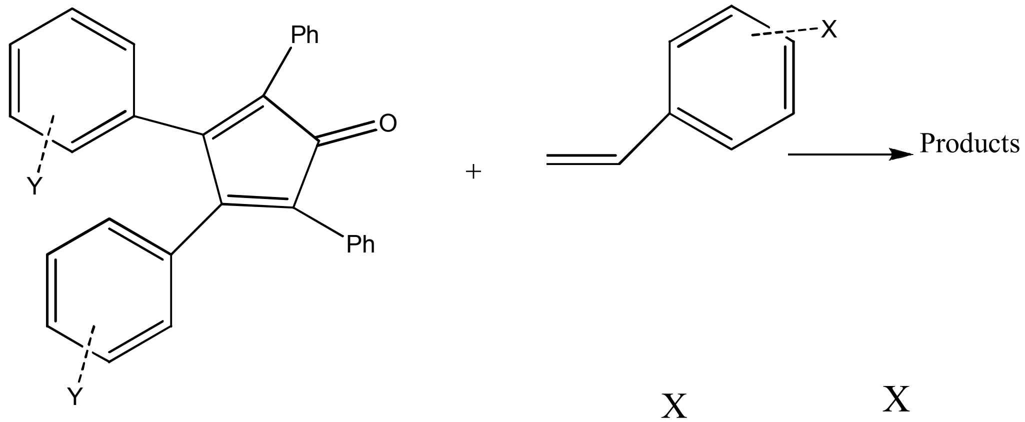
	R	R1		
4	OMe	H	H	
5	H	OMe	H	
6	H	CH_3	CH_3	
7	CH_3	H	H	trans
8	H	CH_3	H	
9	H	H	H	

type I (2)



	R1	R2	R3	R4
10	H	H	CN	H
11	CN	H	H	CN
12	CN	H	CN	H
13	H	H	CN	CN
14	H	CN	CN	CN
15	CN	CN	CN	CN

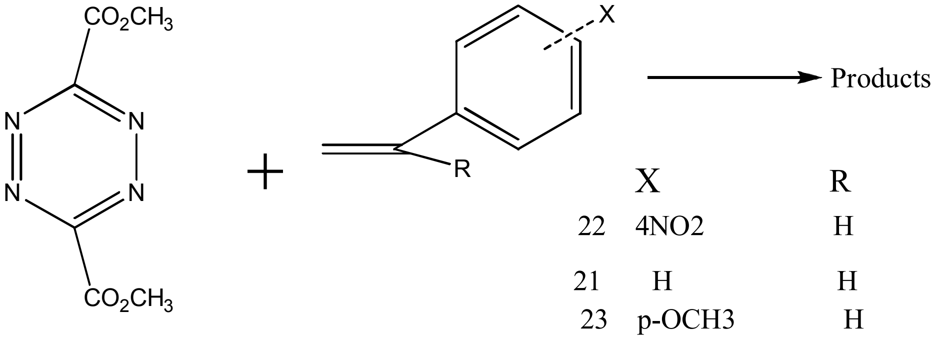
type II (1)



Y = H 24
Y = OCH_3 25
Y = $N(CH3)_2$ 26

X	X
21=H	28 =p-Cl
27= N $(CH3)_2$	29= m-NO_2
23= p-OCH_3	22=p-NO_2

typeIII(1)

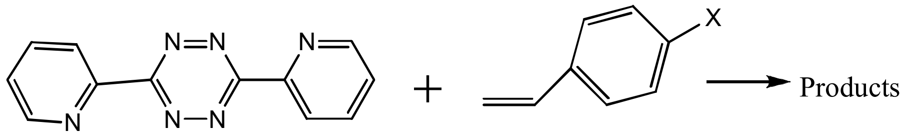


37

	X	R
22	4NO2	H
21	H	H
23	p-OCH3	H
38	H	N-morpholino

37+21-23,38 ⟶ products

type III(2)



39

X- 23 p-OMe 41 p-Cl
28 Me 22 p- NO2
21 H 40 p-Me

39+21-23,40,41 ⟶ products

Scheme II

Computational and Statistical Details

MM2 optimized structures of the dienes and the dienophiles scheme II were further optimized with PM3 basis set using Chemoffice Ultra 11 .The semiempirical calculations were carried out in the gas phase at restricted closed shell Hartree-Fock(RHF) level. Except for compounds with nitro substituents where an open shell restricted Hartree-Fock were used. All structures were optimized using the eigen vector following algorithm.

The bivariate and partial correlations matrices were computed using SPSS version 11.Correlation between two variables were considered significant at $p < 0.05$ or better. The multivariate correlations were computed using the same program following the higher R^2 and more important the significant $p< 0.05$ or less.

The ridge regression were applied to reactions type I (1), type I (3), type II (1), type II (2), And type III (3) using Matlab R2011b.

Results and Discussion

Table 1 showed the collected experimental and the calculated quantum descriptors of the three types of DA reactions log k ,HOMOs , LUMOs of the dienes and dienophiles together with the energy differences ΔE HOMO $_{\text{diene}}$-LUMO $_{\text{dienophile}}$ (HOC) and ΔE HOMO $_{\text{dienophile}}$-LUMO $_{\text{diene}}$ (LUC).

Type I (1)

Diene	Dienophile	K	LogK	HOD	LUD	HODPH	LUDPH	HOC	LUC
3	1	9210	-1.0357	-0.3387	0.0124	-0.4002	-0.0553	0.2834	0.4126
4	1	84.1	-3.0752	-0.3218	0.0134	-0.4002	-0.0553	0.2665	0.4136
6	1	33.6	-3.4737	-0.3348	0.0096	-0.4002	-0.0553	0.2795	0.4098
7	1	22.7	-3.644	-0.3355	0.0086	-0.4002	-0.0553	0.2802	0.4088
8	1	15.4	-3.8125	-0.3403	0.0091	-0.4002	-0.0553	0.285	0.4093
9	1	68.3	-4.1656	-0.3445	0.0081	-0.4002	-0.0553	0.2892	0.4083
3	2	0.000333	3.5224	-0.3387	0.0124	-0.4238	-0.0934	0.2453	0.4362
4	2	86.1	1.935	-0.3218	0.0134	-0.4238	-0.0934	0.2284	0.4372
5	2	2.96	0.4713	-0.3301	0.0067	-0.4238	-0.0934	0.2367	0.4305
6	2	2.5	0.3979	-0.3348	0.0096	-0.4238	-0.0934	0.2414	0.4334
7	2	0.175	-0.757	-0.3355	0.0086	-0.4238	-0.0934	0.2421	0.4324
8	2	0.0741	-1.1302	-0.3403	0.0091	-0.4238	-0.0934	0.2169	0.4329
9	2	0.00169	-2.7721	-0.3445	0.0081	-0.4238	-0.0934	0.2511	0.4319

