

Semi-Empirical Computation on Mechanism of Imidazolines and Benzimidazoles Synthesis and Their QSAR Studies

SWAPNALI HAZARIKA^{1,*}, DILIP KONWAR² and MANAS JYOTI BORA²

¹Chemical Engineering Division, CSIR-North East Institute of Science and Technology, Jorhat-785 006, India

²Synthetic Organic Chemistry Division, CSIR-North East Institute of Science and Technology, Jorhat-785 006, India

*Corresponding author: E-mail: shrljt@yahoo.com

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A green, mild and anaerobic synthesis of imidazolines and benzimidazoles from aldehydes and diamines using $I_2/KI/K_2CO_3/H_2O$ system has been investigated by semi-empirical methods. The observed efficient direction of the above synthesis has been modeled from a comparison of the energies of four possible transition states arising from mono and di additions of iodines in the configured molecules. In the reaction I_1 B is the most favorable transition state [TS] which is shown to be 20 Kcal/mol by PM₃ analyses. The resulting trends of relative transition states energies are in excellent agreement with the experimental observations. Also, the bond order, bond length, heat of formation is in good agreement to the formation of product B. In order to establish the suitable mechanism of the reaction a quantitative structure activity relationship analysis has been made using hydrophobicity as the molecular descriptor. In this analysis the values of refractivity, polarizability, hydration energy, electron affinity, ionization potential and dipole moment of the compounds have been correlated with their hydrophobicity which has been taken as the molecular property.

Keywords: Imidazoline, Benzimidazole, Water media, *ab initio*, Semi-empirical transition states, Hydrophobicity, QSAR.

INTRODUCTION

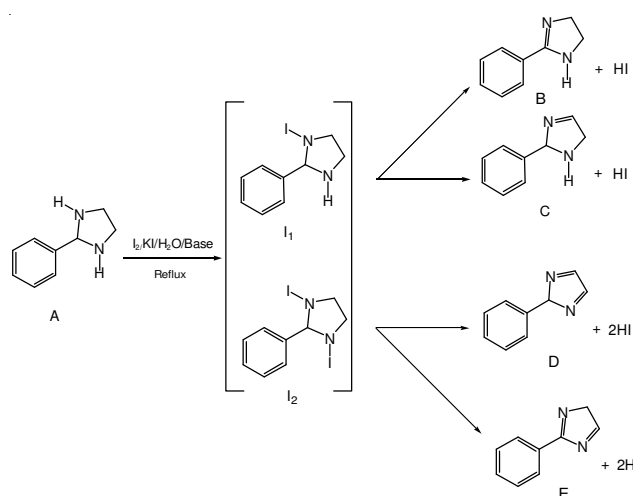
Imidazoline and benzimidazole derivatives are found in many biologically active compounds and they show biological activities in anti-ulcer, anti-tumor and anti-viral effects *etc.* Also, in organic synthesis, imidazoline units are also used as synthetic intermediates, chiral auxiliaries, chiral catalysts and ligands for asymmetric catalysis¹. On the other hand, I_2 has been used extensively as a synthetic reagent due to its inherent properties of low toxicity, electrophilicity and easy handling. Accordingly, we reported Bronsted acid catalyzed oxidation of alcohols to aldehydes and ketones in the presence of DMSO, where the catalyst HI was generated in a redox process of N_2H_4 and I_2 ². We also reported the use of I_2 for the deprotection of keto and aldoximes/imines and oxidation of alcohols to aldehydes and ketones in water^{3,4}.

Recently, a practical, inexpensive and green method for the synthesis of imidazolines and benzimidazoles in water using $I_2/KI/K_2CO_3/H_2O$ system under anaerobic conditions is also reported in the literature¹. In this communication, we report a validation of this proposal by quantum mechanical calculations. The QSAR analyses of the final products are also presented here.

