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## Journal of Liquid Chromatography & Related Technologies

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597273>

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**To cite this Article** Kim, Ho Seob , Lee, Sung Kwang and Lee, Dai Woon(1997) 'Study of Retention Behavior of Pesticides for Reversed Phase Liquid Chromatographic Separation by Quantitative Structure-Retention Relationships', Journal of Liquid Chromatography & Related Technologies, 20: 6, 871 – 885

**To link to this Article:** DOI: 10.1080/10826079708013659

**URL:** <http://dx.doi.org/10.1080/10826079708013659>

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# STUDY OF RETENTION BEHAVIOR OF PESTICIDES FOR REVERSED PHASE LIQUID CHROMATOGRAPHIC SEPARATION BY QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIPS

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## ABSTRACT

Regression models that are useful for the explanation of the reversed phase liquid chromatographic retention behavior of the pesticides ; triazines, phenoxyacetic esters and acetanilides were studied by quantitative structure - retention relationships (QSRRs). Descriptors were theoretically calculated by MM+ and AM1 method. The retention of triazines and phenoxyacetic esters in methanol-water was explained by solvation energy of specific site of solute, total solvation energy and polarizability which were chosen as nonspecific descriptors for acetonitrile-water. The retention of acetanilides was dependent not only on solvent-accessible surface area but on conformation of solute.

## INTRODUCTION

The increasing use of HPLC for pesticide analysis is the result of its suitability for determining thermally labile and polar pesticides and its compatibility with on-line analysis.<sup>1</sup> There are many chromatographic methods for the determination of pesticide residues in crops, food and environmental samples.<sup>2</sup>

In order to develop the new chromatographic methods suitable for pesticide analysis, it is important to understand the retention phenomena of solutes.

Therefore, as the first step for elucidating the retention phenomena, we investigated the retention behavior of test solutes such as triazines, phenoxyacetic esters and acetanilides using quantitative structure - retention relationships (QSRRs).

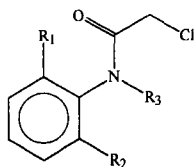
Quantitative structure-retention relationships (QSRRs) are well known methodologies of relating chemical structures of solute with the chromatographic retention parameters.<sup>3</sup> Through the statistical methods, retention data are characterized by various combinations of solute descriptors. QSRRs models obtained can be used to identify the most informative structural descriptors, describing the retention behavior of solutes and predicting the retention of solutes in a given chromatographic system.

When retention data are dependent on the molecular structure, QSRRs studies are suitable for testing new structurally related descriptors and they may be useful to discern new method for representing chemical structures.

Although there are many available descriptors commonly used in QSRRs studies, non-specific descriptors, shape descriptors, physicochemical descriptors, topological descriptors, and intermolecular descriptors<sup>3,4</sup> it has been difficult to describe the structural effect of solute on retention due to the lack of physical meaning of descriptors. But molecular mechanics and quantum chemical methods enables us to easily determine the structurally related descriptors.

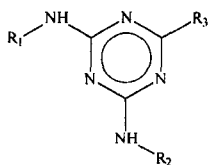
We have tried to find the structurally related descriptors that could be available to explain the retention behavior of the solutes by applying molecular mechanics and quantum chemical calculations to this QSRRs study.

## Acetanilides



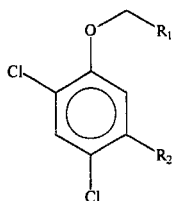
No.	1	2	3
R <sub>1</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H
R <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H
R <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	CHMeCH <sub>2</sub> OCH <sub>3</sub>	<i>i</i> -C <sub>3</sub> H <sub>5</sub>

## Triazines



No.	1	2	3	4	5
R <sub>1</sub>	C <sub>2</sub> H <sub>5</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>
R <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>
R <sub>3</sub>	Cl	Cl	OCH <sub>3</sub>	Cl	SCH <sub>3</sub>

## Phenoxyacetic esters



No.	1	2	3	4	5
R <sub>1</sub>	COMe	COMe	(CH <sub>2</sub> ) <sub>2</sub> COMe	CO <sub>2</sub> CMe <sub>2</sub> C <sub>3</sub> H <sub>7</sub>	CO <sub>2</sub> CMe <sub>2</sub> C <sub>3</sub> H <sub>7</sub>
R <sub>2</sub>	H	Cl	H	H	Cl

Figure 1. Structures of solutes.(continued)

Figure 1. Structures of solutes.