Type I (2)

Diene	Dienophile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
3	10	1	-5	-0. 7	-0.0124	-0.3947	-0.0124	0.3263	0.4071
3	11	91	-3.041	-0.3387	-0.0124	-0.4056	-0.0488	0.2899	0.418
3	12	81	-3.0915	-0.3387	-0.0124	-0.4041	-0.0458	0.2929	0.4165
3	13	45500	-0.342	-0.3387	-0.0124	-0.4074	-0.0423	0.2955	0.4198
3	14	480000	0.6812	-0.3387	-0.0124	-0.4154	-0.0721	0.2666	0.4278
3	2	43000000	2.6335	-0.3387	-0.0124	-0.4238	-0.0934	0.2453	0.4362

Type I (3)

Diene	Dienophile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
15	18	24.1	1.382	-0.3344	-0.0247	-0.3588	-0.0965	0.2379	0.3341
15	19	83.7	1.9227	-0.3344	-0.0247	-0.3963	-0.1168	0.2176	0.3716
15	20	23.5	1.3711	-0.3344	-0.0247	-0.3415	-0.0953	0.2391	0.3168
15	18	5.96	0.7752	-0.334	-0.036	-0.3588	-0.0965	0.2375	0.3228
15	19	19.2	1.2833	-0.334	-0.036	-0.3963	-0.1168	0.2172	0.3603
15	24	5.62	0.7497	-0.334	-0.036	-0.3415	-0.0953	0.2387	0.3055
16	18	0.113	-0.9469	-0.336	-0.037	-0.3588	-0.0965	0.2395	0.3218
16	19	0.382	-0.4179	-0.336	-0.037	-0.3963	-0.1168	0.2192	0.3593
16	20	0.101	-0.9957	-0.336	-0.037	-0.3415	-0.0953	0.2407	0.3045
17	15	0.0008	-3.098	-0.3609	-0.0675	-0.3588	-0.0965	0.2644	0.2913
17	19	0.0012	-2.74723	-0.3609	-0.0675	-0.3963	-0.1168	0.2441	0.3288
17	20	0.0007	-3.1403	-0.3609	-0.0675	-0.3415	-0.0953	0.2656	0.274

Type II (1)

Diene	Dienephile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
24	27	338	-2.4711	-0.3284	-0.3284	-0.2882	0.0048	0.3332	0.228
24	23	102	-2.9914	-0.3284	-0.3284	-0.3202	-0.0028	0.3256	0.260
24	21	73	-3.1367	-0.3284	-0.3284	-0.3341	-0.0053	0.3231	0.27390
24	28	78	-3.1079	-0.3284	-0.3284	-0.3323	-0.0145	0.3139	0.2721
24	29	79	-3.1024	-0.3284	-0.3284	-0.368	-0.0711	0.2573	0.3078
24	22	88	-3.0555	-0.3284	-0.3284	-0.3736	-0.0755	0.252	0.3134
25	27	176	-2.7545	-0.3197	-0.3197	-0.2882	0.0048	0.324	0.2318
25	23	52.5	-3.2798	-0.3197	-0.3197	-0.3202	-0.0028	0.3169	0.2638
25	21	44.6	-3.3507	-0.3197	-0.3197	-0.3341	-0.0053	0.3144	0.2777
25	28	44.5	-3.3516	-0.3197	-0.3197	-0.3323	-0.0145	0.3052	0.2759
25	29	62	-3.2076	-0.3197	-0.3197	-0.368	-0.0711	0.2486	0.3116
25	22	83	-3.0809	-0.3197	-0.3197	-0.3736	-0.0755	0.2442	0.3172
26	27	37	-3.4318	-0.2904	-0.2904	-0.2882	0.0048	0.2952	0.2424
26	23	37	-3.4310	-0.290	-0.2904	-0.3202	-0.0028	0.2876	0.2744
26	21	15.5	-3.8097	-0.2904	-0.2904	-0.3341	-0.0053	0.2851	0.2883
26	28	31	-3.5086	-0.2904	-0.2904	-0.3323	-0.0145	0.2759	0.2865
26	29	48	-3.3188	-0.2904	-0.2904	-0.368	-0.0711	0.2193	0.3222
26	22	86	-3.0655	-0.2904	-0.2904	-0.3736	-0.0755	0.2149	0.3278

Type II (2)

Diene	Dienophile	K	log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
16	31	3290	-1.4828	-0.334	-0.036	-0.3402	-0.0507	0.2833	0.3042
16	32	6160	-1.2104	-0.334	-0.036	-0.3733	-0.0758	0.2582	0.3373
16	33	4060	-1.3915	-0.334	-0.036	-0.3256	-0.0498	0.2842	0.2896
17	31	78.1	-3.1073	-0.336	-0.037	-0.3402	-0.0507	0.2853	0.3032
17	32	95.8	-3.0186	-0.336	-0.037	-0.3733	-0.0758	0.2602	0.3363
17	33	145	-2.8125	-0.336	-0.037	-0.3256	-0.0498	0.2862	0.2886
16	34	359	-2.4449	-0.334	-0.036	-0.344	-0.0126	0.3214	0.308
16	35	620	-2.2076	-0.334	-0.036	-0.3873	-0.0717	0.2623	0.3513
16	36	424	-2.3726	-0.334	-0.036	-0.326	-0.0115	0.3225	0.29
16	21	334	-2.4763	-0.334	-0.036	-0.3341	-0.0053	0.3287	0.2981
16	22	580	-2.2365	-0.334	-0.036	-0.3736	-0.0755	0.2585	0.3376
16	23	466	-2.3316	-0.334	-0.036	-0.3202	-0.0028	0.3312	0.2842
17	21	8.7	-3.5834	-0.336	-0.037	-0.3341	-0.0053	0.3307	0.2971
17	22	14.8	-3.7986	-0.336	-0.037	-0.3736	-0.0755	0.2605	0.3366
17	23	13.4	-3.6162	-0.336	-0.037	-0.3202	-0.0028	0.3332	0.2832
30	21	9.38	-4.0278	-0.3535	-0.0404	-0.3341	-0.0053	0.3482	0.2937
30	22	15	-3.8239	-0.3535	-0.0404	-0.3736	-0.0755	0.278	0.3332
30	23	15.8	-3.8013	-0.3535	-0.0404	-0.3202	-0.0028	0.3507	0.2798