RESULTS AND DISCUSSION

Energies: The synthesis of imidazolines goes *via* two steps in the reaction mixture. In the presence of $I_2/KI/$

K_2CO_3/H_2O system intermediate "A" is first formed from aryl/acyl aldehyde and diamines and that is anaerobically oxidized to form intermediates I_1 and I_2 that may produce four compounds B & C and D & E eliminating HI and 2HI respectively which are scavenged by the base in the reaction mixture **Scheme-I** (Table-1).



Scheme-I: Formation of possible products [B, C, D & E] *via* intermediates I_1 & I_2

TABLE I
SYNTHESIS OF IMIDAZOLINES AND BENZIMIDAZOLES FROM ALDEHYDES AND DIAMINES USING I₂/KI/K₂CO₃/H₂O SYSTEM IN WATER


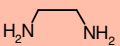
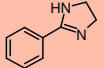
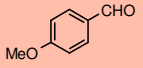
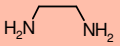
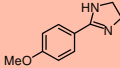
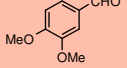

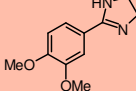
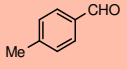
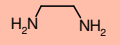
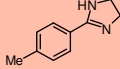
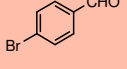

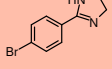
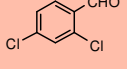

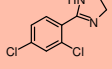
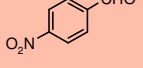
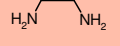
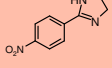
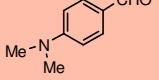
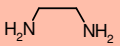
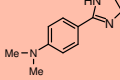

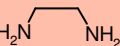
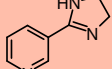
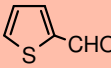

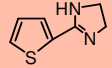
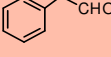

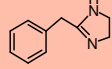
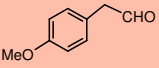

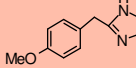

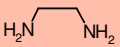
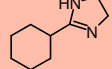

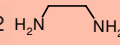
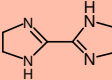
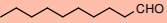

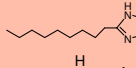


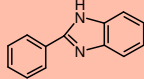
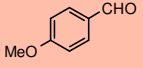

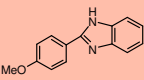
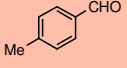

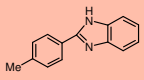


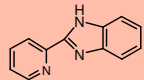
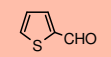

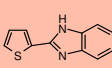
Entry	Aldehyde	Diamine	Product	Time (min)	Yield (%)	Physical state * m.p. °C
1				30	90	98-101
2				30	95	140
3				30	95	129-231
4				30	88	180
5				30	85	242-246
6				35	80	105-108
7				35	80	231
8				30	80	258-260
9				45	75	102-106
10				45	75	178
11				30	80	oil
12				30	85	104-106
13				30	84	132
14		2 		45	60	287
15				30	75	67-70
16				45	75	295
17				45	78	223-226
18				45	75	277
19				50	65	216-119
20				50	65	330

Fig. 1 presents the geometries of the four transition states *i.e.*, TsI₁B, TsI₁C, TsI₂D and TsI₂E corresponding to the four reaction channels as predicted. Table-2 reports the total energies and heat of formation of the starting compound 'A', intermediate I₁ and I₂ and the final products B, C, D and E in Kcal/mol and a.u. units. Both the AM1 and PM3 analyses of the products and intermediates show that the product 'B' has the lowest heat of formation *i.e.*, 41.0689499 Kcal/mol [AM1] and 57.1361720 Kcal/mol [PM₃], respectively. Also, the intermediates I₁ has lower heat of formation *i.e.*, 45.4810 Kcal/mol then intermediate I₂, which clearly supports that the reaction goes via the intermediate I₁.