**Table 1**  
**Capacity Factors (log k') of Triazines, Phenoxyacetic Esters, and Acetanilides with MeOH-H<sub>2</sub>O and MeCN-H<sub>2</sub>O Eluents**

Solute	No.	75%MeOH-H <sub>2</sub> O	65% MeCN-H <sub>2</sub> O
Triazine	1	-0.180	-0.017
	2	-0.009	0.135
	3	0.130	0.169
	4	0.171	0.290
	5	-0.350	0.426
Phenoxy-acetic ester	1	0.631	0.431
	2	0.492	0.609
	3	0.636	0.719
	4	1.469	1.504
	5	1.628	1.670
Acetanilide	1	0.399	0.552
	2	0.397	0.546
	3	-0.024	0.230

## MATERIALS AND METHODS

Five triazines, five phenoxyacetic esters and three acetanilides (Fig. 1) were purchased from PolyScience (Niles, IL, USA) and their retention data are listed in Table 1. Methanol and acetonitrile (HPLC grades) were all from Baxter (Muskegon, MI, USA). Water was purified by using a Milli-Q water purification system (Millipore, Bedford, MA, USA).

### Apparatus

All chromatograms were obtained using a Samsung Electron Devices SLC liquid chromatography (Suwon, Korea) system. Shodex C18 column (4.6 × 250mm, Showa Denko, Tokyo, Japan) for triazines and Shiseido Superiorex ODS column (4.6 × 250mm, Tokyo, Japan) for phenoxyacetic esters and acetanilides were used. Triazines were measured at 220nm and phenoxyacetic esters and acetanilides were measured at 230nm.

Table 2

Regression Model for Triazines Separated with 75% MeOH-H<sub>2</sub>O

Coefficient	Std. Error	Std Coefficient	Tolerance	Descriptor
0.224	0.011	0.996	1.000	NPSSE*
-2.036	0.105	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.990		Std. Error=0.019		N=5
				F=417.346

\*NPSSE: nonpolar saturated water solvation surface energy in (kcal).

Table 3

Regression Model for Triazines Separated with 65% MeCN-H<sub>2</sub>O

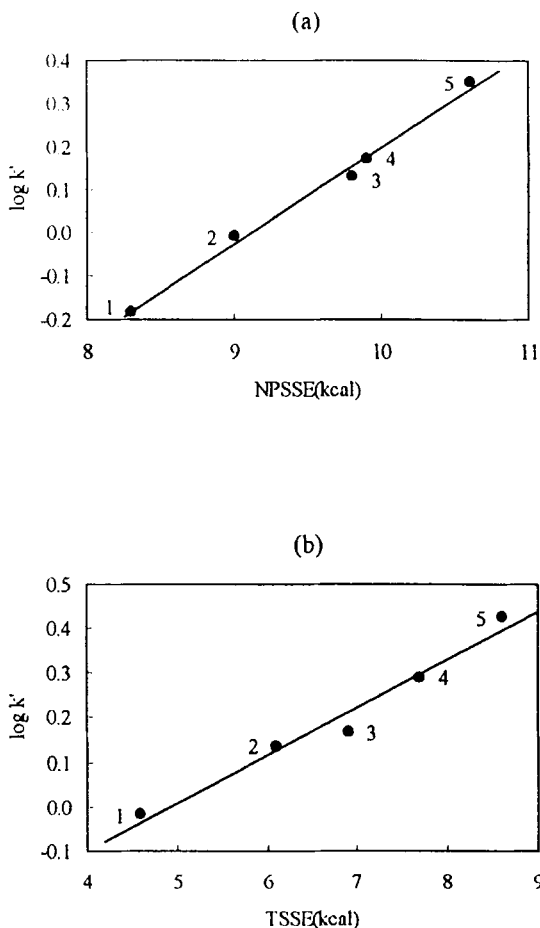
Coefficient	Std. Error	Std Coefficient	Tolerance	Descriptor
0.108	0.011	0.985	1.000	TSE*
-5.333	0.077	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.960		Std. Error=0.034		N=5
				F=96.070

\*TSSE: total water solvation surface energy in (kcal).