Type III (1)

Diene	Dienophile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
37	22	872	-2.0595	-0.3587	-0.0797	-0.3736	-0.0755	0.2832	0.2939
37	21	6500	-1.1871	-0.3587	-0.0797	-0.3341	-0.0053	0.3634	0.2544
37	23	25400	-0.5952	-0.3587	-0.0797	-0.3302	-0.0028	0.3559	0.2405
37	38	4.70e05	0.6721	-0.3587	-0.0797	-0.2972	0.0037	0.3624	0.2175

Type III (2)

Diene	Dienophile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
39	23	5.26	-2.279	-0.3618	-0.0607	-0.3202	-0.0028	0.359	0.2595
39	40	2.85	-2.5452	-0.3618	-0.0607	-0.3281	-0.0049	0.3569	0.2674
39	21	2.15	-2.6676	-0.3618	-0.0607	-0.3341	-0.0053	0.3565	0.2734
39	41	1.76	-2.7545	-0.3618	-0.0607	-0.3323	-0.0145	0.3473	0.2716
39	22	0.83	-3.0809	-0.3618	-0.0607	-0.3736	-0.0755	0.2863	0.3129

Type III (3)

Diene	Dienophile	K	Log K	HOD	LUD	HODPH	LUDPH	HOC	LUC
42	31	3.45	-4.4622	-0.3434	-0.0502	-0.3402	-0.0507	0.2927	0.29
42	32	3.08	-4.5114	-0.3434	-0.0502	-0.3733	-0.0758	0.2676	0.3231
42	33	3.71	-4.4306	-0.3434	-0.0502	-0.3256	-0.0498	0.2936	0.2754
43	31	323	-2.4908	-0.3491	-0.054	-0.3402	-0.0507	0.2984	0.2862
43	32	284	-2.5467	-0.3491	-0.054	-0.3733	-0.0758	0.2733	0.3193
43	33	399	-2.4698	-0.3491	-0.054	-0.3256	-0.0498	0.2993	0.2716
42	34	1.71	-4.767	-0.3434	-0.0502	-0.344	-0.0126	0.3308	0.2938
42	35	1.6	-4.7959	-0.3434	-0.0502	-0.3873	-0.0717	0.2717	0.3371
42	36	1.76	-4.7545	-0.3434	-0.0502	-0.326	-0.0115	0.3319	0.2758
43	34	159	-2.7986	-0.3491	-0.054	-0.344	-0.0126	0.3365	0.29
43	35	152	-2.9031	-0.3491	-0.054	-0.3873	-0.0717	0.2774	0.3333
43	36	170	-2.7696	-0.3491	-0.054	-0.326	-0.0115	0.3376	0.272
42	21	5.2	-4.284	-0.3434	-0.0502	-0.3341	-0.0053	0.3381	0.2839
42	22	3.02	-4.52	-0.3434	-0.0502	-0.3736	-0.0755	0.2679	0.3234
42	23	10.7	-3.9706	-0.3434	-0.0502	-0.3202	-0.0028	0.3406	0.27
44	21	3.64	-4.4389	-0.3609	-0.0675	-0.3341	-0.0053	0.3556	0.2666
44	22	2.25	-4.6478	-0.3491	-0.0675	-0.3736	-0.0755	0.2854	0.3061
44	23	24.1	-3.618	-0.3491	-0.0675	-0.3202	-0.0028	0.3581	0.2527
43	45	9.16	-4.0381	-0.334	-0.036	-0.3304	0.0067	0.3407	0.2944
43	46	9.74	-4.0114	-0.334	-0.036	-0.3182	0.0068	0.3408	0.2822
43	45	23.5	-3.6289	-0.3491	-0.054	-0.3304	0.0067	0.3558	0.2764
43	46	26.7	-3.5735	-0.3491	-0.054	-0.3182	0.0068	0.3559	0.2642

Table 1 Experimental and quantum descriptors of the eight reactions Studied k = rate constant ref. 3,5 ,HOD (ev)=HOMO orbital of the diene LUD(ev)= LUMO orbital of the diene , HODPH (eV)= HOMO orbital of the Dienophile, LUDPH(eV) = LUMO orbital of the dienophile, HOC(eV) = Energy difference between HOD and LUDPH, and LUC (eV)= Energy difference between LUD and HODPH.

Generally it is seen from table 1 that ED substituent increase the HOMO energy levels and raised the LUMO levels slightly. While EW substituent lowers the HOMO levels slightly , but has larger effects on the LUMO levels.

The difference between energy levels HOMO $_{diene}$- LUMO $_{dienophile}$ (HOC)and HOMO $_{dienophile}$-LUMO $_{diene}$ (LUC) were calculated for all reactions as shown in table1.

The value of this difference determines whether the reaction is normal, neutral or inverse type.[3] Hence if

HOC<LUC the reaction is normal type ,and when

HOC >LUC the reaction is inverse type . While in case of neutral type HOC and LUC energy values are approximately equal.

As shown from table 1 , the mean of the energy difference of HOC is smaller than mean of LUC energy difference of all reactions of type I ;
type I (1)
HOC =0.2597eV< LUC=0.4228eV.
Type I (2)
HOC =0.2861eV< LUC = 0.4209eV,
type I (3)
HOC = 0.2385eV<LUC 0.3242 eV ,
which indicate that the interactions of HOMO $_{diene}$ and LUMO $_{dienophile}$ orbitals dominates the reactions. Contrary , in case of inverse electron demand type III means of LUC energy values are always smaller than that of HOC mean values:
Type III (1)
HOC= 0.3387eV > LUC = 0.2516eV,
type III (2)
HOC = 0.3412eV > LUC =0.2769eV.
Type III (3)
HOC =0.3165eV >LUC =0.29014eV , this indicate that the reactions are mainly govern by the HOMO $_{dienophile}$ and LUMO $_{diene}$ orbitals interactions. On other hand, for type II the means of the HOC and the LUC energy differences are about equal,:
HOC =0.2854eV LUC =0.2819eV,
type II (2),
HOC =0.2991eV LUC =0.3084eV. Which showed that the FMO interactions of the diene and the dienophile have the same impact on the course of the reaction.

Correlation Matrices and Multivariate Correlations

For each reaction bivariate and partial correlation matrices were computed in order to evaluate the correlation between each pair of descriptors and especially to notice that between the experimental descriptor and other quantum descriptors .Then linear regressions were made to find the predictive factors of the reactions. A correlation was considered significant
if p value< 0.05 or less and less important r^2.

