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A QSAR Model for Predicting Mutagenicity of Nitronaphthalenes and Methylnitronaphthalenes

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Abstract A quantitative structure-activity relationship model for prediction of mutagenicity of nitronaphthalenes and methylnitronaphthalenes was developed using some fundamental quantum chemical descriptors. The cumulative cross-validated regression coefficient value for the optimal quantitative structure-activity relationship model is 0.711, showing a good predictive capability for mutagenicity of nitronaphthalenes and methylnitronaphthalenes. Results from this study indicate that mutagenicity of nitronaphthalenes and methylnitronaphthalenes increases with increasing frontier molecular orbital energy value, i.e., the sum of the energy of the highest occupied molecular orbital and the energy of the lowest unoccupied molecular orbital, or decreasing the energy of the second highest occupied molecular orbital, final heat of formation, and core–core repulsion energy values.

Keywords Nitronaphthalenes · Methylnitronaphthalenes · QSARs · Mutagenicity

Nitrated PAHs (nitro-PAHs) are identified as a series of pollutants with long-term toxicity, originating from both emissions in diesel vehicle exhaust (Bamford and Baker 2003; McDonald et al. 2004; Wichmann 2007) and reactions of the parent PAHs in the atmosphere. Gas-phase reactions of the parent PAHs are initiated by hydroxyl (OH) radicals during the day and by nitrate (NO_3) radicals (in the presence of NO_x) during the night (Atkinson and Arey 1994; Hanna et al. 2004; Hien et al. 2007; Őberg 2005). 1- and 2-nitronaphthalenes (NN) and methylnitronaphthalenes (MNN) are two-ring nitro-PAHs found in the gas-phase in ambient atmosphere. Some previous studies have shown that many of them have direct mutagenicity and carcinogenicity (Durant et al. 1996; Tokiwa et al. 1994) and are responsible for the mutagenicity of ambient air samples and particles emitted into the atmosphere (Pamela et al. 1996; Tsapakis and Stephanou 2007). Thus, the investigations on them are important and significant for human health.

The mutagenic properties of nitroaromatics result from the metabolic activation by mammalian or bacterial enzymes (Tsakovska et al. 2008). Reduction of the nitro-group leads to nitroso compounds, hydroxylamines, and amines. Further activation of the hydroxylamines by *O*-acylation, produces electrophilic species (nitrenium ions) which react with bionucleophiles like proteins (e.g., hemoglobin) or DNA bases to form covalent adducts (Verma and Hansch 2008). Since these DNA adducts can disturb the replication process, mutations are induced. Generally, the parameter-mutagenic activity (*MA*) represents the ability of mutagenicity of components and is usually determined by the Salmonella mutagenicity assay, for the assay has been proved to be highly sensitive to the frameshift mutagens found in ambient particulate extracts. However, considering large expenditures of money and time, it is difficult to determine all the mutagenic activities of NNs and MNNs in ambient atmosphere (Pamela et al. 1996). Quantitative structure-activity relationships (QSARs) have been applied successfully to various areas of toxicology to predict the toxicity of organic chemicals to environmentally important species and to elucidate their link to characteristics of the molecular structure of the compounds (Cronin et al. 1998; Mohan et al. 2007; Niu

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and Yu 2004; Yan et al. 2005). Hence, it is necessary to develop quantitative structure-activity relationship between mutagenicity and molecular structural descriptors to obtain the predicted value of *MA* effectively and efficiently. Once a reliable model is established, we can predict the activities of compounds and find which structural factors play an important role on the activities.

The aim of this study is to develop a reliable predictive QSAR model for estimating the *MA* values of NNs and MNNs and extracting the dominant quantum chemical descriptors relating to the mutagenicity of NNs and MNNs.

Materials and Methods

The mutagenic activities of NN and MNN standards were determined using a microsuspension-preincubation modification of the Ames Salmonella bacterial reversion assay in strain TA98 without microsomal activation by Pamela et al. (1996). The results from the experiments showed that the ambient mutagenic activities of these compounds ranged from 4.4 rev μg^{-1} for 2M1NN to 9,000 rev μg^{-1} for 2M6NN. The activity of 2-NN was over an order of magnitude greater than the activity of 1-NN. Similarly, the MNN isomers with the nitro-group on the β-carbon were generally more mutagenic than those isomers with the nitro-group on the α-carbon. Due to the disturbance of 2M5NN, the *MA* value of 2M3NN was not detected (Pamela et al. 1996). The results of mutagenic activities to the NN and MNN standards are reproduced in Table 1. The 15 nitro-PAHs with *MA* values determined constitute the training set of the study. The 2M3NN without experimentally detected *MA* value will be predicted by the QSAR model.

