March 2010 ISSN: 0974 - 7516 Volume 6 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 6(1), 2010 [1-7]

Reduction of aromatic nitro compounds by $CH_3^{\cdot}CHOH$: 3D SAR approach

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Received: 5th October, 2009 ; Accepted: 15th October, 2009

ABSTRACT

A 3D SAR study on reduction of aromatic nitro compounds by $CH_3^{\cdot}CHOH$ has been carried out using heterogeneous set of Quantum molecular descriptors, which includes Electron density on some atoms and Net charge on particular atoms in the molecule along with the HOMO and LUMO. The results have shown that electron density and net charge on atom 2 and 3 plays a dominating role with the combination of LUMO in this regard. The results are validated by the cross validation parameters and critically discussed with a variety of statistical parameters. The three dimensional features for the reduction are studied by quantum molecular modeling and superimposing of molecules.

KEYWORDS

SAR;
Modeling;
Quantum parameter;
Regression analysis.

INTRODUCTION

Over the last decade Aromatic Nitro compounds is the most tempting area for the Computational chemists who are working theoretically on various molecular properties and biological responses. The Aromatic Nitro compounds show the versatile utility and variety of bio-chemical activities. Various groups has studied the effect and significance of the hydrophobic, Physicochemical, topological, intuitions as well as the steric parameters in the modeling of various biological activities/ functions of several Aromatic Nitro compounds[1-3]. In a review based on the role of hydrophobic parameters in QSAR studies, the Hansch group[1] has reported that the use of steric parameter σ yielded an excellent statistics on a set of 13 aromatic nitro compounds. Inspired by the work of Hansch[1], and in the continuation of our earlier works[4-11], we have revisited the work of Hansch[1] to see if we can further develop a significant QSAR model with entirely different set of parameters. In order to achieve this objective, we have used a large set of Quantum chemical parameters viz., Electron density on different atoms like electron density at atom 2, 3 and 4 (ED_2, ED_3 and ED_4), Net charge on various atoms like Net charge on atom 2, 3 and 4 (NC_2, NC_3, NC_4), HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital).

To acquire a significant and predictive model, we have used a maximum R^2 method which was followed by stepwise regression analyses[12-14]. The predictive ability of the model is discussed on the basis of the various cross validation parameters. To facilitate further validation of our model, we have used quantum molecular modeling parameters, and on the basis of these param-

eters, we have analyzed the structural behavior of these molecules. For the molecular modeling, we have optimized the geometries of molecules using the molecular mechanics method by applying the MM+ force field method and these optimized molecules are superimposed over the parent molecule to understand the effect of structural deformation on the function of these compounds.

The basic structures of aromatic nitro compounds used in the present study and various substituents are presented in TABLE 1 along with their observed activities. The parameters that we have used for the prediction of function/activity are presented in TABLE 2.

EXPERIMENTAL

Biological activity

The biological activity for the set of 12 compounds used in the present study, as expressed logK, were taken from the literature[1].

Modeling and 3D parameters

All the modeling parameters and 3D parameters were calculated from the optimized molecule in minimum energy conformer with the help of computer software Hyperchem7 (Demo version)[20] and ChemSW (Free ware)[21]. Since the calculation methods of these parameters with the software are well documented in the literature, it is not necessary to duplicate the same here.

Regression analysis

Regression analyses were made using maximum R^2 method[12-15] adopting step-wise regression. Regression results were further validated with the help of verity of cross-validation parameters.

RESULT AND DISCUSSION

The set of 12 aromatic nitro compounds and their adopted activities i.e., the reduction of aromatic nitro compounds by CH_3C^*HOH have been expressed as logK and are presented in TABLE 1. As may be seen from TABLE 1, a very low-level degeneracy is present in the activity logK. As a result of the occurrence of degeneracy in activity logK, it becomes essential to examine the degeneracy in the molecular descriptors also. A perusal of TABLE 2, which contains the quantum molecular parameters calculated for Aromatic nitro compounds, shows that low level of degeneracy is observed in the quantum molecular parameters. Balaban[15,16] has shown that parameters, in spite of their degeneracy, can be used successfully in developing statistically significant QSAR models.