Normal electron demand reactions (type I)

The reaction of tetracyanoethylene and maliec anhydride with substituted dienes[4] is the first representative reaction of normal electron demand. As shown in table below.

Table 2 Bivariate correlation, reaction of tetracyanoethylene and malice anhydride with Substituted dienes .

Correlations

		LOGK	HOD	LUD	HODPH	LUDPH	HOC	LUC
LOGK	Pearson Correlation	1	.300	.380	-.738**	-.738**	-.781**	.811**
	Sig. (2-tailed)	.	.320	.201	.004	.004	.002	.001
	N	13	13	13	13	13	13	13
HOD	Pearson Correlation	.300	1	.531	-.059	-.059	-.393	.156
	Sig. (2-tailed)	.320	.	.062	.847	.847	.184	.611
	N	13	13	13	13	13	13	13
LUD	Pearson Correlation	.380	.531	1	.117	.117	-.072	.063
	Sig. (2-tailed)	.201	.062	.	.702	.702	.816	.837
	N	13	13	13	13	13	13	13
HODPH	Pearson Correlation	-.738**	-.059	.117	1	1.000**	.941**	-.984**
	Sig. (2-tailed)	.004	.847	.702	.	.	.000	.000
	N	13	13	13	13	13	13	13
LUDPH	Pearson Correlation	-.738**	-.059	.117	1.000**	1	.941**	-.984**
	Sig. (2-tailed)	.004	.847	.702	.	.	.000	.000
	N	13	13	13	13	13	13	13
HOC	Pearson Correlation	-.781**	-.393	-.072	.941**	.941**	1	-.959**
	Sig. (2-tailed)	.002	.184	.816	.000	.000	.	.000
	N	13	13	13	13	13	13	13
LUC	Pearson Correlation	.811**	.156	.063	-.984**	-.984**	-.959**	1
	Sig. (2-tailed)	.001	.611	.837	.000	.000	.000	.
	N	13	13	13	13	13	13	13

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2 showed linear correlation between log k and :

HOC(r=-0.781,sig. =0.002) , LUC (r = 0.811, sig.= 0.001),
HODPH (r= -0.738, sig.=0.004), LUDPH (r = -0.738,sig.=0.004).

The negative sign of r value, for HOC, indicate an inverse proportionality , hence the rate increase as the value of HOC decreased i.e. the reaction is HOMO-controlled type I. Partial correlation of the above reaction also showed that HOC control the reaction r= -0.7812 with significance less than 0.01 which indicate strong correlation.

A multivariate regression showed predicators of the correlation.

Log k = 70+361 HODPH -0.7HOC +516 LUC.
N=13 r=0.875 r^2=0.765 sig. =0.003
Log k = - 63.7 - 6 HOC + 151 LUC.
N= 13 r= 0.811 r^2= 0.657 sig. 0.005
Log k = -71 + 517.8 LUC + 361 HODPH.
N=13 r=0.875 r^2 = 0.765 sig. = 0.001
Log k = 20.6 - 850HOC - 3 LUDPH
N =13 r = 0.781 r^2= 0.61 sig.=0.009

Again the negative sign of HOC, LUDPH in the last equation also indicates that
the reaction is of type I HOMO-controlled.

The second representative reaction of type I is the reaction of cyano-substituted dienophiles with cyclopentadiene type I(2) [4] .The bivariate correlation of the descriptors of this reaction table 3

below showed linear correlation of log k with HOC

(r=-0.914,sig.0.011)and LUDPH (r=-0.914, sig.=0.011),. LUC
(r=0.963,sig.0.002), HODPH (r=-.963,sig..002).

This indicate that lowering HOC and LUDHP increase the rate of reaction, which means that the reaction is of type I.

Table 3 Bivariate correlation. Reaction of cyano-substituted dienophiles with cyclopentadiene type I (2).

Correlations

		HODPH	LUDPH	HOC	LUC	LOGK
HODPH	Pearson Correlation	1	.988**	.988**	-1.000**	-.963**
	Sig. (2-tailed)	.	.000	.000	.	.002
	N	6	6	6	6	6
LUDPH	Pearson Correlation	.988**	1	1.000**	-.988**	-.914*
	Sig. (2-tailed)	.000	.	.	.000	.011
	N	6	6	6	6	6
HOC	Pearson Correlation	.988**	1.000**	1	-.988**	-.914*
	Sig. (2-tailed)	.000	.	.	.000	.011
	N	6	6	6	6	6
LUC	Pearson Correlation	-1.000**	-.988**	-.988**	1	.963**
	Sig. (2-tailed)	.	.000	.000	.	.002
	N	6	6	6	6	6
LOGK	Pearson Correlation	-.963**	-.914*	-.914*	.963**	1
	Sig. (2-tailed)	.002	.011	.011	.002	.
	N	6	6	6	6	6

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The partial correlation of the descriptors of type I (2) reaction indicate linear correlations between log k and :

HOC (r = -0.9136 , 011), LUC(r=.9635,sig..002) ,
HODPH (r=-.9635,sig..002),
and LUDPH (r =-0.9136, sig.= 0.011)

Also these suggest that the reaction is HOMO-controlled relative to the diene.

Only univariate correlation was found to be significant (.011) between log k and HOC

$$\text{Log k} = 25.5 - 93.9\ \text{HOC}$$

$$N = 5 \quad r = 0.914 \quad r^2 = 0.835 \quad \text{sig.} = 0.011$$

However the introduction of other descriptor gave an insignificant correlation (> 0.05).

The third example of type I is the reaction of plyhalogenated cyclopentadiene with Aryltriazoolinediones[6]. As shown in table 4 the bivriate correlation of the descriptors of the reaction indicate correlation between log k and:

HOC (r=-0.76, sig.0.004),LUC (r=0.639, sig.= 0.025) ,

HOD (r =0.893, sig. <0.01), LUD (r =0.936, sig. < 0.01).

The negative sign of(r = -0.76)for HOC suggests that the reaction is mainly controlled by the HOMO diene and LUMO dienophile interactions.

Table 4 Bivariate correlation. Reaction of polyhalogenated cyclopentdiene with aryltriazolinediones type I (3).

