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Correlation between the Reactant Complex or Transition State Conformations and the Reactivity of 4-Nitrophenyl Benzoate and Its Sulfur Analogues with Anionic Nucleophiles by Comparative Molecular Field Analysis (CoMFA)

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A comparative molecular field analysis (CoMFA) was carried out for the correlation of the transition state structures and the reaction rates for the S_N2 reaction of 4-nitrophenyl benzoate and its sulfur analogs with anionic nucleophiles. The CoMFA analysis showed that both steric and electrostatic effects are important, and the steric contribution increased when nucleophiles are alkoxides or arylsulfides. In this study, we have demonstrated that the CoMFA analysis can be expanded beyond the scope of dealing with reactants and products. The reactant complex and transition state conformations generated along the reaction path can be more appropriately used for the correlation of structures and reaction rates.

Introduction

In our previous works,¹ we have demonstrated that CoMFA is a powerful and valuable tool for describing the relationship between the LUMO energy and the rate constants of S_N2 reactions of benzyl benzenesulfonate with *p*-methoxybenzylamines and also for studying the substituent effects of the Pd(II) catalyzed rearrangement of allylic esters. However, in both cases, the conformations used for the CoMFA studies were either from reactants or products. In theory, however, it might be possible or more appropriate to use the conformations generated as the reaction proceeds along the reaction path for the CoMFA analysis to correlate with the reaction rates. For that purpose, we chose the kinetic data for a typical S_N2 reaction from the literature for our studies.

Recently Um *et al.*² carried out the kinetic study of the S_N2 reaction between 4-nitrophenyl benzoates and various anionic nucleophiles to investigate the effect of polarizability on the reaction rates. In the study, they found that the substitution of oxygen with more polarizable sulfur in the leaving group or in the carbonyl group of **1** changed the reactivity significantly, depending on the degree of polarizability of the attacking nucleophiles. The reactivity of the polarizable substrates **2** and **3** increases significantly toward the polarizable nucleophiles (ArS^-), and decreases toward the nonpolarizable nucleophiles (RO^-) indicating that the effect of polarizability on the rate is important in the system.

In our study, we investigated the same system theoretical-

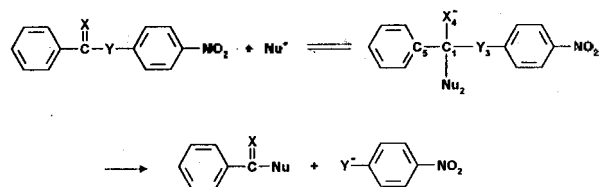
ly to establish the relationships between the reactivity and the reactant complex and the transition state structures-reactivity relationship by the comparative molecular field analysis (CoMFA).³

Method

Starting geometries of the molecules were generated by the BUILD option in SYBYL (version 6.1a)⁴ and the geometry optimization for the reactants and the reactant complexes and the reaction path calculations were carried out by MO-PAC⁵ using the PM3 method.⁶ Locations and geometries of the stationary points on the potential energy surfaces were obtained by the reaction coordinate method⁷ refined by the NLLSQ (Non-Linear Least Squares) gradient norm minimization⁸ or EF (Eigenvector Following) routine⁹ and characterized by confirming only one negative eigenvalue in the Hessian matrix.¹⁰

Comparative Molecular Field Analysis (CoMFA). The optimized molecules were aligned by the least square fitting of the C_1 , Nu_2 , Y_3 , X_4 , and C_5 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 cover molecules completely with additional 4.0 Å in all directions. As a probe $sp^3 C^+$ ion was used.

A statistical analysis of the interaction energy and the target property ($\log k$ in Table 1)² was carried out by the partial



- 1 : X=Y=O, 4-nitrophenyl benzoate
 2 : X=O, Y=S, S-4-nitrophenyl thiobenzoate
 3 : X=S, Y=O, 4-nitrophenyl thionbenzoate

least-square (PLS) method¹¹ with leave-1-out cross-validation.¹² The final CoMFA model was calculated using no cross-validation with an optimum number of components from the cross-validation results.