The correlation among the 3D descriptors like Electron density, net charge, HOMO and LUMO and activities/Function shows (TABLE 3) that Electron density at atom2 and 3, Net charge at atom 2 and 3 and LUMO highly mutually correlated, while this is not so with other parameters used. Furthermore, the data presented in TABLE 3 (Correlation matrix) express that the quantum molecular or 3 D descriptors ED_2, ED_3, NC_2, NC_3, and LUMO shows significant correlation with the activity/function (logK). The univariat models are shown below:

$$\mathbf{logK = 7.9073(\pm 1.243)\ NC_2 + 8.4074} \quad (1)$$

n = 12, Se = 0.2258, R = 0.8955, R^2 = 0.8019, F = 40.467, Q = 3.97

$$\mathbf{logK = -7.8897(\pm 1.1607)\ ED_2 + 39.9735} \quad (2)$$

n = 12, Se = 0.2140, R = -0.9067, R^2 = 0.8221, F = 46.203, Q = 4.24

$$\mathbf{logK = 22.0128(\pm 2.9421)\ NC_3 + 3.4701} \quad (3)$$

n = 12, Se = 0.1975, R = 0.9211, R^2 = 0.8484, F = 55.982, Q = 4.66

$$\mathbf{logK = -22.0128(\pm 2.9421)ED_3 + 91.5214} \quad (4)$$

n = 12, Se = 0.1975, R = -0.9211, R^2 = 0.8484, F = 55.982, Q = 4.66

$$\mathbf{logK = -33.6410(\pm 6.1388)LUMO + 3.3931} \quad (5)$$

n = 12, Se = 0.2536, R = -0.8661, R^2 = 0.7502, F = 30.031, Q = 3.42

Equations (1-5) signifies the presence of Net charge on atom 2 and 3 and the Electron density at the atom 2 and 3 along with the LUMO for the modeling activity/function logK. The Comparison of eq. (1) to (5) shows that the atom 3 plays the dominating role over the atom2 in terms of net charge as well as electron density it also exhibits the domination of Atom 3 over the quantum parameter LUMO in directing the activity/function.

To understand the structural requirement and quantum chemical behavior in respect of reduction activity/function of aromatic nitro compounds bi-parametric combinations were tested, among those bi-parametric combinations, combination of Net charge and electron density at 3rd atom with the net charge and electron density at atom 2 and 4 shows the significant result with the activity/function. But the best result demonstrated

TABLE 1 : Various substituents of 4-X-$C_6H_4NO_2$ reduction by $CH_3\dot{C}HOH$ in N_2O-saturated aqueous solution

Comp. no.	X	logK(Obs.)
1	NO_2	9.38
2	CN	9.08
3	SO_2NH_2	8.90
4	CHO	9.26
5	CF_3	8.63
6	COMe	9.00
7	CO_2Me	8.93
8	$CONH_2$	8.63
9	H	8.52
10	Me	8.18
11	OMe	8.04
12	OH	7.85

in combination with LUMO by electron density and net charge at atom 3. Model obtained from above parameters are as:

logK = -22.6015 (± 2.9757) ED_3 - 2.3131
(± 2.1787) HOMO – 94.3897 **(6)**

n = 12, Se = 0.1963, R = 0.9302, R^2 = 0.8653, F = 28.910, Q = 4.74

logK = 22.6015 (± 2.9757) NC_3 + 2.3131
(± 2.1787) HOMO + 3.9835 **(7)**

n = 12, Se = 0.1963, R = 0.9302, R^2 = 0.8653, F = 28.910, Q = 4.74

logK = -20.5310 (± 2.7473) ED_3 - 1.0151
(± 0.5421) NC_4 + 86.1402 **(8)**

n = 12, Se = 0.1766, R = 0.9439, R^2 = 0.8909, F = 36.758, Q = 5.34

logK = 20.5310 (± 2.7473) NC_3 - 1.0151
(± 0.5421) NC_4 + 4.0162 **(9)**

n = 12, Se = 0.1766, R = 0.9439, R^2 = 0.8909, F = 36.758, Q = 5.34

logK = -20.5310 (± 2.7473) ED_3 + 1.0151
(± 0.5421) ED_4 + 82.0798 **(10)**

n = 12, Se = 0.1766, R = 0.9439, R^2 = 0.8909, F = 36.758, Q = 5.34

logK = 20.5310 (± 2.7473) NC_3 + 1.0151
(± 0.5421) ED_4 - 0.0442 **(11)**

n = 12, Se = 0.1766, R = 0.9439, R^2 = 0.8909, F = 36.758, Q = 5.34

logK = -50.5310 (± 14.1313) ED_3 + 46.4115
(± 22.9668) LUMO + 204.4902 **(12)**

n = 12, Se = 0.1727, R = 0.9464, R^2 = 0.8957, F = 38.664, Q = 5.48

logK = 50.0925 (± 14.1313) NC_3 + 46.4115
(± 22.9668) LUMO + 4.1203 **(13)**

TABLE 2 : 3D Parameters used in present study

Comp. No.	NC_2	NC_3	NC_4	ED_2	ED_3	ED_4	HOMO	LUMO
1	3.887	3.721	3.718	0.113	0.279	0.282	-0.311	-0.188
2	3.940	3.761	3.805	0.059	0.239	0.195	-0.312	-0.158
3	3.879	3.743	3.759	0.121	0.257	0.241	-0.310	-0.167
4	3.933	3.748	3.889	0.066	0.252	0.111	-0.247	-0.163
5	3.975	3.769	3.906	0.025	0.231	0.094	-0.282	-0.153
6	3.944	3.753	3.895	0.056	0.247	0.105	-0.242	-0.162
7	3.948	3.758	3.880	0.052	0.242	0.120	-0.271	-0.159
8	3.966	3.764	3.881	0.034	0.236	0.119	-0.258	-0.157
9	3.978	3.770	3.897	0.022	0.230	0.103	-0.312	-0.154
10	4.006	3.778	3.815	0.006	0.222	0.185	-0.312	-0.150
11	4.055	3.792	3.632	-0.055	0.208	0.368	-0.261	-0.141
12	4.055	3.792	3.629	-0.055	0.208	0.371	-0.271	-0.141

***NC_2 = net charge on second carbon, NC_3 = net charge on third carbon, NC_4 = net charge on fourth carbon, ED_2 = Electron density on second carbon, ED_3 = Electron density on third carbon, ED_4 = Electron density on fourth carbon, HOMO = Highest occupied molecular orbital, LUMO = Lowest unoccupied molecular orbital**

n = 12, Se = 0.1727, R = 0.9464, R^2 = 0.8957, F = 38.664, Q = 5.48

Comparison and analysis of eq. (6) to (13) shows that the electron density on particular atom and the net charge on particular or same atom play the role with same magnitude with different effect in exhibition of reduction activity or function. It also demonstrate that the magnitude of electron density reduces with the combination of HOMO and LUMO while it is in fashion with the combination of net charge on particular atom, the similar behavior is shown by the net charge in the combination with HOMO, LUMO and electron density at particular atom. Comparison also conform the results of univariate regression analysis.

As we pass from model 6 to 13, increase in the value of R shows the significant role of Net charge and electron density on atom 3 with the combination of LUMO and Net charge and Electron density at atom 4 in the modeling of reduction activity/function. Model also demonstrates that the Net charge and Electron Density at atom 3 in the molecule play the dominating role over the Net charge and Electron density at atom 4 and LUMO in the modeling of reduction activity. Comparison of magnitude of Net charge and Electron density at atom 4 and LUMO, express the significance of LUMO in combination over the atom 4. High value of R and significant lowering in the standard error (Se) also conform the suitability of the models for the pre-

diction of reduction activity/Function. The model 12 and 13 gives the best result with the high r value and less Se value. Comparison of both equation shows that the electron density has the inverse relation with the reduction activity/function in numerical manner while the Net charge and LUMO having the direct relationship with the activity/function. As the correlation matrix shows the ED_3 and NC_3 having the exact but opposite impact i.e. inverse relationship between them.

The higher magnitude of the residue of compound **(3)** from both eq. (12) and (13) indicate towards the possibilities of further improvement in the predictive potential of the model and exceptional behavior of the compound **(3)**, so for the improvement in the model we outlier the compound no **(3)** based on the magnitude of the residue.