Correlations

		HODPH	LUDPH	HOC	LUC	LOGK
HODPH	Pearson Correlation	1	.965**	.634*	-.821**	-.128
	Sig. (2-tailed)	.	.000	.027	.001	.692
	N	12	12	12	12	12
LUDPH	Pearson Correlation	.965**	1	.657*	-.793**	-.132
	Sig. (2-tailed)	.000	.	.020	.002	.682
	N	12	12	12	12	12
HOC	Pearson Correlation	.634*	.657*	1	-.933**	-.760**
	Sig. (2-tailed)	.027	.020	.	.000	.004
	N	12	12	12	12	12
LUC	Pearson Correlation	-.821**	-.793**	-.933**	1	.639*
	Sig. (2-tailed)	.001	.002	.000	.	.025
	N	12	12	12	12	12
LOGK	Pearson Correlation	-.128	-.132	-.760**	.639*	1
	Sig. (2-tailed)	.692	.682	.004	.025	.
	N	12	12	12	12	12

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The partial correlation matrix of reaction type I (3) showed correlation of log k with:

HOC (r = -0.76, sig. = 0.004), LUC (r = 0.6386, sig. 0.025),

HOD (r=0.8926,sig. < 0.01) and LUD (r=0.9356, sig. <0.01).

The negative sign of r for the correlation of HOC with log k means that the reaction belongs to the normal electron type.

However the best multivariate correlations were

$$\text{Log } k = 45.151 - 140 \text{ HOC} + 117 \text{ LUDPH}$$
$$N = 12 \qquad r = 0.902 \qquad r^2 = 0.814 \qquad \text{sig.} = 0.001$$
$$\text{Log } k = 45.151 - 23.9 \text{ HOC} + 116.5 \text{ HOD}$$
$$N = 12 \qquad r = 0.902 \qquad r^2 = 0.814 \qquad \text{sig.} = 0.001$$

In the last equation as HOC decrease and HOD increase the rate increase which indicate normal electron demand type of reaction.

Neutral electron demand reactions (type II)

In case of neutral electron demand reactions, two example were chosen from the literature the first one is the reaction of tetrasubstituted cyclopentadienones with substituted styrenes .[4]The correlations between experimental and quantum descriptors as show in table are weak (sig.> .05) except for

HOD (r =-0.626, sig. = 0.05) and LUD (r =-0.63, sig. = 0.05) .

The partial correlation of this reaction indicate also poor correlation between experimental and quantum descriptors e.g.

HOC (r=-0.4423, sig. 0.066), LUC (r = 0.2066 , sig. = 0.411).

Table 5 Bivariate correlation . Reaction of tetrasubstituted cyclopentadienones with Substituted strenes type II (1).

Correlations

		LOGK	HOD	LUD	HODPH	LUDPH	HOC	LUC
LOGK	Pearson Correlation	1	-.626**	-.630**	.179	-.060	.223	-.305
	Sig. (2-tailed)	.	.005	.005	.477	.813	.374	.218
	N	18	18	18	18	18	18	18
HOD	Pearson Correlation	-.626**	1	.999**	.000	.000	-.442	.207
	Sig. (2-tailed)	.005	.	.000	1.000	1.000	.066	.411
	N	18	18	18	18	18	18	18
LUD	Pearson Correlation	-.630**	.999**	1	.000	.000	-.442	.207
	Sig. (2-tailed)	.005	.000	.	1.000	1.000	.066	.410
	N	18	18	18	18	18	18	18
HODPH	Pearson Correlation	.179	.000	.000	1	.916**	.822**	-.978**
	Sig. (2-tailed)	.477	1.000	1.000	.	.000	.000	.000
	N	18	18	18	18	18	18	18
LUDPH	Pearson Correlation	-.060	.000	.000	.916**	1	.897**	-.896**
	Sig. (2-tailed)	.813	1.000	1.000	.000	.	.000	.000
	N	18	18	18	18	18	18	18
HOC	Pearson Correlation	.223	-.442	-.442	.822**	.897**	1	-.895**
	Sig. (2-tailed)	.374	.066	.066	.000	.000	.	.000
	N	18	18	18	18	18	18	18
LUC	Pearson Correlation	-.305	.207	.207	-.978**	-.896**	-.895**	1
	Sig. (2-tailed)	.218	.411	.410	.000	.000	.000	.
	N	18	18	18	18	18	18	18

**. Correlation is significant at the 0.01 level (2-tailed).

The second example of type II reaction is the reaction of polyhalogenated Cyclopentadiene with N-arylmaleimides, aryl acrylates and styrenes.[6] The bivariate correlation matrix of this reaction showed poor correlation as well, between log k and the quantum descriptors:

HOC(r =-0.394, sig. =0.105), LUC (r =0.145, sig. =0.567) ,

while significant correlation with

HOD (r =0.66,sig. =.003), and LUD (r = 0.748, Sig. < 0.001).

These results indicate the dependence of the reaction rate on both HOC and LUC which means that the above reaction belongs to neutral type(type II).

Table 6 Bivariate correlation. Reaction of polyhalogenated cyclopentadiene with N-aryl maleimides, aryl acrylates and substituted Styrenes type II (2).

Correlations

		LOGK	HOD	LUD	HODPH	LUDPH	HOC	LUC
LOGK	Pearson Correlation	1	.660**	.748**	-.094	-.267	-.394	.145
	Sig. (2-tailed)	.	.003	.000	.710	.284	.105	.567
	N	18	18	18	18	18	18	18
HOD	Pearson Correlation	.660**	1	.987**	-.063	-.151	-.358	.130
	Sig. (2-tailed)	.003	.	.000	.804	.550	.144	.607
	N	18	18	18	18	18	18	18
LUD	Pearson Correlation	.748**	.987**	1	-.070	-.137	-.342	.137
	Sig. (2-tailed)	.000	.000	.	.784	.588	.165	.587
	N	18	18	18	18	18	18	18
HODPH	Pearson Correlation	-.094	-.063	-.070	1	.831**	.798**	-.998**
	Sig. (2-tailed)	.710	.804	.784	.	.000	.000	.000
	N	18	18	18	18	18	18	18
LUDPH	Pearson Correlation	-.267	-.151	-.137	.831**	1	.977**	-.834**
	Sig. (2-tailed)	.284	.550	.588	.000	.	.000	.000
	N	18	18	18	18	18	18	18
HOC	Pearson Correlation	-.394	-.358	-.342	.798**	.977**	1	-.816**
	Sig. (2-tailed)	.105	.144	.165	.000	.000	.	.000
	N	18	18	18	18	18	18	18
LUC	Pearson Correlation	.145	.130	.137	-.998**	-.834**	-.816**	1
	Sig. (2-tailed)	.567	.607	.587	.000	.000	.000	.
	N	18	18	18	18	18	18	18

**. Correlation is significant at the 0.01 level (2-tailed).

The significant multi-correlations found were

Log k = -55.7 - 424.9 HOD + 2298.9 LUD -18.6 LUDPH – 20 LUC .