The description of the molecular structure using appropriate molecular descriptors and selection of suitable modeling methods are the most important. With the development of the computer technology and quantum chemistry, the quantum chemical descriptors can clearly describe the molecular properties and can be gotten accurately and easily. Numerous studies have been published on the applications of quantum chemical descriptors in QSAR or quantitative structure-property relationships (QSPR) (Niu and Yu 2004; Thanikaivelan et al. 2000). So the quantum chemical descriptors which are potentially more powerful than the other approaches were adopted in the QSAR model in this study.

For the current study, Parameterized Model revision 3 (PM3) Hamiltonian method was applied for computing the quantum chemical descriptors. A total of 15 descriptors reflecting the overall character of the nitro-PAHs molecules were used in this study. These are molecular weight (M_w), final heat of formation (ΔH_f), total energy (*TE*), electronic energy (*EE*), core-core repulsion energy (*CCR*), average molecular polarizability (α), dipole moment (μ), the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the second highest occupied molecular orbital (E_{HOMO-1}), the energy of the lowest unoccupied molecular

Table 1 The nitronaphthalenes and methylnitronaphthalenes under study and their mutagenicity*

No.	Nitro-PAHs name	Abbr.	*MA* (rev μg^{-1}) (*Obs.*)	log*MA* (*Obs.*)	log*MA* (*Pred.*)	*Diff.*	*SE.*
1	1-nitronaphthalene	1NN	180	2.255	2.033	0.222	±0.179
2	2-nitronaphthalene	2NN	4,000	3.602	3.441	0.161	±0.170
3	2-methyl-1-nitronaphthal	2M1NN	4.4	0.643	1.203	−0.560	±0.278
4	1-methyl-8-nitronaphthal	1M8NN	25	1.398	1.243	0.155	±0.272
5	2-methyl-8-nitronaphthal	2M8NN	14	1.146	2.282	−1.136	±0.157
6	2-methyl-4-nitronaphthal	2M4NN	310	2.491	2.408	0.083	±0.149
7	1-methyl-5-nitronaphthal	1M5NN	1,800	3.255	2.477	0.779	±0.145
8	2-methyl-5-nitronaphthal	2M5NN	300	2.477	2.303	0.174	±0.156
9	1-methyl-4-nitronaphthal	1M4NN	1,100	3.041	2.305	0.736	±0.156
10	2-methyl-3-nitronaphthal	2M3NN			3.029		±0.142
11	1-methyl-6-nitronaphthal	1M6NN	3,800	3.580	3.920	−0.340	±0.221
12	1-methyl-2-nitronaphthal	1M2NN	320	2.505	3.131	−0.626	±0.147
13	1-methyl-3-nitronaphthal	1M3NN	7,100	3.851	4.079	−0.228	±0.241
14	1-methyl-7-nitronaphthal	1M7NN	4,600	3.663	3.723	−0.060	±0.199
15	2-methyl-7-nitronaphthal	2M7NN	7,700	3.886	3.674	0.212	±0.193
16	2-methyl-6-nitronaphthal	2M6NN	9,000	3.954	3.525	0.429	±0.178

* *Obs.*: Observed values determined by Pamela et al. (1996); *MA* values of these compounds were determined using a microsuspension-preincubation modification of the Ames Salmonella bacterial reversion assay in strain TA98 without microsomal activation; *Diff.*: difference between observed and predicted log*MA* values; *SE.*: Standard errors for the predicted log*MA* values

orbital (E_{LUMO}), the energy of the second lowest unoccupied molecular orbital (E_{LUMO+1}), largest positive atomic charge on a nitrogen atom (Q_N^+), most positive net atomic charges on a hydrogen atom (Q_H^+), largest negative atomic charge on a oxygen atom (Q_O^-), and largest negative atomic charge on a carbon atom (Q_C^-). The values of the some selected molecular descriptors are listed in Table 2 and the others for the studied compounds are available on request. The unit of ΔH_f is kilocalorie, and units of energy, charge, dipole and polarizability are electron volts (eV), atomic charge units (a.c.u) and atomic units (a.u.), respectively. In addition, three combinations of frontier molecular orbital energies, $E_{LUMO} - E_{HOMO}$, $(E_{LUMO} - E_{HOMO})^2$, and $E_{LUMO} + E_{HOMO}$ were also selected as predictive variables because many studies have applied these parameters as quantum chemical descriptors and proved to be significant in QSAR models (Chen et al. 2001; Niu and Yu 2004). The $E_{LUMO} - E_{HOMO}$ and $E_{LUMO} + E_{HOMO}$ can be related to absolute hardness and electronegativity, respectively (Faucon et al. 1999; Pearson 1986).