PM₃ values

a₁ = activation energy = I₁B-I₁ = 19.70 Kcal/mol

a₂ = activation energy = I₁C-I₁ = 29.33 Kcal/mol

a₃ = activation energy = I₂D-I₂ = 29.83 Kcal/mol

a₄ = activation energy = I₂E-I₂ = 57.25 Kcal/mol

TsI₁B; TsI₁C; TsI₂D & TsI₂E = Transition state energies [Ts] of the respective reactions in Kcal/mol

AM₁ values

a₁ = activation energy = I₁B-I₁ = -15.79 Kcal/mol

a₂ = activation energy = I₁C-I₁ = -6.13 Kcal/mol

a₃ = activation energy = I₂D-I₂ = -9.74 Kcal/mol

a₄ = activation energy = I₂E-I₂ = -3.87 Kcal/mol

TsI₁B; TsI₁C; TsI₂D & TsI₂E = transition state energies [Ts] of the respective reactions in Kcal/mol

The activation energy among the four reactive channels *ie* TsI₁B, TsI₁C, TsI₂D & TsI₂E, the transition state energy or the activation energy for TsI₁B is the lowest *ie* 20 Kcal/mol that clearly shows the formation 'B' is the most favored channel and that was experimentally found¹. The value of the imaginary frequency for the TsI₁B is -168.74 Kcal/mol A².

Geometrical parameters and analyses of frequencies:

Table-3 refers the PM₃ analyses of starting compound 'A', transition states & products A, B, C, & D.

The geometries of the transition states corresponding to the four reactive channels TsI₁B, TsI₁C, TsI₂D and TsI₂E are displayed in Figs. 1 and 2 represents the bond lengths of the four reaction channels in their transition states. Figs. 3 and 4 shows the bond orders of four reaction channel transition states.

Table-4 refers the bond Lengths of the transition states I₁-B, I₁-C, I₂-D & I₂-E in Å. The bond length of 7C-8N is 1.3544 Å, the shortest bond length in I₁-B among the other three reaction channels indicating the strongest bond, but the bond length of 7C-11N *i.e.*, 1.4291 Å is little longer than 7C-8N which indicates a new bond could be formed. Also, the bond