R= 0.957 $r^2 = 0.916$ sig. <0.001

Log k = 10.005 – 22 HOC -20 LUC

R = 0.499 $r^2 = 0.249$ sig. =0.117

Log k =23 + 78 HOD – 5LUDPH

R = 0.681 $r^2 = 0464$ sig. = 0.009

Log k = 12 +415 LUD -2 HODPH

R = 0.749 $r^2 = 0.561$ sig. = 0.002

The most significance showed by the first equation indicate that all quantum descriptors

.

Inverse electron demand reactions (type III)

Three examples of reactions were chosen to represent the inverse electron demand DA reaction. The first one was the reaction of tetrazine-3,6-dimethylcarboxylate with substituted styrenes .[4] The Bivariate correlation matrix (table 7) of the descriptors of this reaction showed that the correlation between log k and LUC is significant (r =-0.969, sig. =0.031). The partial correlation matrix showed a significant correlation between log k and LUC (r = -0.9687, sig. = 0.031) also. The negative sign of r is indicative of a LUMO-controlled relative to the diene.

Univariate and multivariate correlation also confirmed this conclusion:

have the same impact on the rate of reaction . Which belongs to neutral type reaction

$$\text{Log k} = 19.8 - 19.5\ \text{HOC} - 55.6\ \text{LUC}$$
$$R = 0.999 \quad r2 = 0.997 \quad \text{sig.} = 0.051$$
$$\text{Log k} = 7.925 - 034.7\ \text{LUC}$$
$$R = 0.969 \quad r2 = 0.938 \quad \text{sig.} = 0.031$$

Table 7 Bivariate correlation matrix . Reaction of tetrazine-3,6-dimethyl carboxylate with Substituted styrenes type III (1).

Correlations

		HODPH	LUDPH	HOC	LUC	LOGK
HODPH	Pearson Correlation	1	.924	.924	-1.000**	.969*
	Sig. (2-tailed)	.	.076	.076	.	.031
	N	4	4	4	4	4
LUDPH	Pearson Correlation	.924	1	1.000**	-.924	.802
	Sig. (2-tailed)	.076	.	.	.076	.198
	N	4	4	4	4	4
HOC	Pearson Correlation	.924	1.000**	1	-.924	.802
	Sig. (2-tailed)	.076	.	.	.076	.198
	N	4	4	4	4	4
LUC	Pearson Correlation	-1.000**	-.924	-.924	1	-.969*
	Sig. (2-tailed)	.	.076	.076	.	.031
	N	4	4	4	4	4
LOGK	Pearson Correlation	.969*	.802	.802	-.969*	1
	Sig. (2-tailed)	.031	.198	.198	.031	.
	N	4	4	4	4	4

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The reaction of substituted styrenes and di (2-pyridyl)-1,2,4,5-tetrazine type III (2)[6] was also an inverse electron demand .The bivariate matrix showed correlation between log k and LUC (r=-.916, sig...029).

The partial correlation showed the same (r = -0.9157, sig. = 0.029) between LUC and log k .While multiple regression showed a poor correlation sig. ($p>0.05$)

Log k =7.7 – 9 HOC - 26 LUC.
R = 0.938 $r^2 = 0.88$ sig. =0.12 Log k =1 – 13 LUC.
R = 0.916 $r^2 = 0.838$ sig. = 0.029

Table 8 Bivariate correlation matrix . Reaction of di (2-pyridyl)-1,2,4,5-tetrazine with substituted styrenes type III(2)

Correlations

		HODPH	LUDPPH	HOC	LUC	LOGK
HODPH	Pearson Correlation	1	.977**	.977**	-1.000**	.916*
	Sig. (2-tailed)	.	.004	.004	.	.029
	N	5	5	5	5	5
LUDPPH	Pearson Correlation	.977**	1	1.000**	-.977**	.852
	Sig. (2-tailed)	.004	.	.	.004	.067
	N	5	5	5	5	5
HOC	Pearson Correlation	.977**	1.000**	1	-.977**	.852
	Sig. (2-tailed)	.004	.	.	.004	.067
	N	5	5	5	5	5
LUC	Pearson Correlation	-1.000**	-.977**	-.977**	1	-.916*
	Sig. (2-tailed)	.	.004	.004	.	.029
	N	5	5	5	5	5
LOGK	Pearson Correlation	.916*	.852	.852	-.916*	1
	Sig. (2-tailed)	.029	.067	.067	.029	.
	N	5	5	5	5	5

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

The reactions of polyhalogenated cyclopentadienes with N-aryl maleimides, aryl acrylates, substituted styrenes and aryloxyethenes were other example of inverse electron demand Reactions type III (3) .[6]

The bivariate correlation matrix of the descriptors of this reaction table 9 showed no Significant correlation between log k and quantum descriptors , as well as the partial correlation matrix.

Table 9 Bivariate correlation matrix . Reaction of polyhalogenated cyclopentadieneWith N-aryl maleimides, aryl acrylates, substituted styrenes and aryloxy ethenes Type III(3).

Correlations

		LOGK	HOD	LUD	HODPH	LUDPH	HOC	LUC
LOGK	Pearson Correlation	1	-.207	-.098	.101	-.009	.036	-.132
	Sig. (2-tailed)	.	.355	.663	.654	.970	.872	.557
	N	22	22	22	22	22	22	22
HOD	Pearson Correlation	-.207	1	.985**	.096	.121	-.096	.229
	Sig. (2-tailed)	.355	.	.000	.670	.592	.671	.305
	N	22	22	22	22	22	22	22
LUD	Pearson Correlation	-.098	.985**	1	.134	.174	-.039	.197
	Sig. (2-tailed)	.663	.000	.	.553	.438	.863	.379
	N	22	22	22	22	22	22	22
HODPH	Pearson Correlation	.101	.096	.134	1	.829**	.810**	-.945**
	Sig. (2-tailed)	.654	.670	.553	.	.000	.000	.000
	N	22	22	22	22	22	22	22
LUDPH	Pearson Correlation	-.009	.121	.174	.829**	1	.977**	-.763**
	Sig. (2-tailed)	.970	.592	.438	.000	.	.000	.000
	N	22	22	22	22	22	22	22
HOC	Pearson Correlation	.036	-.096	-.039	.810**	.977**	1	-.814**
	Sig. (2-tailed)	.872	.671	.863	.000	.000	.	.000
	N	22	22	22	22	22	22	22
LUC	Pearson Correlation	-.132	.229	.197	-.945**	-.763**	-.814**	1
	Sig. (2-tailed)	.557	.305	.379	.000	.000	.000	.
	N	22	22	22	22	22	22	22

**. Correlation is significant at the 0.01 level (2-tailed).

Ridge regression

The correlation obtained for all types of reactions varied between good to poor but definitely with poor predictive power . As shown from the correlation matrices of the three types of reactions Tables 2-9 most of the predicator variables(independent variables) are highly correlated among themselves ,the coefficients of the resulting least squares fit, may be very imprecise. By allowing a small amount of bias in the estimates , more reasonable coefficients may be obtained.

