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Tan, Zhengde; Deng, Jiyong; Zhang, Shihua; Yu, Xinliang
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Prediction of Monomer Reactivity in Radical Copolymerizations from Transition State Quantum Chemical Descriptors

Zhengde Tan, Jiyong Deng

College of Chemistry and Chemical Engineering, Hunan Institute of Engineering, China

Shihua Zhang

Network Information Centre, Hunan Institute of Engineering, China

Xinliang Yu

College of Chemistry and Chemical Engineering, Hunan Institute of Engineering, China

Abstract: In comparison with the Q-e scheme, the Revised Patterns Scheme: the U, V Version (the U-V scheme) has greatly improved both its accessibility and its accuracy in interpreting and predicting the reactivity of a monomer in free-radical copolymerizations. Quantitative structure-activity relationship (QSAR) models were developed to predict the reactivity parameters u and v of the U-V scheme, by applying genetic algorithm (GA) and support vector machine (SVM) techniques. Quantum chemical descriptors used for QSAR models were calculated from transition state species with structures $C^1H_3-C^2HR^3\bullet$ or $\bullet C^1H_2-C^2H_2R^3$ (formed from vinyl monomers $C^1H^2=C^2HR^3 + H\bullet$), using density functional theory (DFT), at the UB3LYP level of theory with 6-31G(d) basis set. The optimum support vector regression (SVR) model of the reactivity parameter u based on Gaussian radial basis function (RBF) kernel ($C = 10$, $\epsilon = 10^{-5}$ and $\gamma = 1.0$) produced root-mean-square (rms) errors for the training, validation and prediction sets being 0.220, 0.326 and 0.345, respectively. The optimal SVR model for v with the RBF kernel ($C = 20$, $\epsilon = 10^{-4}$ and $\gamma = 1.2$) produced rms errors for the training set of 0.123, the validation set of 0.206 and the prediction set of 0.238. The feasibility of applying the transition state quantum chemical descriptors to develop SVM models for reactivity parameters u and v in the U-V scheme has been demonstrated.

Keywords: *Genetic algorithm, quantum chemistry, radical copolymerizations, structure-activity relations, support vector machine, transition state.*

Introduction

The relationship between the composition of a binary mixture of the monomer feed and that of the resulting copolymer is one of the most important aspects in copolymerization studies^[1]. For the copolymerization of monomers 1 and 2 (or a radical M_1 with a monomer M_2), the copolymer composition equation can be expressed as^[1,2]

$$R_p = R_m(r_{12}R_m + 1)/(r_{21} + R_m) \quad (1)$$

where R_m is the ratio of $[M_1]$ to $[M_2]$ in the monomer mixture and R_p is the ratio of $[M_1]$ to $[M_2]$ in the polymer formed, r_{12} and r_{21} are the monomer reactivity ratios. Therefore Equation 1 is extremely useful in predicting and controlling the composition of any copolymer produced from any pair of monomers at any concentration ratios^[1,2]. But Equation 1 may be limited because of the shortage of the values of r_{12} and r_{21} . The Q-e scheme can be used to estimate the monomer reactivity ratios with following equations^[1-3]

$$r_{12} = (Q_1/Q_2)\exp[-e_1(e_1 - e_2)] \quad (2)$$

$$r_{21} = \frac{Q_2}{Q_1}\exp[-e_2(e_2 - e_1)] \quad (3)$$

where Q_1 and Q_2 denote the conjugative effects of M_1 and M_2 respectively, e_1 and e_2 describe their respective polarity. Alfrey and Price^[4] assumed that the parameter Q may reflect the general reactivity of a monomer (or a radical), that is, the energetic property or the thermodynamic property, as it governs reactivity in all chemical processes. In addition, the parameter e may reflect the supposed permanent electric charge resulting in mutual attraction or repulsion between the two monomers (or radicals). Published studies show that the parameter Q is dependent on the reaction free energy of the free-radical reaction and the electronegativity of the monomer (or the average electronegativity of the monomer and the radical); and the parameter e is related to the electronegativity of the monomer or both the monomer and the corresponding radical^[1-3].