Results and Discussion

First, we chose the 18 reactant complexes and the transition state structures whose nucleophiles are ArO^- . Tables 2 and 3 show the CoMFA analyses for 18 TS structures and the corresponding reactant complexes. The Model 1, in which both steric and electrostatic fields were considered, shows a relatively good correlation ($r^2_{\text{cross}} : 0.560$) and the fractions of steric and electrostatic field contribution are 0.691 and 0.310, respectively.¹³ The Model 3, in which only electrostatic field was considered, shows even better correlation than the Model 1 ($r^2_{\text{cross}} : 0.822$) and Model 2, in which only steric field was considered with poor correlation ($r^2_{\text{cross}} : 0.076$). This CoMFA analysis result shows that the electrostatic property of the transition state structures correlates to the reactivity better than the steric property in this system.

For the reactant complex structures, Model 4 (both the steric and the electrostatic field) and 6 (only the electrostatic field) show excellent correlations ($r^2_{\text{cross}} : 0.854$ and 0.715), and the correlation in Model 5 (only the steric field) is not so bad ($r^2_{\text{cross}} : 0.305$). This means that the steric property of the reactant complex structures contributes some extent to the reactivity. The plot between the calculated $\log k$ values

Table 1. Summary of second-order rate constants (k) for the reactions of 1, 2, and 3 with various types of anionic nucleophiles in absolute ethanol at 25.0 ± 0.1 °C^a

Nu ⁻	$k \times 10^2, \text{M}^{-1}\text{s}^{-1}$		
	1	2	3
1 EtO ⁻	1160	1260	140
2 CF ₃ CH ₂ O ⁻	1320	1140	238
3 <i>p</i> -CNPhO ⁻	0.100	1.40	1.40
4 <i>m</i> -ClPhO ⁻	1.89	15.1	16.4
5 <i>p</i> -ClPhO ⁻	4.52	27.6	34.7
6 PhO ⁻	8.91	38.8	33.3
7 <i>p</i> -CH ₃ PhO ⁻	18.4	69.3	55.5
8 <i>p</i> -CH ₃ OPhO ⁻	36.7	114	102
9 <i>p</i> -ClPhS ⁻	0.0761	1040	5180
10 PhS ⁻	2.87	1570	7360

^aRef. 2

versus the observed ones shows good linearity as shown in Figure 1.

The CoMFA contour map for Model 4 is shown in Figure 2. Negative charge favorable contours around the phenyl oxide ring and the nitro group mean that more negative charge around them will increase the reactivity. Positive charge favorable contours under the para position of phenyl oxide mean that more positive charge around them will increase the reactivity. This CoMFA map can explain well the experimental results.

These results suggest that the reactant complex structure-reactivity relation is better than the transition state structure-reactivity relation in analyzing the controlling factor for the reactivity in this system. Therefore, only the reactant complex structures were used in Models 7-12. The CoMFA results for the reactions of the substrates (1, 2, and 3) with the charge localized nucleophiles (EtO⁻, CF₃CH₂O⁻) and for the reactions of the substrates (1, 2, and 3) with the charge delocalized and polarizable nucleophiles (PhS⁻, *p*-ClPhS⁻) are shown in Table 4 and 5, respectively. For alkoxide, Model 8, in which only steric field was considered, shows the best correlations (cross-validated $r^2 : 0.904$). Then, Model 9 also shows a good correlation (cross-validated $r^2 : 0.406$). This suggests that the steric factor is more important than the electrostatic factor for the reactivity.

For arylsulfide, however, the steric and the electrostatic correlations are almost same. Models 10-12 show good correlations (cross-validated $r^2 : 0.829, 0.777, \text{ and } 0.829$), so the steric field contributes almost same as the electrostatic field.