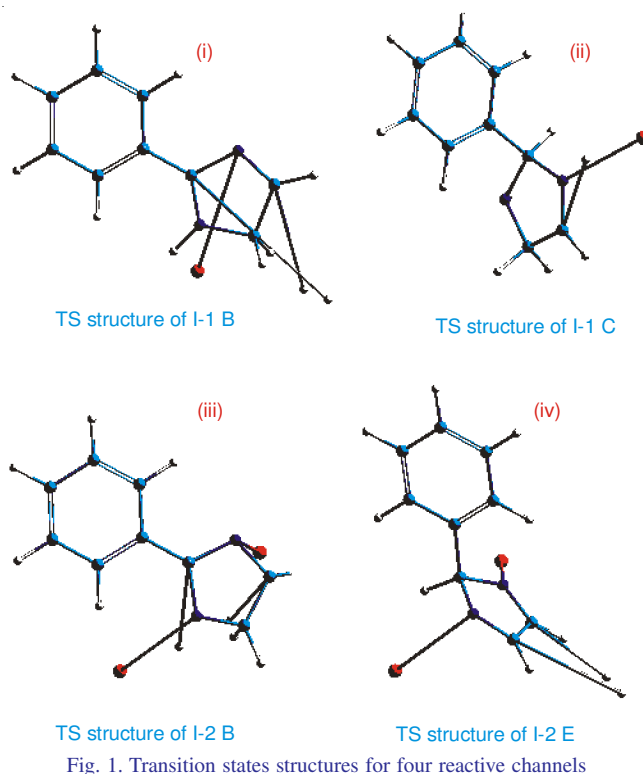


Fig. 1. Transition states structures for four reactive channels

TABLE-2
AM1 AND PM3 ANALYSES OF REACTANT, INTERMEDIATE AND PRODUCT

Sl. No.	Compds.	AM1		PM3	
		Total energy (K Cal/mol)/[a.u]	Heat of formation (K Cal/mol)	Total energy (K Cal/mol)/[a.u]	Heat of formation (K Cal/mol)
1	A	-36333.2589209/[-57.899577601]	28.8406931	-9911.5934709/[-63.601902830]	41.9801611
2	B	-35613.8737581/[-56.753187261]	41.0689499	-39266.627148/[-62.574104092]	57.1361720
3	C	-35605.4763130/[-56.739805348]	49.4663950	-39256.852882/[-62.558528119]	66.9104373
4	D	-34874.6028103/[-55.575107538]	73.1829917	-38598.774390/[-61.509834227]	95.1786175
5	E	-34880.9299941/[-55.585190346]	66.8558079	-38605.420373/[-61.520425064]	88.5326341
6	I ₁	-42637.4123686/[-67.945685014]	45.4810684	-47582.710339/[-75.826361621]	80.5058404
7	I ₂	-48940.5366016/[-77.990152301]	63.1506584	-55253.129258/[-88.049708181]	119.7294691

TABLE-3
TOTAL ENERGY OF THE INTERMEDIATES [I₁, & I₂] AND TRANSITION STATES OF THE FOUR REACTION CHANNELS⁴

S. No.	Compounds	Total energy [Kcal/mol]		Heat of Formation [kcal/mol]
		PM ₃ /AM ₁	PM ₃ /AM ₁	
1	I ₁	-42637.4123686/-47582.7103396	-67.945685014/ -75.826361621	45.4810684/80.5058404
2	I ₂	-48940.5366016/-55253.1292589	-77.990152301/-88.049708181	63.1506584/119.7294691
3	Ts I ₁ - B	-42617.6914884/-47598.5039100	-67.945362189/-75.853281120	45.6836478/63.6132624
4	Ts I ₁ - C	-42608.0801666/-47588.8440000	-67.898942108/-75.826213375	74.8132704/80.5988676
5	Ts I ₂ - D	-48910.7089119/-55262.8867000	-77.942619801/-88.066137003	92.9783481/109.4200219
6	Ts I ₂ - E	-48881.2866739/-55257.0000000	-77.895733416/-88.076512374	122.4005861/102.9092483