Although very widely used, the Q-e scheme has serious shortcomings. For example, the assumption that permanent electric charges exist on all the species involved, including hydrocarbons, is very unlikely. Moreover, the assumption that the polarity of a monomer being identical to that of the corresponding radical derived from that monomer is under debate^[1,3-5].

Recently, the Revised Patterns Scheme, the U-V scheme, has greatly improved both its accessibility and its accuracy, which can be expressed by Equation 4¹³⁻⁶¹.

$$\log r_{12} = \log r_{1s} - u_2 \pi_1 - v_2 \quad (4)$$

where r_{1s} is the monomer reactivity ratio of the monomer 1 (M_1) and styrene; u_2 , v_2 , and π_1 are the counterparts of e_2 , Q_2 , and e_1 in the $Q-e$ scheme, respectively. Thus, u_2 represents the polarity of the double bond in the monomer, arising from the influence of substituents, and accounts for electronic effects, dipole effects, or specific interactions between monomers. v_2 describes the intrinsic reactivity of the monomer M_2 (i.e., the energetic property or the reaction free energy of the free-radical reaction). In addition, the U-V scheme can be used for the prediction of transfer constants (C_2) by using the relationship:

$$\log(1/C_2)_1 = \log r_{1s} - u_2 \pi_1 - v_2 \quad (5)$$

The U-V scheme may be limited when u and v values of the monomer of interest are unknown. Therefore, the development of reliable quantitative structure-activity relationship (QSAR) models for the prediction of the basic parameters u and v is of real interest, particularly for new monomers for which experimental investigation would be expensive. QSAR approaches can conserve resources and accelerate the process of development of new molecules⁷⁻¹¹. Yi et al. developed QSAR models for parameters u and v with quantum chemical descriptors calculated from radicals $C^1H_3-C^2HR_3\cdot$. Correlation coefficients for the training sets were 0.941 for the parameter u and 0.947 for the parameter v ; and correlation coefficients for the test sets were 0.947 for u and 0.934 for v ¹².

Reactivity parameters, such as u and v , are related to the reaction rate constants and activation energies. This means molecular descriptors from the transition state complexes $C^1H_3-C^2HR_3\cdot$ or $\cdot C^1H_2-C^2H_2R^3$ (formed from the vinyl monomer + $H\cdot$) should be related to u and v parameters. The purpose of this work is to calculate quantum chemical descriptors from transition state structures ($C^1H_3-C^2HR_3\cdot$ or $\cdot C^1H_2-C^2H_2R^3$) and predict the u and v values in the U-V scheme.

Methods

Tables 1 and 2 shows experimental values of parameters u and v of 50 vinyl monomers with structures $C^1H_2=C^2HR^{3[6]}$. The entire set of reactivity parameters u ranged from -3.50 to 1.18 and v ranged from -2.06 to 1.44. Moreover, the entire sets were characterized by a high degree of structural variety. For example, the monomers included halides, ketones, sulfides, esters, ethers, aromatic rings, and so on. The experimental data of 50 reactivity parameters u and v in Tables 1 and 2 were randomly divided into three sets: a training set (30 monomers, Nos. 1-30), a validation set (10 monomers, Nos. 31-40), and a test set (10 monomers, Nos. 41-50). The training set was used to build models, the validation set was used to optimize the parameters of models, and the test set was used to evaluate the prediction ability.

The transition state complexes $C^1H_3-C^2HR_3\cdot$ (or $\cdot C^1H_2-C^2H_2R^3$) derived from the addition of vinyl

monomers ($C^1H_2=C^2HR^3$) with the radical $H\cdot$ were fully optimized and calculated with density functional theory (DFT) in Gaussian 09 program (Revision A.02), at the UB3LYP level of theory with 6-31G(d) basis set. Frequency calculations show that each transition state complex had a single imaginary vibrational frequency¹³¹.