Ridge regression is one method to address these issues . Often , small amounts of bias lead to dramatic reductions in the variance of the estimated model coefficients. The following Table 10 showed the amended correlations of some of the example reactions:

Table- 10 Correlation of some of the reactions studied after Ridge regression

No.	Ridge Correlation	Reaction Type
1	Logk=-0.2712HOD+0.930 5LUD -0.8168HOC +1.1602LUC	Type I (1)
2	Logk=-0.3703HODPH +1.827LUDPH-0.3672HOC +0.006LUC	Type I(3)
3	Logk=0.1104HODPH-0.0598LUDPH-0.392HOC-0.3265LUC	Type II(1)
4	Logk=-3.0604HOD+3.6568LUD-0.3592HODPH-0.6405LUDPH+0.0545HOC-0.1067LUC	Type II(2)
5	Logk=-0.0517HOD+0.2878LUD-1.1601HODPH+0.1747LUDPH+0.1864HOC-0.3793LUC	Type III(3)

Figure 1 Ridge trace plot for reaction type I (1) . Note the stability of the estimate value.

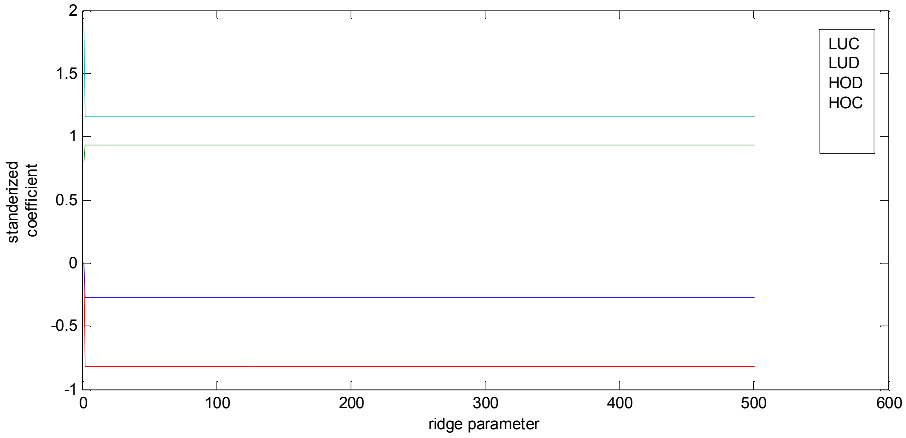


Figure 2 Ridge trace plot for reaction type I (3). Note the stability of the estimated values.
log k = -0.3703HODPH + 1.827LUDPH - 0.3672HOC + 0.0064LUC.

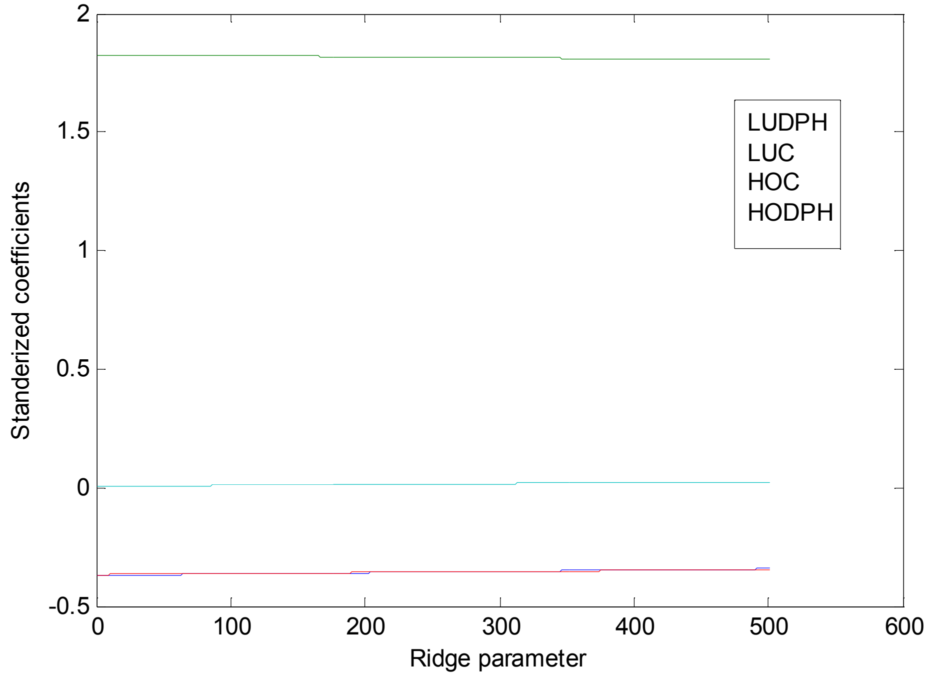


Figure 3 Ridge trace plot for reaction type II (1). Note the unstability of HOD and LUD hence dropped from the correlation.
log k=0.1104HODPH -0.0598LUDPH -0.392HOC - 0.3265LUC.