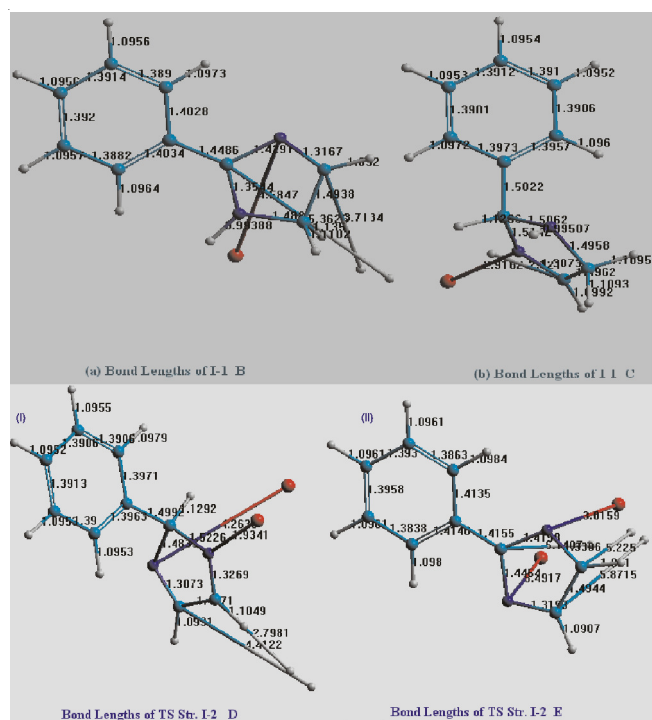


Fig. 2. Bond Lengths of transition states of B, C, D & E

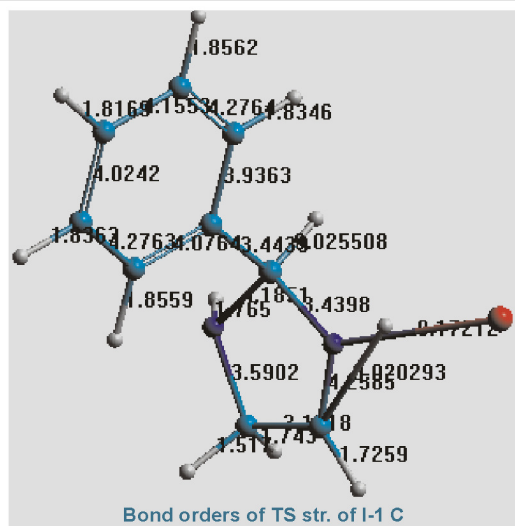
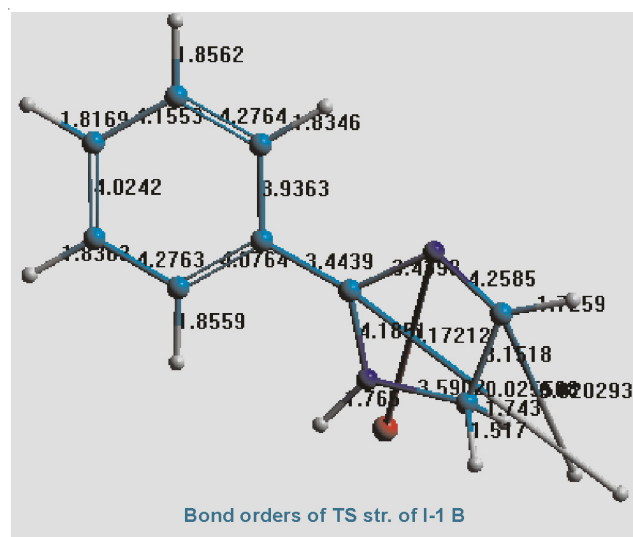


Fig. 3. Bond Orders of transition states of B & C

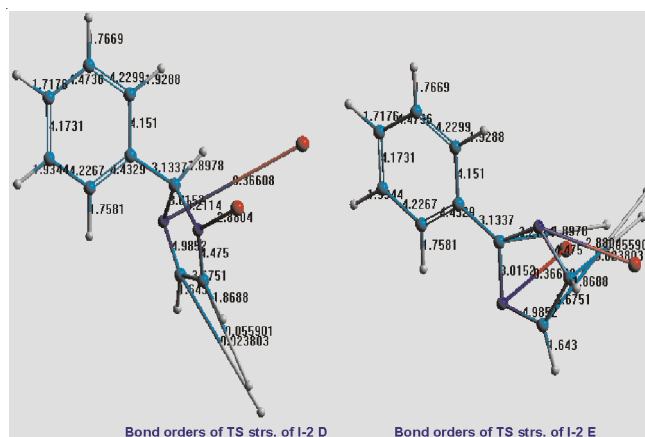


Fig. 4. Bond orders of transition states of D and E

length of I_1N-I_3I , 4.5847 which is longest among other reaction channels that can be easily eliminated to form product "B". Which is experimentally correct. Among the two reactive channels I_1-B & I_1-C ; I_1-B is longer *i.e.*, 5.3626 Å or by 3.4523 Å in 7C-19H indicates the C19 proton can form easily HI in the reaction mixture. Though in the case of I_2-D & I_2-E reaction channels 7C-19 H proton in I_2-E shows higher value *i.e.*, 6.1406 Å due to presence of two iodine atoms in the intermediate stage, but the heat of formation of the systems is much more higher than the heat of formation of I_1-B , therefore it can be neglected.

Bond order analyses: The extent of bond formation or bond breaking along a reaction pathway is provided by the concept of bond order (BO). This theoretical tool has been used to study the molecular mechanism of chemical reactions [r]. The bond orders of the TSs of four reaction channels implemented in Hyper chem. 7.5. The results are included in Table-5.

Table-6 refers the bond orders of transition states of four reactive channels [I_1-B , I_1-C , I_2-D & I_2-E]. In the first two reaction channels I_1-B & I_1-C , the bond orders of 7C-11N are 3.4426 Å & 2.9335 Å that are less in bond orders than 7C-8N, 4.182 & 2.9434 which clearly indicates 7C-8N bond comparatively stronger than 7C-11N. Also, the bond orders of 7C-19 H bond are 0.02545 & 1.9103, respectively which show that the 7C-19 H in the reaction channel I_1-B is comparatively weak and liable to break easily to give product "B" which was experimentally found. Also, the bond orders of C7-N8 in I_1-B is 4.182, the highest among the four reaction channels which clearly indicates that there is no breaking of that bond or form a C=N bond after oxidation by the system *i.e.* $I_2/KI/K_2CO_3/H_2O$.