Isocratic elution was carried out with 75% (v/v) methanol-water and 65% (v/v) acetonitrile-water. The flow rate was 1.0mL/min. The retention times for all solutes were measured three times and their average values were used for further analysis.

### Descriptor Generation

A IBM compatible PC using the HyperChem (Hypercube, Waterloo, Ontario, Canada) was used for getting the descriptors. The geometry optimization calculation of each solute was carried out by MM+ (5) in a periodic box.



**Figure 2.** Plots of  $\log k'$  vs. (a) nonpolar saturated water solvation surface energy (NPSSE) with 75% MeOH-H<sub>2</sub>O (b) total water solvation surface energy (TSSE) with 65% MeCN-H<sub>2</sub>O for triazines.

Total energy and the energy of the individual bonding component (bonds, angles, dihedrals, van der Waals interactions, hydrogen bonding, electrostatic energy) resulting from optimization calculation were taken as descriptors. Using optimized geometry, single point calculations were done with a semi-empirical method, AM1.<sup>6,7</sup> Then, total energy in semi-empirical calculation, the energy components, heat of formation, dipole moment, and components of dipole moment were considered as descriptors.

**Table 4****Regression Model for Phenoxyacetic Esters Separated with 75% MeOH-H<sub>2</sub>O**

Coefficient	Std. Error	Std Coefficient	Tolereane	Descriptor
0.727	0.045	0.994	1.000	PSSE*
3.110	0.136	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.985		Std. Error=0.066		N=5 F=259.740

\*PSSE: polar water solvation surface energy in (kcal).

**Table 5****Regression Model for Phenoxyacetic Esters Separated with 65% MeCN-H<sub>2</sub>O**

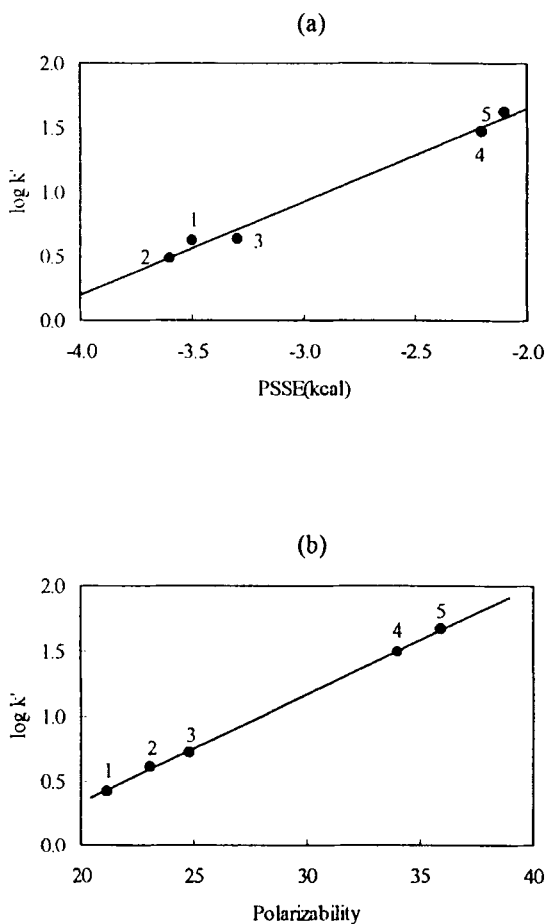
Coefficient	Std. Error	Std Coefficient	Tolereane	Descriptor
0.083	0.001	1.000	1.000	Polarizability
-1.333	0.032	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.999		Std. Error=0.015		N=5 F=5671.190

In addition, solvent-accessible surface area, solvent-accessible molecular volume, 1-octanol/water partition coefficient (log P), molar refractivity and polarizability were also calculated with ChemPlus (Hypercube, Waterloo, Ontario, Canada). On the other hand, total water solvation surface energy, nonpolar saturated water solvation surface energy, nonpolar unsaturated water solvation surface energy, and polar water solvation surface energy were calculated with PCMODEL (Vernon, USA), respectively.

