Theoretical Study on the [3,3]-Sigmatropic Rearrangement of Allylic Esters by Comparative Molecular Field Analysis (CoMFA)

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A comparative molecular field analysis (CoMFA) on the substituent effect of the palladium (II) catalyzed [3,3]-sigmatropic rearrangement of allylic esters was studied to show a good correlation between the electrostatic property of substituents and the reaction rate. The CoMFA result suggests that the reaction rate will increase as the electron-donating ability of substituents increases.

Introduction

In our previous works, we have demonstrated that the CoMFA is a powerful and valuable tool for describing the relationship between the LUMO energy and rate constants of S_N2 reactions of benzyl benzenesulfonate with *p*-methoxybenzylamines.[1] A comparative molecular field analysis (CoMFA), a new 3-D QSAR (quantitative structure-activity relationship) concept developed by Cramer *et al.*[2], has become a popular and valuable tool in drug design.[3] A traditional QSAR requires predetermined parameters representing the physicochemical properties of the molecules which are normally derived empirically and are sometimes difficult to get. On the other hand, the CoMFA method only requires the fundamental properties of the molecules, steric and electrostatic properties which are obtainable by theoretical calculations and thus, the CoMFA method offers clear advantage over the conventional QSAR.

We have envisioned that this new QSAR technique mainly conceived for drug design could be used to find the relationship between molecules and any physicochemical properties exprssed by the molecules.

To this end, in this paper, we have used the CoMFA method to study substituent effects of the Pd(II) catalyzed allylic ester rearrangement of allylic esters reported by Chi,[4] who has shown that the Hammett plot between the second-order rate constants and σ gave a good linear correlation (correlation coefficient = 0.977 and ρ = −1.05, Table 1) and suggested that positive charges over the neighboring oxygen atoms sould be delocalized in the transition state.

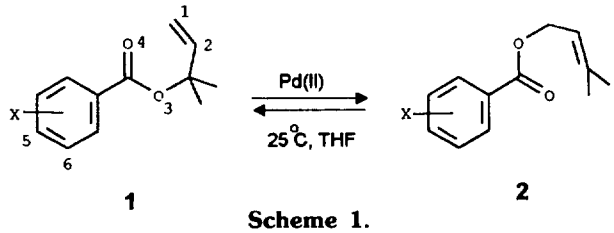
Results and Discussion

Starting geometries of the molecules were generated by the BUILD option of SYBYL (version 6.0)[5] and the geometry optimizations and the charge calculation were carried out by MOPAC[6] using AM1 method.[7] The optimized molecules were aligned by least squares fitting of the C1, C2, O3, O4, C5, and C6 atoms of the molecule (Scheme 1). Then the CoMFA analysis was performed by using the QSAR option in SYBYL. The CoMFA grid spacing was 2.0 Å in all, *x*, *y*, and *z* directions and the grid region generated automatically by the program was large enough to contain molecules completely with additional 4.0 Å in all directions. As probes sp^3 C^+ and H^+ ion were used.

Table 1. The second-order rate constants[a]

Substrate	Substituent (*X*)	k_x ($min^{-1}M^{-1}$)	log k'[b]
1a	*p*-CH_3O	130	0.31
1b	*p*-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*-CF_3	17.7	−0.55
1i	*p*-CF_3	19.4	−0.51
1j	*m*-NO_2	10.1	−0.80
1k	*p*-NO_2	11.1	−0.75

[a]Ref. 4. [b]Log k' is log k_x/k_H.



Scheme 1.

A statistical analysis of the interaction energy and the target property (log k' in Table 1)[4] was carried out by the partial least-squares (PLS) method[8] with leave-1-out crossvalidation.[9] The final CoMFA model was calculated using no cross-validation with an optimum number of components from the cross-validation results.