Totally, 23 quantum chemical descriptors¹⁴⁻¹⁶¹ were calculated for each transition state complex. These descriptors include the average molecular polarizability (α), the total dipole moment (μ), the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of alpha spin states ($E_{\alpha\text{HOMO}}$ and $E_{\alpha\text{LUMO}}$), the energies of HOMO and LUMO of beta spin states ($E_{\beta\text{HOMO}}$ and $E_{\beta\text{LUMO}}$), the energy gap between HOMO and LUMO of alpha spin states ($E_{\alpha g}$), the energy gap between HOMO and LUMO of beta spin states ($E_{\beta g}$), Mulliken atomic charges of C^1 , C^2 and X^3 (Q_{MC^1} , Q_{MC^2} and Q_{MX^3}), Mulliken charges of C^1 , C^2 and X^3 with hydrogens summed into heavy atoms (q_{MC^1} , q_{MC^2} and q_{MX^3}), Mulliken atomic spin densities (D_{MC^1} , D_{MC^2} and D_{MX^3}), atomic polar tensor (APT) charges (Q_{AC^1} , Q_{AC^2} and Q_{AX^3}), and APT charges with hydrogens summed into heavy atoms (q_{AC^1} , q_{AC^2} and q_{AX^3}). Here X^3 is the atom joining directly to C^2 . The descriptor α was defined as:

$$\alpha = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \quad (6)$$

Where α_{xx} , α_{yy} , and α_{zz} are principal components of the polarizability tensor and can reflect electric perturbation in the x -, y -, and z -coordinates. APT charge on an atom is related to trace of the corresponding tensor of derivatives of dipole moment with respect to Cartesian coordinates of that atom¹⁷¹.

Support vector machine (SVM) is a set of learning algorithm mainly used to resolve the classification and regression problem^{18,9,18-231}. In SVM, systems use the input data into a high dimensional feature space and subsequently carry out the linear regression in the feature space. For a given data set $(x_1, y_1), (x_2, y_2), \dots, (x_p, y_p)$, where $x_i \in \mathbb{R}^n$, $y_i \in \mathbb{R}$ ($i = 1, 2, \dots, l$), the linear critical function of support vector regression (SVR) is listed as below^{10,18,19,221}:

$$f(x) = \sum_i^n \phi(x_i) \omega + b \quad (7)$$

where n is the total number of input-output pairs, $\phi(x)$ is called as the feature mapping function, x is the input space, $f(x)$ is the output, and w and b are the coefficients. SVR problem is equivalent to the solution of quadratic convex programming:

$$\min_{w, b, \xi, \xi^*} J(w, \xi, \xi^*, b) = \frac{1}{2} \|w\|^2 + C \sum_i (\xi_i + \xi_i^*) \quad (8)$$

subject to:

$$y_i - \phi^T(x_i)w - b \leq \varepsilon + \xi_i \quad (9)$$

$$\phi^T(x_i)w + b - y_i \leq \varepsilon + \xi_i^* \quad (10)$$

where C is a regularized constant determining the trade-off between the training error and the model flatness, ε is

Table 1. Transition state descriptors and u values for 50 monomers.