Model obtained after the outlier are as:

$$\log K = 64.8376 (\pm 10.2784) NC_3 + 67.4002 (\pm 16.3788) LUMO + 3.9676 \quad (14)$$

n = 11, Se = 0.1147, R = 0.9790, R^2 = 0.9584, F = 92.170, Q = 8.54

$$\log K = -64.8376 (\pm 10.2784) ED_3 + 67.4002 (\pm 16.3788) LUMO + 263.318 \quad (15)$$

n = 11, Se = 0.1147, R = 0.9790, R^2 = 0.9584, F = 92.170, Q = 8.54

Both the equations 14 and 15 demonstrate the similar results and also conforms the previous findings about the behavior and role of the parameter Net charge and electron density at atom 3 and LUMO for the modeling of reduction activity/function. The higher r value and low Se conforms the outlier and exceptional behavior of compound **(3)**. Equation (14) and (15) also having one outlier (Comp. no. **(2)**) and it shows the probability of improvement in prediction and modeling of reduction activity for this class of compounds. The models obtained after the deletion of compound no. **(2)** are as follows:

TABLE 3 : Correlation matrix obtained between biological activity and various parameters

	logK	ED_2	ED_3	ED_4	NC_2	NC_3	NC_4	HOMO
logK	1.0000							
ED_2	-.90668	1.00000						
ED_3	-.92111	.95332	1.00000					
ED_4	.46273	-.37905	-.28807	1.00000				
NC_2	.89546	-.99805	-.95079	.38462	1.00000			
NC_3	.92111	-.95332	-1.0000	.28807	.95079	1.00000		
NC_4	-.46273	.37905	.28807	-1.0000	-.38462	-.28807	1.00000	
HOMO	-.04405	.26922	.18635	.14074	-.29486	-.18635	-.14074	1.00000
LUMO	-.86614	.90200	.98330	-.19545	-.90221	-.98330	.19545	.26014
	LUMO							
LUMO	1.00000							

TABLE 4 : Cross validation parameters

Eq.	Compd. used	Parameters used	R^2_A	r_{cv}^2	PRESS	SSY	PRESS/SSY	S_{PRESS}
1	12	NC_2	-	0.75	0.510	2.064	0.25	0.22
2	12	ED_2	-	0.78	0.458	2.116	0.22	0.21
3	12	NC_3	-	0.82	0.390	2.184	0.18	0.20
4	12	ED_3	-	0.82	0.390	2.184	0.18	0.20
5	12	LUMO	-	0.67	0.643	1.931	0.33	0.18
6	12	ED_3, HOMO	0.835	0.84	0.347	2.227	0.16	0.13
7	12	NC_3, HOMO	0.835	0.84	0.347	2.227	0.16	0.13
8	12	ED_3, NC_4	0.867	0.88	0.281	2.293	0.12	0.12
9	12	NC_3, NC_4	0.867	0.88	0.281	2.293	0.12	0.12
10	12	ED_3, ED_4	0.867	0.88	0.281	2.293	0.12	0.12
11	12	ED_4, NC_3	0.867	0.88	0.281	2.293	0.12	0.12
12	12	ED_3, LUMO	0.873	0.90	0.268	2.306	0.12	0.12
13	12	NC_3, LUMO	0.873	0.90	0.268	2.306	0.12	0.12
14	11	NC_3, LUMO	0.948	0.96	0.105	2.425	0.04	0.07
15	11	ED_3, LUMO	0.948	0.96	0.105	2.425	0.04	0.07
16	10	NC_3, LUMO	0.986	0.99	0.026	2.330	0.01	0.04
17	10	ED_3, LUMO	0.986	0.99	0.026	2.330	0.01	0.04

PRESS-predictive residual sum of square; SSY-Sum of the squares of response values, r^2_{cv}-Cross-validated predictive correlation coefficient, R^2_A-adjusted r^2, S_{PRESS}-uncertainty of prediction

TABLE 5 : Observed and calculated activity logK with residue from eq. (16)

Comp.No.	logK(Obs.)	logK(Calc.)	Residue
1	9.38	9.37	0.01
2	9.08*	8.78	0.30
3	8.90*	9.33	-0.43
4	9.26	9.27	-0.01
5	8.63	8.60	0.03
6	9.00	9.02	-0.02
7	8.93	8.90	0.03
8	8.63	8.66	-0.03
9	8.52	8.48	0.04
10	8.18	8.24	-0.06
11	8.04	7.94	0.10
12	7.85	7.94	-0.09

Data point not included in calculation from eq. (16)

TABLE 6 : Observed and calculated activity logK with residue from eq. (17)