When C^+ and H^+ were used as the probes and both steric and electrostatic factors were considered (Model 1, Model 3, and Model 5), the cross-validated r^2 values (r^2_{cross} : 0.699, 0.714, and 0.663) were generally quite high (Table 2). However, Model 2, in which only the electrostatic field considered, gave the higher cross-validated r^2 value, 0.898, and no-validated r^2 value, 0.993. This means that the electrostatic property of the molecule is the major determining factor on the reaction rate of the [3,3]-sigmatropic rearrangement reaction. The plot between the calculated log k' values versus the observed ones shows an excellent linearity as in Figure 1 indicating a good predictability. This result is consistent

Table 2. CoMFA-PLS Analyses of Model 1, Model 2, Model 3, and Model 5

	Model 1	Model 2	Model 3	Model 4	Model 5
Probe atom	C^+	C^+	C^+	C^+	H^+
Field	Steric		Steric		Steric
	Electrostatic	Electrostatic	Electrostatic	Electrostatic	Electrostatic
Energy cut-off	30/30 kcal	30 kcal	5/30 kcal	5 kcal	30/30 kcal
$R^2_{cross\text{-}val.}$	0.699	0.898	0.714	0.825	0.663
No. of component	2	3	2	3	3
Relative contribution					
Steric	0.323		0.297		0.317
Electrostatic	0.677	1	0.703	1	0.683
$R^2_{no\text{-}val.}$	0.966	0.993	0.947	0.989	0.972
Standard error	0.074	0.037	0.093	0.046	0.072

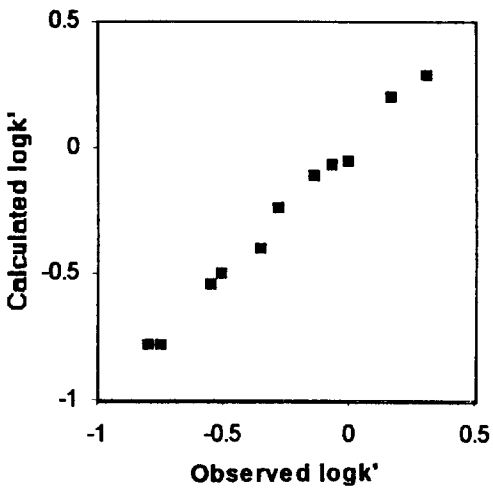


Figure 1. Plot of log k' calculated using Model 2 versus observed log k'.

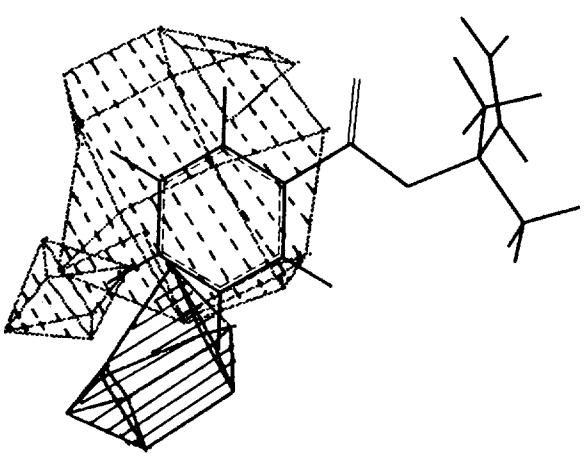


Figure 2. Electrostatic map by Model 2. Dot line contrours encompass regions where a more negative electrostatic interaction would improve the rate constant. Real line contours surround regions where a more positive electrostatic interaction would enhance the rate constant.

with the previous finding and also supports the reaction mechanism proposed by CHi.[4]

The CoMFA contour map for Model 2 (Figure 2) shows that more negative charge around the phenyl ring will increase the target property, a rate constant, indicating that electrondonating groups on the phenyl ring will increase the reaction rate.

In conclusion, this study again demonstrates that the CoMFA technique is a powerful and valuable tool for describing the kinetic data of the [3,3]-sigmatropic rearrangement reaction and the result is in good agreement with the experimental data as well as with the result that was obtained by the conventional analysis.

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