No.	Monomer	α	$E_{\text{eHOMO}}/\text{a.u.}$	$Q_{\text{AC}}/\text{electron}$	$u(\text{exp.})$	$u(\text{calc.})$
Training set						
1	Acrylate, butyl	81.525	-0.226004	-0.015174	-2.22	-2.22
2	Butadiene-1-carboxylate, ethyl	87.107	-0.204126	0.115617	-2.57	-2.57
3	Pyridine, 4-vinyl-	77.618	-0.193613	0.079870	-0.94	-0.94
4	Vinyl benzoate	95.609	-0.199616	0.446112	-0.86	-0.86
5	Carbazole, N-vinyl -	151.658	-0.196652	0.389249	-0.25	-0.25
6	Acrolein	32.337	-0.215000	-0.131978	-2.75	-2.75
7	Acrylonitrile	33.902	-0.237902	0.125046	-2.60	-2.60
8	Vinyltrimethylsilane	74.106	-0.194325	-0.286116	-1.41	-1.41
9	Acrylate, 2-chloroethyl	67.461	-0.218034	-0.068475	-2.38	-2.38
10	Vinyl isobutyl ether	68.950	-0.153907	0.406922	0.41	0.41
11	Vinyl 2-chloroethyl ether	56.734	-0.161437	0.391636	1.18	1.18
12	Vinyl phenyl sulfide	101.974	-0.161535	0.056216	0.20	0.04
13	Vinyl tert-butyl sulfide	82.491	-0.155164	0.033071	0.41	0.41
14	Styrene, p-methyl-	96.941	-0.163916	0.058980	-0.20	-0.20
15	Styrene, p-l-(2-hydroxypropyl)-	125.611	-0.158901	0.094502	-0.60	-0.60
16	Acrylate, 2-nitrobutyl	91.689	-0.215196	-0.073653	-2.39	-2.39
17	Styrene, 2,5-dichloro-	107.470	-0.188014	0.094944	-1.98	-1.61
18	p-Vinylbenzoic acid	97.001	-0.201456	0.037973	-1.03	-1.04
19	Allyl chloride	40.795	-0.199831	-0.035940	-0.39	-0.39
20	Acrylate, benzyl	106.321	-0.238936	-0.010546	-2.68	-2.68
21	Vinyl chloroacetate	55.560	-0.208285	0.451477	1.04	0.20
22	Pyridine, 2-vinyl-	78.959	-0.182180	0.064983	0.98	0.21
23	Styrene, p-chloromethyl-	112.527	-0.177209	0.086353	-0.62	-0.62
24	Vinylisocyanate	40.953	-0.181584	0.329776	0.29	0.29
25	Vinyl dichloroacetate	65.958	-0.217299	0.461101	-0.98	-0.98
26	Vinyl dodecyl ether	158.316	-0.146817	0.392157	0.44	0.44
27	Pyridine, 2-methyl-5-vinyl-	93.445	-0.172672	0.088674	-1.04	-1.04
28	Vinyl acetate	46.474	-0.197016	0.428884	-0.44	-0.44
29	Vinyl ethyl sulfoxide	64.659	-0.195200	-0.050033	-1.02	-1.02
30	Acryloyl chloride	44.601	-0.261455	-0.279107	-3.50	-3.50
Validation set						
31	Vinyl stearate	223.967	-0.195524	0.457350	-1.19	-1.14
32	Vinyl isobutyl sulfide	83.076	-0.155534	0.087930	0.14	-0.08
33	Vinyl isothiocyanate	54.529	-0.227898	0.656401	-1.56	-1.10
34	Vinyl methyl ketone	44.882	-0.233541	-0.049383	-2.46	-2.52
35	Vinyl hendecanoate	149.227	-0.172121	0.281400	-0.34	-0.54
36	p-Vinylbenzylmethylcarbinol	116.505	-0.192609	0.065644	-0.66	-0.81
37	Acrolein, methyl-	44.033	-0.231786	-0.003509	-1.73	-2.40
38	Acrylamide	40.464	-0.218094	0.001179	-1.82	-1.84
39	Vinyl ethyl sulfide	60.693	-0.151921	0.048392	0.66	0.49
40	Vinyl ethyl oxalate	73.913	-0.206961	0.464290	-1.11	-0.60
Test set						
41	Allyl acetate	57.652	-0.191875	-0.005274	-0.37	0.00
42	Styrene	76.991	-0.191317	0.054793	0.00	-0.39
43	Acrylate, methyl	47.599	-0.237418	-0.004654	-2.34	-2.27
44	Butadiene, 2-chloro-	51.765	-0.215561	-0.010861	-2.18	-1.81
45	Butadiene, 2-fluoro-	41.187	-0.217407	0.005885	-1.32	-1.75
46	Acrylate, ethyl	58.979	-0.227301	-0.007137	-1.99	-1.87
47	Propene, 3,3,3-trichloro-	63.047	-0.235506	-0.100136	-2.35	-1.93
48	Pyridine, 2-vinyl-5-ethyl-	105.055	-0.177101	0.061485	-0.20	-0.51
49	Vinyl chloride	29.774	-0.193432	0.277557	-0.90	-0.50
50	Vinyl chloromethyl ketone	53.411	-0.247365	-0.003617	-1.58	-1.94