**Regression Analysis**

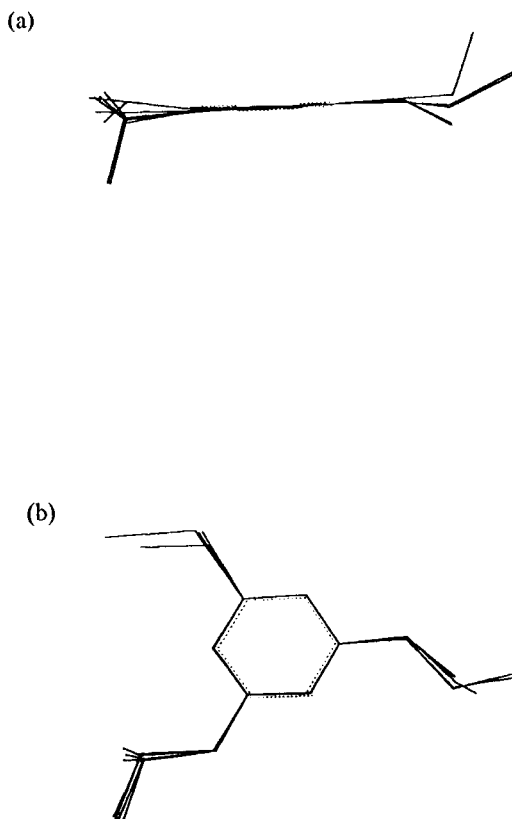
Multiple linear regression analysis<sup>8</sup> for descriptor selection was carried out by a stepwise procedure, followed by model generation. Preliminary information on the interrelationships among the descriptors was obtained from the correlation matrix. Multicollinearity was also examined using tolerance.





**Figure 3.** Plots of  $\log k'$  vs. (a) polar water solvation surface energy (PSSE) with 75% MeOH-H<sub>2</sub>O (b) polarizability ( $\text{\AA}^3$ ) with 65% MeCN-H<sub>2</sub>O for phenoxyacetic esters.

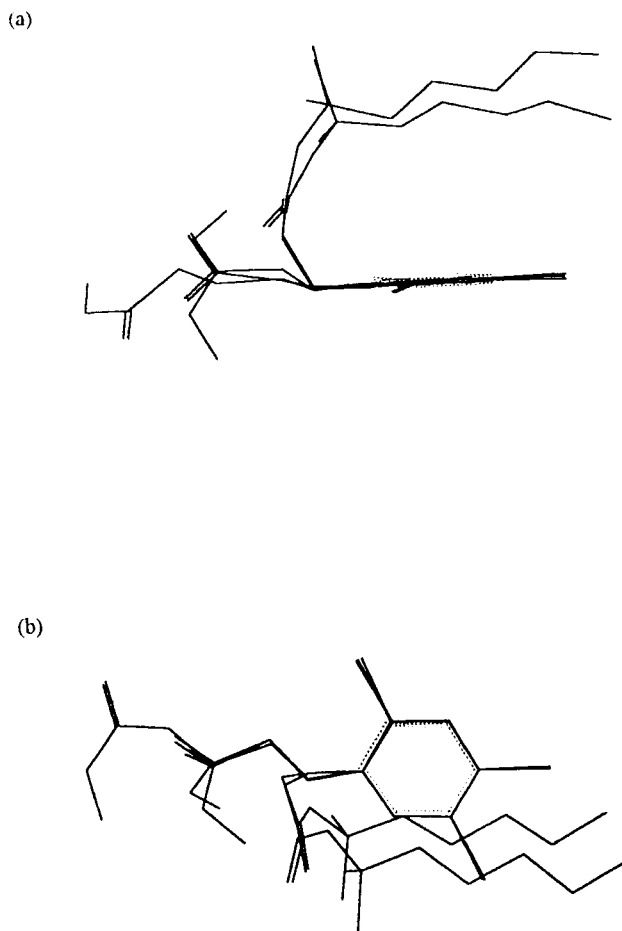
The criteria for judging the best model were multiple correlation coefficient, standard error, and overall F-value for analysis of variance. Statistical calculations were performed with Macintosh Classic II using SYSTAT software (SYSTAT, Evanston, IL, USA).