Also, the bond orders of 7C-19 H bond I_2-D & I_2-E are 1.8724 & 0.0013305, respectively which show that the 7C-19 H in the reaction channel I_2-E is weak and liable to break easily to give product "E".

From the above findings it is stated that the reaction mechanism as put forward for the product formation "B" in the previous report is validated quantum mechanically and is shown in Fig. 5.

Quantitative structure activity relationship [QSAR] analyses of imidazolines and benzimidazoles [1-20]: Quantitative structure activity relationship technique is indispensable in all research as it depends on the three dimensional arrangement of the atoms in a molecule. QSAR is a mathematical

TABLE-4
PM3 ANALYSES OF STARTING COMPOUND 'A', TRANSITION STATES & PRODUCTS A, B, C, & D

Angles	Starting compound (Å)	I-1 B [Ts] ⁰	I-1C [Ts] ⁰	I-2D [TS] ⁰	I-2 E [TS] ⁰	B ⁰	C ⁰	D ⁰	E ⁰
C7-N8-C9	108.537	109.956	107.625	110.391	107.304	107.063	107.011	109.041	108.195
N8-C7-N11	107.14	108.477	104.144	101.751	108.395	111.996	104.982	103.132	110.383
C7-N11-C10	108.415	109.68	111.20	109.293	107.881	111.209	111.052	108.987	109.050

TABLE-5
BOND LENGTHS OF THE TRANSITION STATES I₁-B, I₁-C, I₂-D & I₂-E IN ARMSTRONG

Bonds	I ₁ -B	I ₁ -C	I ₂ -D	I ₂ -E
7C-8N	1.3544	1.5062	1.4835	1.4455
7C-11N	1.4291	1.5142	1.5226	1.4158
9C-8N	1.488	1.4958	1.3073	1.3194
9C-10C	1.4938	1.4962	1.4671	1.4944
10C-11N	1.3167	1.3073	1.3269	1.3306
11N-13I	4.5847	2.9162	1.9341	3.0159
8N-12 H	0.99388	0.99507	4.2636 (N ₈ -I ₁₂)	6.4917 (N ₈ -I ₁₂)
9C-20 H	1.135	1.1093	4.4122	5.8715
9C-21H	1.1102	1.1095	1.0931	1.0907
10C-22H	3.7134	2.121	2.7981	5.225
10 C-23H	1.092	1.0992	1.1049	1.091
7 C-19H	5.3626	1.1236	1.1292	6.1406

TABLE-6
BOND ORDERS OF TRANSITION STATES OF FOUR REACTIVE CHANNELS [I₁-B, I₁-C, I₂-D & I₂-E]

Bonds	I ₁ -B	I ₁ -C	I ₂ -D	I ₂ -E
7C-8N	4.182	2.9434	3.1488	2.7544
7C-11N	3.4426	2.9335	3.089	3.802
9 C-8N	3.5903	3.8493	4.9543	4.3964
9 C-10C	3.1526	3.8177	3.8186	3.6333
10C-11N	4.257	4.6291	4.1359	4.5001
11N-13I	0.17248	1.0762	2.8089	0.37588
8 N -12H	1.7654	1.7295	0.3695 (N ₈ -I ₁₂)	0.0020 (N ₈ -I ₁₂)
9 C-20 H	1.7425	1.9407	0.024908	0.0042434
9 C-21H	1.517	1.934	1.4697	1.5966
10 C-22H	0.020419	0.0674	0.055389	0.0039567
10C-23H	1.7259	1.8134	1.84	1.692
7C-19H	0.02545	1.9103	1.8724	0.0013305

