

## COMPARATIVE MOLECULAR FIELD ANALYSIS OF THE [3, 3] SIGMATROPIC REARRANGEMENT

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**ABSTRACT.** A comparative molecular field analysis (CoMFA) on the substituent effect of the palladium (II) catalysed sigmatropic rearrangement [3, 3] of esters was studied to show a good correlation between electrostatic property of the substituents and the reaction rate. The results suggest that the fact that the reaction rate will increase as the electron donating ability of the substituents increase or in other word the more powerful the electron donating group, the more faster the reaction proceed.

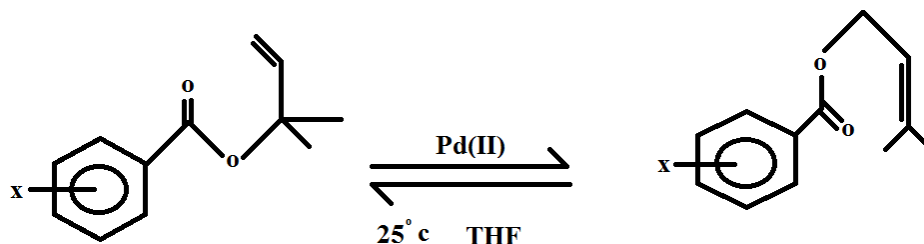
**Keywords:** CoMFA, QSAR, PLS method, [3, 3] sigmatropic rearrangement, ZODIAC 0.65, MOPAC 2007

### INTRODUCTION

Comparative molecular field analysis (CoMFA) a 3D-QSAR (Quantitative Structure Activity Relationship) concept was developed by CRAMER *et al.* [1] in 1988 and since then it became a popular and valuable tool in drug design and molecular modelling [2]. A traditional QSAR method requires predetermined parameters representing the physical and chemical properties of the molecule which is mainly derived empirically and sometimes difficult to get. On the other hand the CoMFA method only requires fundamental properties of the molecules, steric, electrostatic properties which can be obtained by theoretical calculations. So the CoMFA method offers clear advantage over the conventional 3D-QSAR. This QSAR technique mainly used in drug design can also be used to find the relationship between molecules and physiochemical property expressed by the molecule. Moreover the new CoMFA method can be used to study substituent effect on [3, 3] sigmatropic rearrangement.

## RESULTS AND DISCUSSION

Geometries of the molecule were generated by the molecular modelling suite ZODIAC 0.65 version and geometry optimization and the charge calculations were carried out using MOPAC 2007 [3] by Sparkle method. The optimized molecules are represented in the scheme 1. Then the CoMFA analysis was performed using the quantitative calculation in ZODIAC 0.65.



Scheme-1

The CoMFA grid spacing was 2.0 angstrom in all three dimensions (x, y, and z) and the grid is generated automatically by the programme and was large enough to contain completely with addition 4.0 angstrom-5.0 angstrom in all directions. As probes  $\text{sp}^3 \text{C}^+$  and  $\text{H}^+$  ion were used.

Table 1. - The Second order rate constant [4]

Substrate	Substituent	$k_x (\text{min}^{-1}\text{M}^{-1})$	$\log k'$
1a	p- $\text{CH}_3\text{O}$	130	0.31
1b	p- $\text{CH}_3$	92.9	0.17
1c	H	63.2	0
1d	p-Cl	53.1	-0.07
1e	p-Br	46.2	-0.14
1f	m-F	28.5	-0.35
1g	m-Br	32.8	-0.28
1h	m- $\text{CF}_3$	17.7	-0.55
1i	p- $\text{CF}_3$	19.4	-0.51
1j	m- $\text{NO}_2$	10.1	-0.80
1k	p- $\text{NO}_2$	11.1	-0.75

$$\text{Log}k' = \log k_1/k_H$$

A statistical analysis of the interaction energy and the target property ( $\log k'$ ) was carried out by the partial least square (PLS) method [5] with leave-1-out, cross validation [6]. The final CoMFA model was calculated using no cross validation with an optimum number of components from the cross validation results.

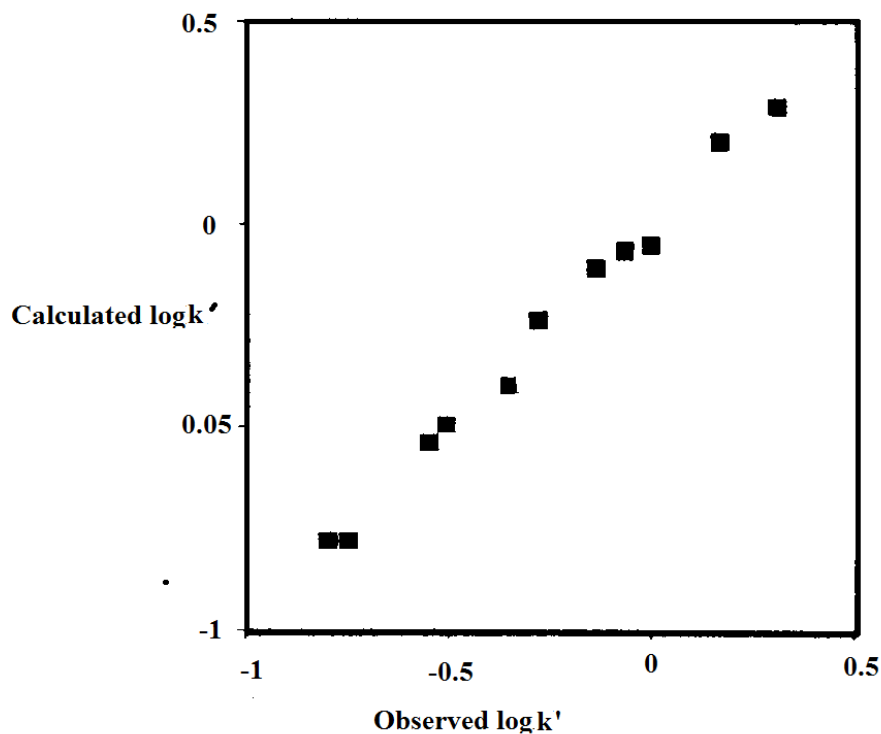
When  $\text{C}^+$  and  $\text{H}^+$  were used as probes and both steric and electrostatic models were considered (M-1, M-2, M-3, and M-5), the cross validated  $r^2$  values ( $r_{\text{cross}}^2$ : 0.698, 0.713, and