Linear or nonlinear statistic methods such as multiple linear regression (MLR), principal component regression (PCR), partial least squares (PLS), different types of artificial neural networks (ANN), genetic algorithms (GA), and support vector machines(SVM), etc., are available in the development of a mathematical relationship between the structural descriptors and biological effects (Gramatica et al. 2007; Hasegawa and Funatsu 1998; Luan et al. 2006; Niu and Yu 2004; Yan et al. 2005). Among these methods, PLS algorithm not only searches the relationship between a matrix Y (containing dependent variables) and a matrix X (containing predictor variables), but also reduces the dimension of the matrices while concurrently maximizing the relationship between the descriptors. In this study, QSPR models were developed using PLS analysis, as implemented in the Simca (Simca-S Version 6.0, *Umetri AB and Erisoft AB*) software. The conditions for the computation were based on the default options of the software. The criterion used to determine the model dimensionality (the number of significant PLS components) is cross-validation (*CV*). With *CV*, the fraction of the total variation of the dependent variables can be predicted by a component, Q^2. If the whole data set is larger than a significance limit (0.097), the tested PLS component is considered significant. The obtained QSAR model is considered to have a good predictive ability when the cumulative cross-validated regression coefficient (Q^2) for the extracted components, Q^2_{cum}, is larger than 0.5. Model adequacy was mainly measured as the number of PLS principal components (k), Q^2_{cum}, the correlation coefficient between observed values and fitted values (R), and the significance level (p). Besides the standard error of predicted values (*SE.*) given by PLS analysis, another standard error (*SE*) was adopted to assess the predictive capability of the regression model. *SE* was defined like that in multiple regression analysis:

$$SE = \sqrt{\frac{\sum_{i=1}^{n} [\log MA(\text{observed})_i - \log MA(\text{predicted})_i]^2}{n - k - 1}} \quad (1)$$

where log*MA* (observed) and log*MA* (predicted) are the observed and predicted (over the test set) values of the

Table 2 Selected quantum chemical descriptors of the nitro-PAHs

No.	ΔH_f	*CCR*	E_{HOMO}	E_{HOMO-1}	E_{LUMO}	E_{LUMO+1}	Q_H^+	Q_C^-
1	8.624	−487.044	−9.382	−9.912	−1.304	−0.384	0.157	−0.386
2	4.131	−491.114	−9.270	−10.068	−1.138	−0.598	0.149	−0.405
3	6.828	−453.156	−9.326	−9.786	−1.299	−0.476	0.146	−0.406
4	16.006	−449.752	−9.180	−9.884	−1.320	−0.438	0.147	−0.160
5	−1.179	−488.891	−9.346	−9.793	−1.317	−0.408	0.165	−0.394
6	−0.558	−490.870	−9.326	−9.819	−1.319	−0.408	0.161	−0.378
7	0.913	−475.973	−9.264	−9.943	−1.338	−0.380	0.144	−0.392
8	−0.977	−487.878	−9.330	−9.795	−1.313	−0.413	0.158	−0.387
9	0.338	−474.267	−9.303	−9.939	−1.364	−0.389	0.162	−0.404
10	−0.571	−471.577	−9.190	−9.986	−1.222	−0.650	0.151	−0.379
11	−5.331	−490.178	−9.172	−10.062	−1.219	−0.623	0.148	−0.388
12	1.054	−476.507	−9.226	−10.062	−1.243	−0.609	0.146	−0.392
13	−4.060	−494.604	−9.120	−10.075	−1.231	−0.659	0.149	−0.378
14	−4.502	−480.406	−9.193	−10.079	−1.198	−0.618	0.154	−0.397
15	−4.826	−490.507	−9.221	−9.955	−1.138	−0.631	0.150	−0.402
16	−6.886	−503.767	−9.264	−9.880	−1.229	−0.597	0.147	−0.395

dependent variable, respectively, and n stands for the number of observations used for model building in the training set.

Results and Discussion

Partial Least Squares (PLS) algorithm reveals the relationship between a matrix **Y** (containing dependent variables) and a matrix **X** (containing predictive variables). However, previous studies found that not all predictive variables were necessary for PLS modeling. So the number of independent variables as molecular structural descriptors should be reduced to obtain an optimal model (Chen et al. 2001; Niu and Yu 2004).

In a PLS model, Variable Importance in the Projection (*VIP*) is a parameter that shows the importance of a variable. Thus terms with large values of *VIP* are the most relevant to explain dependent variables. For the PLS analysis procedure, a PLS model with all the predictive variables was carried out at first. Then the variable with the lowest *VIP* value was eliminated and a new PLS regression was performed. This procedure was repeated until the most important predictive variables were left (Chen et al. 2001; Niu and Yu 2004). The optimal PLS model was selected with respect to the statistics of Q^2_{cum}, R, p, and SE.