**Figure 4.** Optimized triazine structures by MM+. (a) orthogonal view (b) frontview.

## RESULTS AND DISCUSSION

The most informative structural descriptors that are available to elucidate the retention mechanism in a given chromatographic system could be identified with QSRRs. Following MM+ and AM1 calculations, a number of descriptors were examined to characterize the molecular structure.<sup>9,10</sup> Stepwise regression method was applied to select the adequate descriptors that could be used to explain the retention behavior of solutes.



**Figure 5.** Optimized structures of phenoxyacetic esters by MM+. (a) orthogonal view (b) front view.

Among descriptors examined, nonpolar saturated water solvation surface energy (NPSSE) and total water solvation surface energy (TSSE) were selected as the descriptors for triazines with each mobile phase, respectively (Tables 2 and 3). Plots of the observed retention value ( $\log k'$ ) vs. the value of descriptor for triazines with each mobile phase showed good correlations (Fig. 2).

**Table 6****Regression Model for Acetanilides Separated with 75% MeOH-H<sub>2</sub>O**

Coefficient	Std. Error	Std Coefficient	Tolerance	Descriptor
0.005	0.001	0.994	1.000	SASA*
-2.195	0.267	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.977		Std. Error=0.037		N=3
				F=85.004

\*SASA: solvent-accessible surface area (Å<sup>2</sup>).

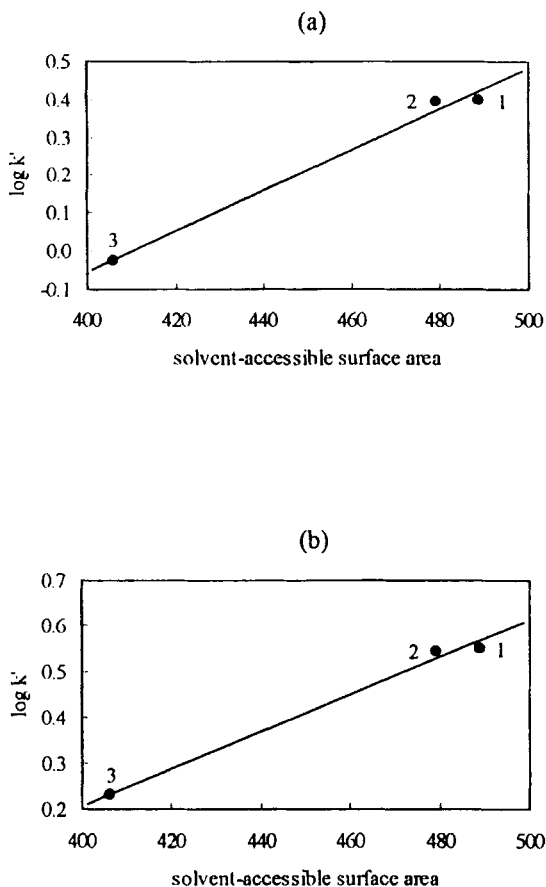
**Table 7****Regression Model for Acetanilides Separated with 65% MeCN-H<sub>2</sub>O**

Coefficient	Std. Error	Std Coefficient	Tolerance	Descriptor
0.004	0.000	0.994	1.000	SASA*
-1.427	0.204	0.000		Constant
R <sup>2</sup> <sub>ADJ</sub> =0.977		Std. Error=0.028		N=3
				F=85.004

\*SASA: solvent-accessible surface area (Å<sup>2</sup>).

Total water solvation surface energy (TSSE) is the energy arising from hydration of solute surface and is the sum of nonpolar saturated water solvation surface energy (NPSSE), nonpolar unsaturated water solvation surface energy (NPUSSE), and polar water solvation surface energy (PSSE). Using methanol as organic modifier, the retention increased with increasing NPSSE of solute. It means that retention depended on the solvation of nonpolar groups of solute with methanol/water eluent.

In the case of acetonitrile as organic modifier, the retention increased with increasing TSSE of solute. From this relationship, it was assumed that retention of solute did not depend on solvation of specific nonpolar or polar group but on solvation of the whole molecule with acetonitrile/water eluent.



**Figure 6.** Plots of  $\log k'$  vs. solvent-accessible surface area ( $\text{\AA}^2$ ) for acetanilides with (a) 75% MeOH-H<sub>2</sub>O (b) 65% MeCN-H<sub>2</sub>O.