TABLE-7
QSAR PROPERTIES OF THE COMPOUNDS

S. No.	Surface area	Volume (Å ³)	Hydration energy (Kcal/mol)	log P	Refractivity	Polarizability	Mass (amu)	Dipole (D)
1	263.262	508.287	-4.060	1.700	44.520	17.450	146.192	2.175
2	322.138	584.489	-5.679	1.448	50.983	19.922	176.218	1.112
3	358.024	658.467	-6.006	1.195	57.447	22.394	206.244	2.754
4	306.531	560.191	-2.852	2.167	49.561	19.285	160.219	1.203
5	307.529	570.071	-3.682	2.492	52.143	20.076	225.088	2.677
6	319.132	590.96	-3.215	2.736	54.130	21.306	215.082	2.079
7	317.191	570.864	-9.014	-0.279	51.343	19.291	191.189	6.313
8	366.021	640.991	-2.445	1.965	58.949	22.471	189.260	2.207
9	251.301	496.697	-5.626	1.318	42.300	16.741	147.180	2.331
10	253.647	484.560	-4.811	-0.452	45.955	16.972	152.214	3.005
11	279.918	563.928	-3.615	1.633	49.069	19.285	160.219	1.808
12	411.340	639.591	-5.253	1.380	55.533	21.757	190.245	2.065
13	304.503	576.166	-0.723	1.663	45.550	18.026	152.239	1.621
14	239.091	480.031	-5.504	-0.331	37.846	17.804	138.172	2.513
15	501.503	777.072	0.686	3.190	61.181	24.305	196.336	2.612
16	302.142	620.572	-7.555	3.334	60.282	23.440	194.236	3.182
17	361.057	696.599	-9.170	3.081	66.745	25.912	224.262	3.029
18	345.334	672.255	-6.351	3.801	65.323	25.275	208.263	1.492
19	290.603	611.387	-8.469	2.886	57.722	22.731	195.224	2.268
20	292.022	596.385	-8.329	1.181	61.716	22.962	200.258	3.579

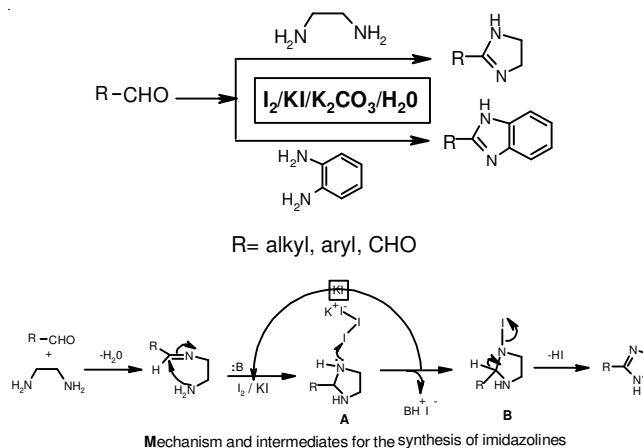


Fig. 5. Mechanism and intermediates for the synthesis of imidazolines

model and it relates the chemical structure and physical property of a compound in a quantitative manner. In our present work we have taken 20 compounds given in Table-7 in the modeling study of octanol water partition co-efficient (log P). The values of log P were determined by using Hyperchem software.

We have selected different descriptors for QSAR study such as, the energy of highest occupied molecular orbital (EHOMO), energy of lowest unoccupied molecular orbital (ELUMO), etc. In addition, the molecular mechanics (MM) parameters such as molar refractivity (MR), van der Waals surface area (SA), hydrophobicity (log P) and molecular volume (V) of the molecules were also selected. The values of surface area, volume, hydration energy, log P, refractivity,