The above described PLS analysis procedure with log*MA* as dependent variable and the 18 quantum chemical descriptors as independent variables, for the 15 nitro-PAHs contained in the training set, led to QSAR Model (1) as the optimal one. The concrete results for Model (1) are shown in Table 3. In Table 3, $R^2_{\text{X(adj)(cum)}}$ and $R^2_{\text{Y(adj)(cum)}}$ stand for cumulative variance of all the **X**'s and **Y**'s explained by all extracted components, respectively, *Eig* stands for the eigenvalue which denotes the importance of the PLS principal components. It thus can be seen from Table 3 that one PLS principal component was selected in Model (1), which explained 57.7% of the variance of the predictive variables, and 76.7% of the variance of the dependent variable. The results showed that the correlation between observed and predicted log*MA* was significant ($R = 0.876$, $p < 0.0001$) for the 15 nitro-PAHs contained in the training set. As the cross-validated Q^2_{cum} value of Model (1) is remarkably larger that 0.50, Model (1) is surely stable and has good predictive ability. Moreover, seen from Table 1, the relative error values of most nitro-PAHs ranged from 1.6% to 11.1%, except for 2M1NN and 2M8NN. Due to their much lower mutagenicity values than others, high relative error values can be achieved for the two nitro-PAHs even if they have the low differences compared with the other nitro-PAHs. Still, the predicted values for the two compounds are also similar to their experimental values. Thus, the QSAR Model is reliable and accurate for prediction. Baesd on Model (1), log*MA* value for 2M3NN was predicted (Table 1).

Table 3 Model fitting results for Model (1)

k	$R^2_{\text{X(adj.)(cum)}}$	$R^2_{\text{Y(adj.)(cum)}}$	*Eig*	Q^2_{cum}	R	p	*SE*
1	0.577	0.767	2.308	0.711	0.876	1.863×10^{-5}	0.532

There are totally four predictive variables included in Model (1). *VIP* values for the independent variables in Model (1) are listed in Table 4. Table 4 also shows the pseudo-regression coefficients of the independent variables and constants transformed from PLS results. The effects of each independent variable on the mutagenicity of the nitro-PAHs can be evaluated from the positive and negative symbols of the coefficients of the independent variables. Based on the unscaled pseudo-regression coefficients above, an analytical QSAR equation can be obtained as follows:

$$\log MA = -10.527 - 2.828E_{\text{HOMO}-1} - 0.050\Delta H_{\text{f}} - 0.021CCR + 2.335(E_{\text{LUMO}} + E_{\text{HOMO}}) \quad (2)$$

It is safe to conclude from this study that the PLS principle component is mainly related to the descriptors including ΔH_{f}, CCR, $E_{\text{HOMO}-1}$, and $E_{\text{LUMO}} + E_{\text{HOMO}}$. The descriptors ΔH_{f}, $E_{\text{HOMO}-1}$, and CCR are more important than $E_{\text{LUMO}} + E_{\text{HOMO}}$ in determination of the log*MA* values of the nitro-PAHs.

According to Eq. 2, log*MA* values increase with larger $E_{\text{LUMO}} + E_{\text{HOMO}}$, indicating a significant correlationship with electrophilic properity of corresponding compounds. The larger $E_{\text{LUMO}} + E_{\text{HOMO}}$ is, the stronger electronegativity is, thereby leading to more easily react with the nucleophile in cellular nucleic acids and enzymes (Bieler et al. 2003; Dearden et al. 1995; Deneer et al. 1987, 1989) and having bigger log*MA* values. Previous studies (Tuppurainen 1999; Yan et al. 2005) also demonstrated that most mutagens are soft electrophilic agents. In addition, the present study suggests that increasing ΔH_{f}, $E_{\text{HOMO}-1}$, and CCR values will lead to the decline of log*MA* values, which is explained that the compounds become more unstable and

Table 4 VIPs and pseudo-regression coefficients in model (1)

Variables	VIP	Coeff (a)[a]	Coeff (b)[b]
$E_{\text{HOMO}-1}$	1.024	−0.295	−2.828
ΔH_{f}	1.009	−0.291	−0.050
CCR	1.000	−0.289	−0.021
$E_{\text{LUMO}} + E_{\text{HOMO}}$	0.967	0.279	2.355
Constants		2.619	−10.527

[a] Coeff (a): Coefficients Scaled and Centered

[b] Coeff (b): Coefficients Unscaled

reactive along with increasing ΔH_f, E_{HOMO-1}, and *CCR* values.

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