Comp.No.	logK(Obs.)	logK(Calc.)	Residue
1	9.38	9.21	0.17
2	9.08*	8.65	0.43
3	8.90*	9.18	-0.28
4	9.26	9.13	0.13
5	8.63	8.47	0.16
6	9.00	8.89	0.11
7	8.93	8.77	0.16
8	8.63	8.53	0.10
9	8.52	8.35	0.17
10	8.18	8.11	0.07
11	8.04	7.82	0.22
12	7.85	7.82	0.03

***Data point not included in calculation from eq. (17)**

TABLE 7 : Modeling parameters used in the present study

Comp.No.	TE	DpM	RMSg
1	10.55	0.004	0.0994
4	11.05	3.26	0.0878
5	9.62	2.312	0.0875
6	10.12	3.778	0.0965
7	11.02	4.027	0.0992

TE=Total Energy, DpM=Dipole moment, RMSg=Root mean square gradiant

TABLE 8 : Distance gradient for the superimposed Molecules in the present study

S.No	Total distance gradient
Case 1.	0.105787
Case 2.	0.105858
Case 3.	0.105829
Case 4.	0.105858
Case 5.	0.105858

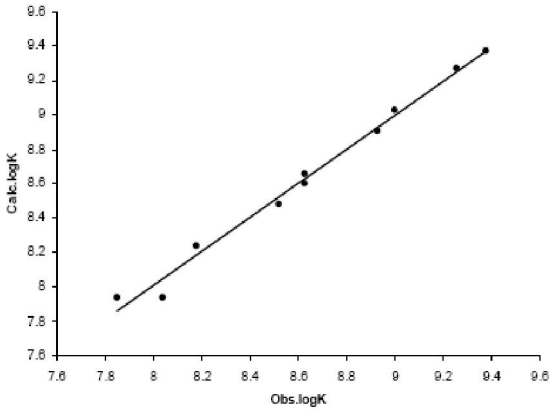

Figure 1 : Graph obtained between obs. and calc. logK values from eq. (16)

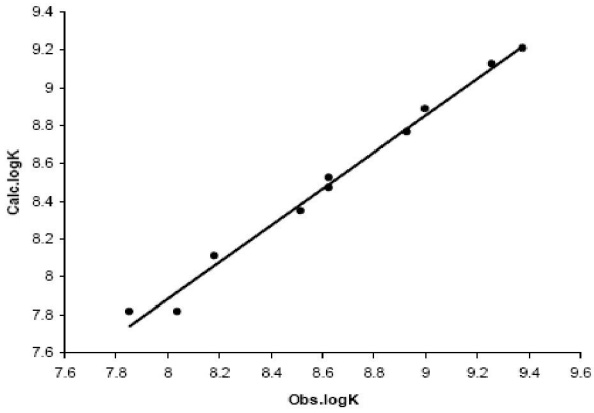

Figure 2 : Graph obtained between obs. and calc. logK values from eq. (17)

logK = 61.321 (± 5.534) NC_3 + 62.0838
(± 8.8103) LUMO + 3.9356 (16)

n = 10, Se = 0.0621, R = 0.9944, R^2 = 0.9889, F = 311.389, Q = 16.25

logK = -61.321 (± 5.534) ED_3 + 62.0838
(± 8.8103) LUMO + 249.2198 (17)

n = 10, Se = 0.0621, R = 0.9944, R^2 = 0.9889, F = 311.389, Q = 16.25

Comparison of eq. (12), (13), (14), (15) and (16), (17) shows that the model obtained for the set of 10 compounds gives the better statistics and most suitable for the prediction of reduction activity of the compounds. It is obvious that reduction in size of data set increases the regression value, but in present case significant lowering of Se and a improvement in the F-statistics along with the significant improvement in the value of Q (quality

factor) from eq. (12) (13) to (16) (17) justify the improvement in statistics and deletion of the compound no **(2)** and **(3)**.

Results from eq. (16) and (17) are graphically presented in figure 1 and 2 respactively.

The predictive potential of the models proposed by us is determined and validated by using variety of cross-validation parameters[11-14]. The various cross-validation parameters thus calculated are given in TABLE 4.

Method of cross-validation evaluates the validity of a model by how well it predicts data rather than how well it fits data particularly for the small set of data. For acquiring the same the method uses cross-validated parameters: R^2_A (Adjusted R^2) PRESS (predicted residual sum squares), SSY (sum of the squares of response value), r^2_{cv} (overall predictive ability), S_{PRESS} (standard error of predicted residual sum squares).