TABLE-8
CALCULATED THERMODYNAMIC PARAMETERS OF THE COMPOUNDS

Structure	Enthalpy (Kcal/mol)	Entropy (Kcal/mol/Kelvin)	Free energy (Kcal/mol)	Heat capacity (Kcal/mol/Kelvin)	Heat of formation (Kcal/mol)	HOMO (eV)	LUMO (eV)
1	5.79	89.62	78.64	35.47	41.28	-9.05	-0.32
2	7.53	103.99	53.08	44.80	2.91	-8.83	-0.27
3	8.17	108.97	54.55	48.75	-3.89	-8.78	-0.23
4	7.003	101.80	75.28	41.448	31.80	-8.96	-0.31
5	6.72	99.80	84.24	39.56	49.16	-9.18	-0.59
6	7.35	103.82	70.81	43.01	31.09	-9.04	-0.68
7	7.44	105.51	82.49	43.82	33.01	-9.57	-1.48
8	8.41	110.44	99.65	50.76	37.44	-8.41	-0.24
9	5.72	89.31	87.57	34.73	48.35	-9.32	-0.64
10	5.55	88.34	80.60	33.14	50.76	-9.09	-0.77
11	6.59	96.39	84.26	40.38	39.16	-9.27	-0.51
12	8.31	110.43	59.24	49.64	1.22	-8.76	0.54
13	6.52	94.52	56.29	40.79	-7.68	-9.16	0.86
14	6.20	92.21	81.93	35.74	32.85	-9.10	-0.15
15	11.34	139.72	53.77	63.15	35.31	-9.21	0.79
16	7.51	106.65	105.57	45.96	71.67	-8.76	-0.61
17	9.25	121.61	79.87	55.24	33.34	-8.59	-0.55
18	8.13	110.79	104.63	49.90	62.20	-8.69	-0.60
19	7.42	104.55	118.03	45.15	81.73	-8.82	-0.80
20	7.25	104.80	107.77	43.57	81.23	-8.79	-0.96

polarizability, mass and dipole moments of the compounds 1-20 [products] were given in Table-8. During the analysis Geometries of the compounds were optimized with Semi Empirical method PM3 using optimization algorithm polak-ribiere under RHF conditions.

From Table-7 it has been seen that greater aliphatic or etheral moiety has least value of heat of formation which is confirmed by comparing the values of compound **3**, **15** and **12**. Small value of dipole moment is observed when methyl ether linkage is present in the compound. In case of benzofused compounds (entries 16-20) dipole moment increases but due to presence of methyl group (aliphatic character) dipole moment decreases appreciably. There is a good linear relationship between log P and ionization potential and electron affinity as shown in Fig. 6. Other properties such as dipole moment, polarizability, molar refractivity and connectivity index have not good relationship with log P. However, effect of molecular structure of the compound on other properties can be analyzed by considering hydrophobicity as the molecular property.

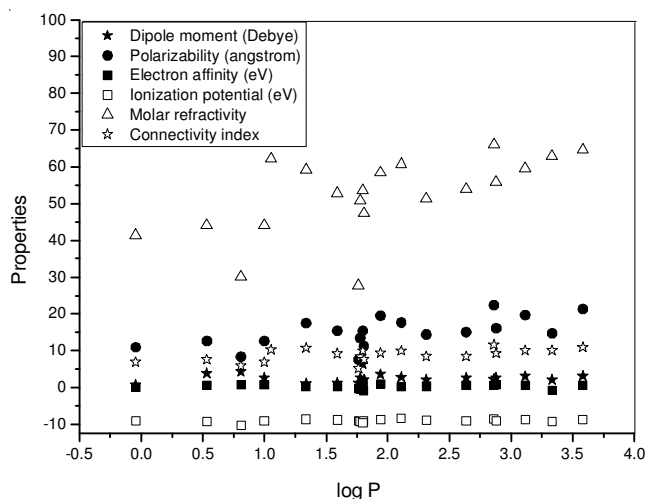


Fig. 6. Plot of log P with other properties of the compounds

The values of thermodynamic parameters of the products were determined by using Scigress 4.2 software and are shown in Table-7. The positive values of heat of formation reflect an endothermic process whereas negative values of entropy implies an association process rather than dissociation. HOMO energy of the molecule associated with the electron donating ability of the molecule and LUMO energy indicates the electron accepting ability. Although, HOMO energy is associated with the electron donating ability of the molecule, high values of HOMO energy indicates a tendency of the molecule to donate electrons to appropriate acceptor molecules with low energy and empty molecular orbital.

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