Table 2. Transition state descriptors and ν values for 50 monomers.

No.	Monomer	$Q_{M^{\cdot}}/\text{electron}$	$D_{M^{\cdot}}/\text{electron}$	$E_{\text{pg}}/\text{a.u.}$	$\nu(\text{exp.})$	$\nu(\text{calc.})$
Training set						
1	Acrylate, butyl	0.619517	-0.067972	0.163555	0.12	0.10
2	Acrylate, ethyl	0.616288	-0.064224	0.164069	0.08	0.08
3	Vinyl isothiocyanate	-0.340547	0.005140	0.179246	0.18	0.18
4	p-Vinylbenzylmethylcarbinol	0.142632	-0.086980	0.193707	0.18	0.18
5	Vinyl ethyl oxalate	-0.426139	0.012963	0.207942	-0.71	-0.71
6	Vinyl 2-chloroethyl ether	-0.438814	0.109968	0.282286	-2.06	-2.01
7	Acrylate, benzyl	0.599957	-0.088491	0.131658	0.28	0.28
8	Acrolein, methyl-	0.428769	-0.102467	0.133677	0.77	0.77
9	Acrylate, methyl	0.602835	-0.082731	0.153543	0.16	0.16
10	Acrolein	0.214832	-0.037543	0.193545	0.56	0.56
11	Acrylonitrile	0.349842	-0.222754	0.215579	0.42	0.42
12	p-Vinylbenzoic acid	0.151699	-0.085617	0.206676	0.50	-0.03
13	Vinylisocyanate	-0.371647	-0.072006	0.237466	-0.91	-1.25
14	Allyl chloride	-0.377408	-0.077934	0.243789	-1.53	-1.53
15	Vinyl dichloroacetate	-0.437571	0.006826	0.237937	-1.30	-1.30
16	Vinyl dodecyl ether	-0.437582	0.117885	0.282686	-1.62	-1.62
17	Vinyl ethyl sulfoxide	0.766972	0.008160	0.149232	-0.94	-0.94
18	Acryloyl chloride	0.269538	-0.072846	0.152812	1.09	1.09
19	Allyl acetate	-0.044120	-0.078036	0.226252	-1.97	-1.97
20	Styrene	0.142227	-0.086213	0.201614	0.00	0.00
21	Butadiene-1-carboxylate, ethyl	-0.086160	-0.235962	0.159707	0.92	0.92
22	Butadiene, 2-chloro-	-0.007180	-0.063717	0.181896	1.44	1.44
23	Butadiene, 2-fluoro-	0.401754	-0.044417	0.184933	0.51	0.51
24	Carbazole, N-vinyl -	-0.625568	-0.060404	0.130622	-0.58	-0.58
25	Propene, 3,3,3-trichloro-	-0.298262	-0.045593	0.199965	-0.84	-0.84
26	Pyridine, 2-methyl-5-vinyl-	0.187799	-0.197409	0.170313	0.28	0.28
27	Vinyltrimethylsilane	0.697164	0.003655	0.231098	-1.15	-1.15
28	Pyridine, 2-vinyl-	0.310417	-0.174770	0.164044	0.32	0.32
29	Vinyl acetate	-0.438523	-0.001582	0.234834	-1.56	-1.34
30	Vinyl benzoate	-0.431653	0.041245	0.199602	-1.45	-1.45
Validation set						
31	Styrene, p-methyl-	0.206484	-0.197495	0.174979	0.08	0.20
32	Styrene, p-1-(2-hydroxypropyl)-	0.209978	-0.200617	0.172788	0.16	0.25
33	Vinyl hendecanoate	-0.436041	0.024143	0.234897	-1.33	-1.03
34	Acrylate, 2-chloroethyl	0.573229	-0.054694	0.219405	0.25	0.14
35	Acrylate, 2-nitrobutyl	0.584817	-0.054855	0.213564	0.44	0.22
36	Acrylamide	0.582601	-0.079071	0.154726	-0.07	0.17
37	Pyridine, 4-vinyl-	0.212819	-0.184798	0.155174	0.30	0.46
38	Styrene, p-chloromethyl-	0.207904	-0.198183	0.169418	0.21	0.29
39	Vinyl ethyl sulfide	0.156101	0.128956	0.220314	-0.77	-0.52
40	Vinyl isobutyl ether	-0.435610	0.115740	0.276534	-1.41	-1.72
Test set						
41	Pyridine, 2-vinyl-5-ethyl-	0.311233	-0.176549	0.164013	0.12	0.32
42	Vinyl chloride	-0.015401	0.064958	0.258229	-1.16	-0.87
43	Vinyl chloroacetate	-0.424592	0.010159	0.232613	-1.65	-1.16
44	Vinyl chloromethyl ketone	0.431368	-0.093433	0.133228	0.97	0.72
45	Vinyl phenyl sulfide	0.200581	0.112593	0.182463	-0.58	-0.54
46	Vinyl stearate	-0.453050	-0.001541	0.234311	-1.15	-1.31
47	Vinyl tert-butyl sulfide	0.138201	0.116519	0.208370	-0.64	-0.59
48	Vinyl isobutyl sulfide	0.152256	0.144593	0.216024	-0.43	-0.50
49	Vinyl methyl ketone	0.420669	-0.115562	0.131660	0.54	0.79
50	Styrene, 2,5-dichloro-	0.216569	-0.197234	0.152417	0.67	0.47