At this stage, it is worthy to comment on cross validation parameter R^2_A values. We observed that as we passes from the model obtained for 12 compounds (eq. (6)) to model obtained for 10 compounds (eq. (16)/(17)) there is significant increase in the value of R^2_A. The values increasing from 0.8354 to 0.9857, as we passes from eq. (6) to eq. (16)/(17). Such an increase in R^2_A values indicate that the deleted compounds have the unfair share in the modeling of respective activity and also showing exceptional behavior from their parent series. The value of R^2_A will decrease if the deletion of the compounds does not reduce the unexplained variation in the model enough to off set the loss of degree of freedom[2,12-15].

PRESS (predicted residual sum of squares) is an important cross-validation parameter as it is a good estimate of the real predictive error of the models. Its value less than SSY (sum of the squares of response value) indicate that the model predicts better than chance and can be considered statistically significant. In the present case all the proposed models have PRESS<<SSY indicating them to be better than chance and statistically significant. Furthermore, the ratio PRESS/SSY is used to estimate the confidence interval of the reduction activity. To have a reliable QSAR model, PRESS/SSY should be smaller than 0.4 and the value of the ratio smaller than 0.1 is indicative of a reasonably good model. In our case the ratio PRESS/SSY ranges between 0.33 – 0.01 indicating that all the proposed models are reasonable QSAR models.

The significant lowering in the value of cross-validation parameters PRESS and PRESS/SSY and excellent increase in value of SSY from eq. (1) to (16)/(17) justify the models.

The indication of the performance of the model is obtained from r^2_{cv} (the overall predictive ability). In our case highest r^2_{cv} is found for the model expressed by equation (16) and (17), indicating that it has an excellent predictive power.

Another useful cross-validated parameter is $S_{PRESS,}$ which is used in deciding uncertainty of prediction. Based on the value of S_{PRESS} once again we observed that the model (16) and (17) has the excellent correlation ability and predictability with the very low level of uncer-

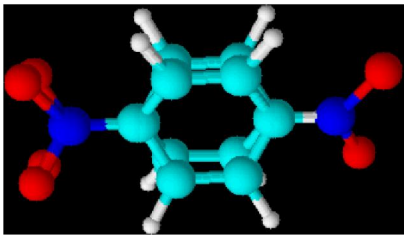

Figure 3 : Superimposed molecule (comp. 1)

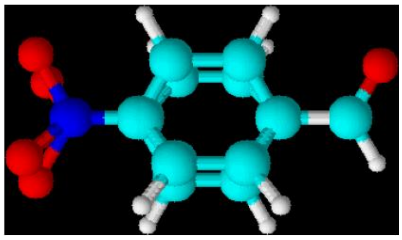

Figure 4 : Superimposed molecule (comp. 4)

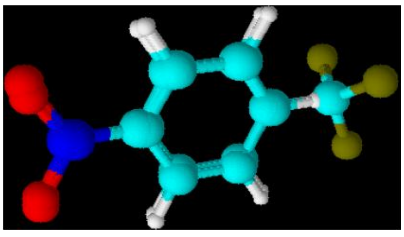

Figure 5 : Superimposed molecule (comp. 5)

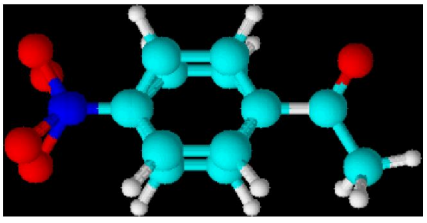

Figure 6 : Superimposed molecule (comp. 6)

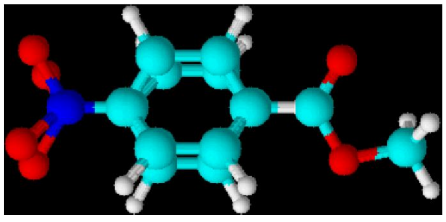

Figure 7 : Superimposed molecule (comp. 7)

tainty of prediction for the reduction activity.

Based on the above study and magnitude of the residues presented along with the observed and calculated activity in TABLE 5 and 6, we have selected five compounds, viz., compounds no. **(1)**, **(4)**, **(5)**, **(6)** and **(7)** to correlate their modeling parameters with the activity logK. We have done it to find out which property or feature is highly responsible for the reduction activity of aromatic nitro compounds.

The parameters calculated for the optimized molecular structures are presented in TABLE 7.