Our studies on the CoMFA analyses show that the steric effect increases when nucleophiles are charge localized alko-

Table 2. CoMFA Analysis of 18 Transition State Structures for Aryloxides

	Model 1	Model 2	Model 3
probe	C ⁺	C ⁺	C ⁺
Field	Both	Steric	Electrostatic
cross-val. r^2	0.560	0.076	0.822
No. of component	5	4	5
no-val. r^2	0.977		0.988
Relative contribution			
Steric	0.690	1.000	
Electrostatic	0.310		1.000

Table 3. CoMFA Analysis of 18 Reactant Complex Structures for the Aryloxides

	Model 4	Model 5	Model 6
probe	C ⁺	C ⁺	C ⁺
Field	Both	Steric	Electrostatic
cross-val. r^2	0.854	0.305	0.715
No. of component	4	5	5
no-val. r^2	0.962		0.963
Relative contribution			
Steric	0.667	1.000	
Electrostatic	0.333		1.000

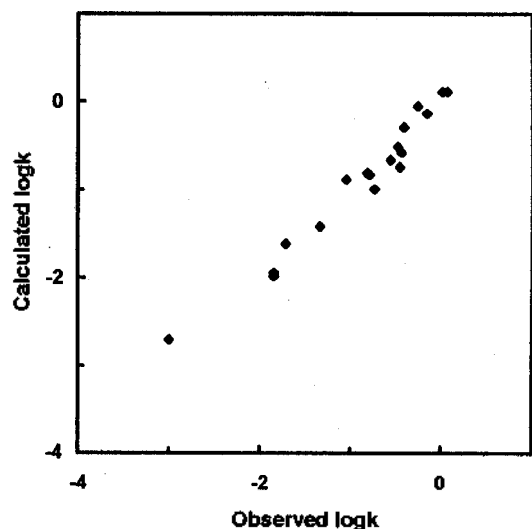


Figure 1. Plot of $\log k$ calculated by Model 4 vs observed $\log k$.

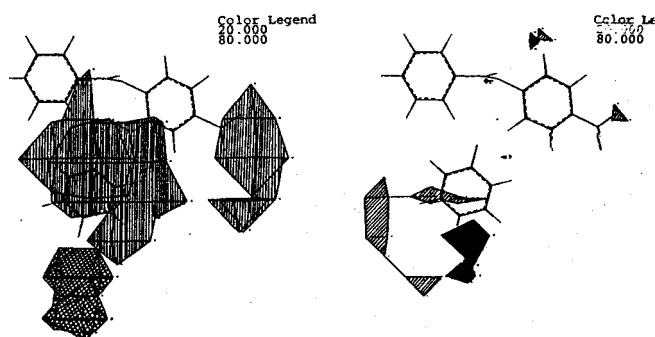


Figure 2. CoMFA contour map by Model 4.

xides or the charge delocalized and polarizable arylsulfides compared with the charge delocalized aryloxides.

In conclusion, we have demonstrated that the CoMFA analysis can be expanded beyond the scope of the reactant and the product. The reactant complex and the transition state conformations generated along the reaction path can be considered for the correlation between structures and reaction rates.

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Table 4. CoMFA Analysis of 6 Reactant Complex Structures for Alkoxides

	Model 7	Model 8	Model 9
probe	C ⁺	C ⁺	C ⁺
Field	Both	Steric	Electrostatic
cross-val. r^2	0.708	0.904	0.461
No. of component	4	4	4
no-val. r^2	1.000	1.000	0.999
Relative contribution			
Steric	0.911	1.000	
Electrostatic	0.089		1.000

Table 5. CoMFA Analysis of 6 Reactant Complex Structures for Arylsulfides

	Model 10	Model 11	Model 12
probe	C ⁺	C ⁺	C ⁺
Field	Both	Steric	Electrostatic
cross-val. r^2	0.829	0.777	0.829
No. of component	2	2	3
no-val. r^2	0.950	0.946	0.985
Relative contribution			
Steric	0.919	1.000	
Electrostatic	0.081		1.000

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- In our previous studies¹, the steric and the electrostatic contribution are 0.357 and 0.643, and 0.323 and 0.677 when the electron donation ability of the substituent is major factor for the reaction.