For phenoxyacetic esters, polar water solvation surface energy (PSSE) arising from hydration of polar group of solute and polarizability were selected as the descriptors with each eluent, respectively (Table 4 and 5). Plots of the observed retention value ( $\log k'$ ) vs. the value of descriptor for phenoxyacetic esters were shown in Fig. 3. Optimized molecular structures of triazines (see Fig. 4) were almost planar. On the other hand, phenoxyacetic esters had planar or C-shaped structures (see Fig. 5) according to substituents at R<sub>1</sub>. If R<sub>1</sub> was isooctyl (phenoxyacetic ester #4 and #5), its structure was C-shaped.

From conformational considerations, phenoxyacetic ester #4 and #5 which have C-shaped structure had double binding site to the  $C_{18}$  ligates compared with phenoxyacetic ester #1, #2 and #3. On the other hand, the penetration of phenoxyacetic ester #4 and #5 into  $C_{18}$  ligates was sterically hindered.

Therefore, it would be needed another effect to describe the retention behavior of phenoxyacetic esters besides binding interaction between solute and  $C_{18}$  ligates. If organic modifier was methanol, it was suggested that the extent of solvation of carbonyl group of  $R_1$  would have an effect on the retention. On the other hand, if organic modifier was acetonitrile, retention of solute was described by bulk property such as polarizability because acetonitrile had no specific functional group such as hydroxyl group in methanol which could interact with carbonyl group.

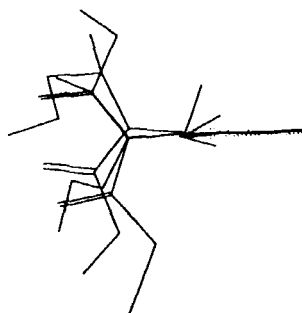
In comparison of descriptors included in retention model, there was a common feature in retention behavior of triazines and phenoxyacetic esters with each organic modifier. Major factor on the retention of the solutes was the extent of solvation of specific sites such as nonpolar or polar group with methanol/water eluent and was bulk property such as total water solvation energy and polarizability with acetonitrile/water eluent.

For acetanilides, solvent-accessible surface area (11) was selected as the descriptor regardless of organic modifier (Table 6 and 7). Plots of the observed retention value ( $\log k'$ ) vs. the value of descriptor for each acetanilide were shown in Fig. 6.

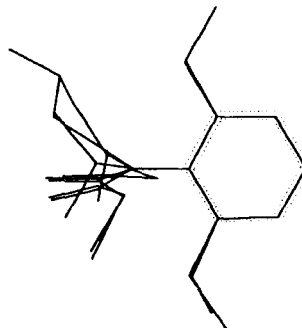
Although solvent-accessible surface area of acetanilide #1 was different from that of acetanilide #2, their retention values were almost same. Since the phenyl group of acetanilides was bisected with the alkyl substituent on nitrogen atom (see Fig. 7), the penetration of solute into  $C_{18}$  ligates would be sterically hindered. If phenyl group would interact with  $C_{18}$  ligates, methylene group was the only difference between acetanilide #1 and #2. Therefore, it was supposed that acetanilide #1 and #2 would show similar retention value because the methylene group was very small part compared with the whole molecule.

In summary, for triazines and phenoxyacetic esters, it was suggested that there were two effects on the retention according to organic modifier, specific solvation effect and nonspecific effect. Specific solvation effect would occur if the organic modifier was methanol, which would solvate the nonpolar site of triazines and the polar site of phenoxyacetic esters.

(a)



(b)



**Figure 7.** Optimized structures of acetanilides by MM+. (a) orthogonal view (b) front view.

On the other hand, if the organic modifier was acetonitrile, nonspecific effect depended on bulk properties of solute such as total water solvation energy and polarizability would be major factor on the retention. For acetanilides, although solvent-accessible surface area was selected as the descriptor regardless of organic modifier, conformation of solute had an additional effect on the retention behavior of solutes.

**ACKNOWLEDGMENTS**

This present study was supported in part by the Basic Science Research Institute Program, Ministry of Education, 1995, Project No. BSRI-95-3425. We thank Mr. Hoon Joo Kim of Lucky Research Park for his assistance in the application of the SYSTAT software.

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Received June 1, 1996  
Accepted June 18, 1996  
Manuscript 4207