0.663) were generally quite high (Tab. 2). In M-2 in which only electrostatic field is considered gave higher cross validated  $r^2$  values 0.898 and non-validated  $r^2$  values 0.991. That probe the electrostatic factor is the major factor on the reaction rate of [3, 3] sigmatropic rearrangements (the graph indicated this).

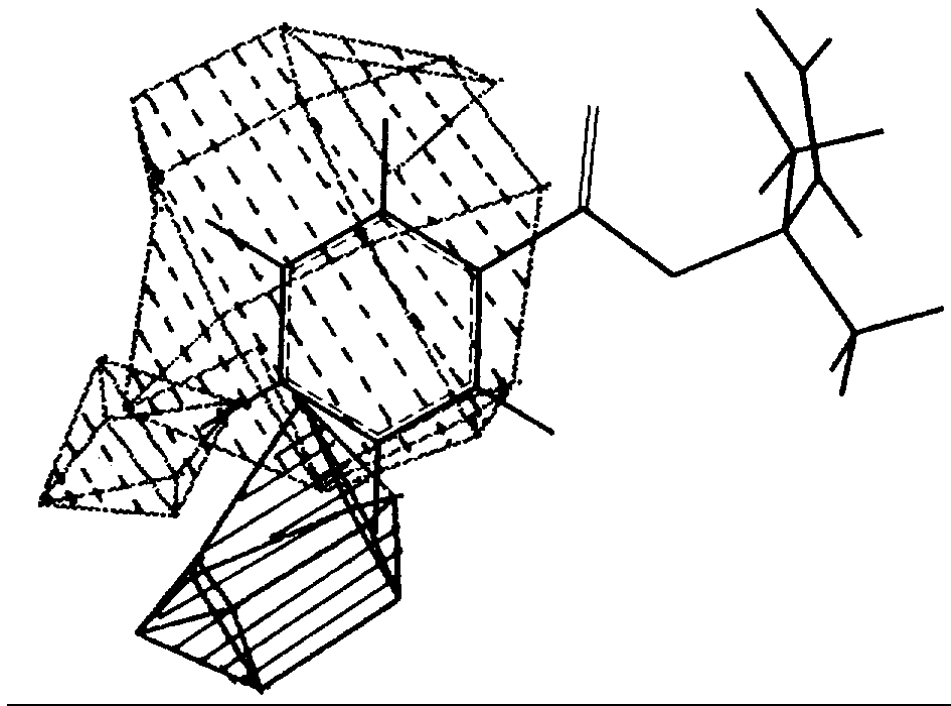
Table 2. CoMFA-PLS analysis of Model 1, Model 2, Model 3, Model 4, Model 5

	M1	M2	M3	M4	M5
<b>Probe Atom</b>	C <sup>+</sup>	C <sup>+</sup>	C <sup>+</sup>	C <sup>+</sup>	C <sup>+</sup>
<b>Field</b>	Steric		Steric		Steric
	Electrostatic	Electrostatic	Electrostatic	Electrostatic	Electrostatic
<b>Energy cut-off</b>	30/30 kcal.	30 kcal.	5/30 kcal.	5 kcal.	30/30 kcal.
<b>R<sup>2</sup><sub>cross-val</sub></b>	0.698	0.898	0.713	0.825	0.663
<b>No. of component</b>	2	3	2	3	3
<b>Relative contribution</b>					
<b>Steric</b>	0.323		0.297		0.317
<b>Electrostatic</b>	0.677	1	0.733	1	0.683
<b>R<sup>2</sup><sub>no-val</sub></b>	0.966	0.991	0.947	0.989	0.972
<b>Standard error</b>	0.074	0.037	0.093	0.046	0.072

The CoMFA method model for M-2 (Figure) shows that more negative charge around the phenyl ring will increase the target property; indicate that the electron donating group on the benzene ring will increase reaction rate.



Graph. Plot of log k' calculated using Model-2 versus observed log k'



Electrostatic model by Model 2. Dot line indicates regions where a more negative electrostatic interaction would improve the rate constant. Real lines indicate regions where a more positive electrostatic interaction would enhance the rate constant.

In conclusion it can be said that the CoMFA method is a powerful technique in analysing the kinetic data of [3, 3] sigmatropic rearrangement.

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