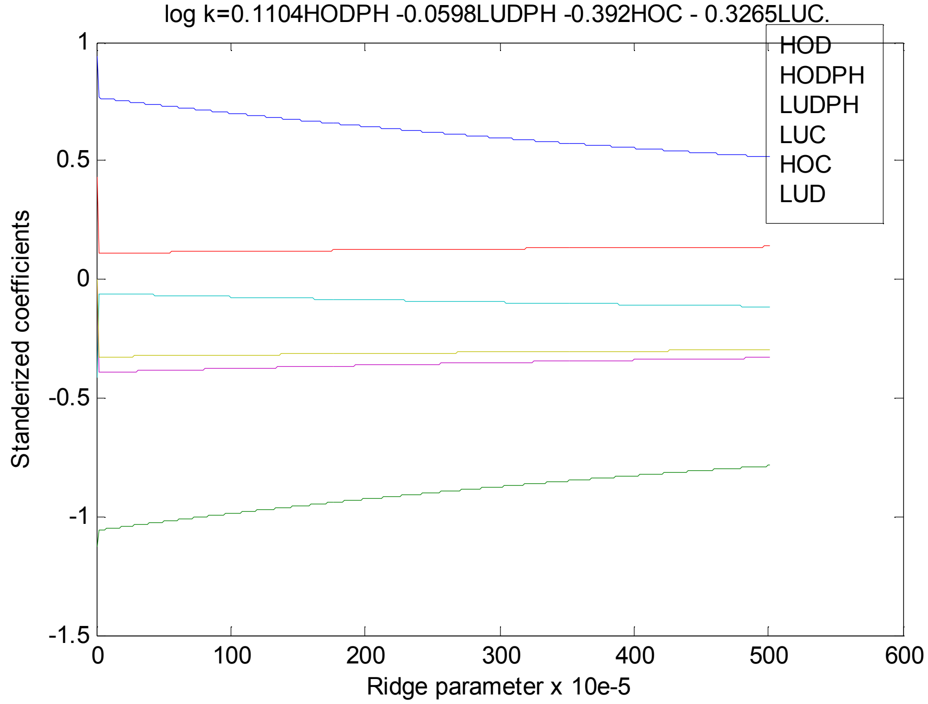


Figure 4 Ridge trace plot for reaction type II (2). Note the stability of the estimate values.
log k= -3.0604HOD + 3.6568LUD +0.3592HODPH -0.6405LUDPH + 0.0545HOC -0.1067LUC.

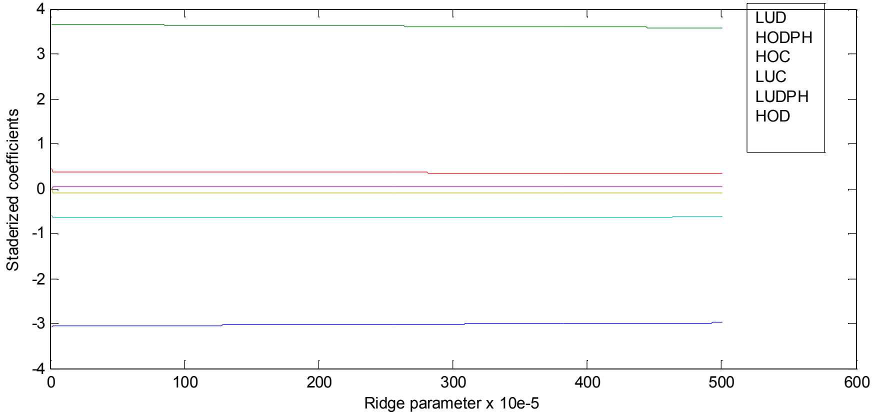
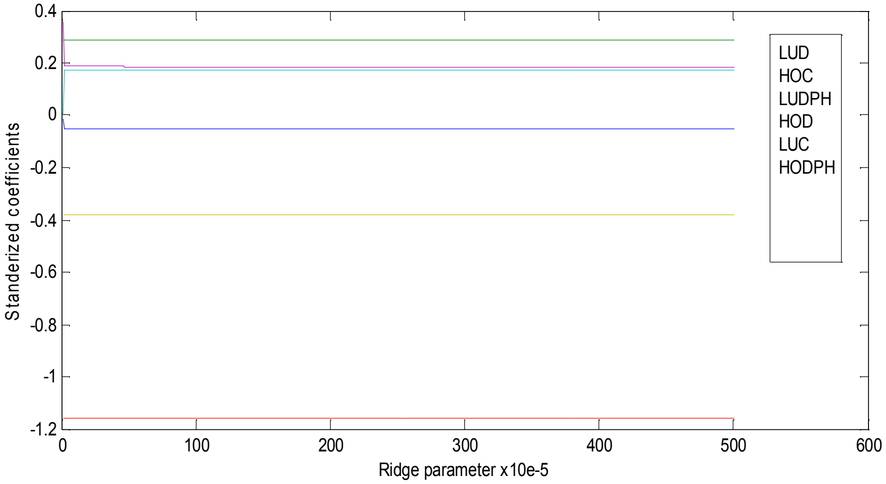


Figure 5 Ridge trace plot for reaction type III (3). Note the stable estimate values.
log k= -0.0517HOD + 0.2878LUD -1.1601HODPH +0.1747LUDPH +0.1864HOC -0.3793LUC.



Figures 1,2,3,4,and 5 showed the ridge trace plot of the three types of reactions. As seen from these figures ,the stability of the estimated coefficients indicate a good estimation . The correlations obtained after ridge regression table 10 are more predictive.

Conclusion

Any biological, physical, chemical system or process is too complicated to be understood 100%. The boundary between these system or processes required experimental approach. To achieving information. This takes us to a domain of multidimensional space. In case of the system we have been considered all the independent variables were theoretical information. And since quantum calculations are beyond experiment. the model we have obtained is still beyond ideal. Besides the correlations between variables are not necessarily linear. Still the statistical art is how to extract conclusions from a noisy data.

References

1.Nicolaou, K.C; Snyder S.A.;Montagnon,T; . Vassilikojinnakis,G.***Angew Chem.Int.Ed***.2002,**41**,1668-1698

2.Brocksom T.J.;NaKamara J.; Ferreira M.L.; and Brocksom U.;.***J.Brz,Chem.Soc***.; 2000, **12(5)**,597-622.

3.a. Fleming I.;Frontier Orbitals and Organic Chemical Reactions, J. Wiley, London 1976.

b. Houk K. N., ***J. Am. Chem. Soc***., 1973, **95**, 4092.

c. Ginsburg D. ,***Tetrahdron*** , 1983, **39,** 2095.

d. Isaccs N.; Physical Organic Chemistry, 2nd edn., Longman,Harlow 1995.

e. Fleming I., Pericyclic Reactions ,Oxford Science Publ. 67, Oxford University Press, 1999.

4. Reiner S.,Orbital energy control of cycloaddition Reactivity, ***Pure Appl. Chem***.,1974, **40**,569-593.

5. Fukui K., Chemical Reactivity Theory- Its Progmatism and Beyond , ***Pure and Appl. Chem.*** 1982, **54(10)**,1825-1836.

6. a. Eibler E., Hocht P., Prantl B., Roβmaier H.,Schuhbauer H.M., Wiest H., and Sauer J., ***Liebigs Ann./Rrcueil***, 1997, 2471-2484.

b. Wijnen J.W., Zavarise S., and Engberts J.B.F., ***J.Org. Chem.***, 1996, **61**, 2001-2005.

7. **a**. Mayers R. H.; Classical and Modern Regression with Applications ,2nd edition Duxbury Press, 1990.

b. Hoerl A. E.,and Kennard R. W. , ***Chemical Engineering Progress***, 1962, **58**, 54-59.