Best model obtained from the modeling parameters is:

$$\log K = 0.0766\ (\pm 0.0252)\ TE + 8.0747 \qquad (18)$$

n =5, Se = 0.189, R = 0.8692, F = 9.273

Model obtained from the modeling parameter exhibits that the reduction activity is directly correlated with the Total energy of the molecule i.e. increase in the total energy increases the reduction activity numerically of the aromatic nitro compounds. It also demonstrates that the conformer having the grater stability is less active and become less reductive in nature.

The superimposing of the molecules having minimum residue with the parent molecule exhibits that the NO_2 and connected C atom present in the benzene ring dominate the distortion, other substitution at 4^{th} position in the ring are not playing the major role in deformation of molecular structure. Superimposed molecules are shown in figure 3 to 7 respectively and distance gradient of the superimposed molecules are presented in TABLE 8.

CONCLUSION

On the basis of result and discussion made above conclusion can be drawn that the nature of the reduction activity is partially structure specific for the particular series.

For the present set of compounds reduction activity is dependent on the electron density and net charge at atom 3 of the molecule along with the partial effect of LUMO. Also it is concluded that, the reduction activity is shown by the compounds at their minimum energy conformer for the present set of compounds.

ACKNOWLEDGEMENT

Authors (M.Thakur) are thankful to DST, Government of India for funding under SERC fast track scheme (SER/FTP/CS-32).

REFERENCES

[1] C.Hansch, A.Kurup, R.Garg, H.Gao; Chem.Rev., **101**, 619 **(2001)**.
[2] S.C.Basak, C.M.Frane, M.E.Rosen, V.R.Magnuson; Med.Sci.Res., **15**, 605 **(1987)**.
[3] M.Thakur, A.Thakur, K.Balasubramanian; J.Chem. Inf.Model., **46(1)**, 103 **(2006)**.
[4] M.Thakur, A.Thakur, P.V.Khadikar, C.T.Supuran; Bioorg.Med.Chem.Lett., **15(1)**, 203 **(2005)**.
[5] A.Thakur, M.Thakur, P.V.Khadikar, C.T.Supurane, P.Sudele; Bioorg.Med.Chem., **12(4)**, 789 **(2004)**.
[6] M.Thakur, A.Thakur, P.V.Khadikar; Bioorg.Med. Chem., **12(4)**, 825 **(2004)**.
[7] A.Thakur, M.Thakur, S.Vishwakarma; Bioorg.Med. Chem., **12(5)**, 1209 **(2004)**.
[8] M.Thakur, A.Thakur, P.Sudele; Indian J.Chem.B, **43**, 976 **(2004)**.
[9] M.Thakur, A.Agrawal, A.Thakur, P.V.Khadikar; Bioorg.Med.Chem., **12(9)**, 2287 **(2004)**.
[10] A.Thakur, M.Thakur, N.Kakani, A.Joshi, A.Gupta; Arkivoc, **10(1)**, 36 **(2004)**.
[11] A.Thakur, M.Thakur, P.V.Khadikar; Bioorg.Med. Chem., **11(23)**, 5203 **(2003)**.
[12] S.Chaterjee, A.S.Hadi, B.Price; Regression Analysis by Examples, 3rd Ed., Wiley VCH: New York, 201 **(2000)**.
[13] H.Waterbeemd; Vande (Ed) 'Chemometric Method in Molecular Design, in Methods and Principles in Medicinal Chemistry', VCH, Weinleium (Ger), **2**, 114 **(1995)**.
[14] J.Devillers, W.Karcherl, (Eds.); 'Applied Multivariate Analysis in SAR and Environmental Statistics, in Chemical and Environmental Sciences', Klawer Academic Pub.Dorderch (Netherland), **(2)**, 204 **(1991)**.
[15] R.G.Parr, W.Yang; 'Density Functional Theory of Atoms and Molecules', Oxford, New York, **(1989)**.
[16] A.T.Balaban; J.Chem.Inf.Comput.Sci., **32**, 23 **(1992)**.
[17] A.T.Balaban, T.S.Balaban; Math.Chem., **8**, 383 **(1991)**.
[18] ACD-Lab Software for Calculating the Referred Physicochemical Parameters; Chemsketh S.O, WWW. Acdlabs.com.
[19] Hyperchem 7, Demoversion from WWW.Hyperchem.com.