a prescribed parameter of the ϵ -insensitive loss function, ξ and ξ^* are positive slack variables for the data points.

Usually, SVR uses the ϵ -insensitive loss function to measure the empirical risk (training error):

$$|f(x) - y|_{\epsilon} = \begin{cases} |f(x) - y| - \epsilon & (|f(x) - y| \geq \epsilon) \\ 0 & (|f(x) - y| < \epsilon) \end{cases} \quad (11)$$

Thus, Equation 7 can be rewritten as:

$$f(x) = \sum_i^n (a_i - a_i^*) \phi(x_i) \cdot \phi(x) + b \quad (12)$$

where α_i and α_i^* are the introduced Lagrange multipliers.

Through selecting the appropriate kernel function, the entire problem can be solved in the input space itself:

$$f(x) = \sum_i^s (a_i - a_i^*) K(x, y) + b \quad (13)$$

where s is the number of input data having nonzero values of (α_i and α_i^*). The kernel function $K(\dots)$ must satisfy the condition of Mercer's theorem so that it corresponds to some type of inner product in the high-dimensional feature space. In general, the Gaussian radial basis function (RBF) is taken as the kernel function of SVM models:

$$K(x_i, x_j) = \exp(-\gamma \|x_i - x_j\|^2) \quad (14)$$

The adjustable parameter γ plays a major role in the performance of the kernel, and should be carefully tuned to the problem at hand. So three parameters C , ϵ and γ in ϵ -SVR models should be adjusted. All SVM models from the present paper were obtained with winSVM (<http://www.cs.ucl.ac.uk/staff/M.Sewell/winsvm/>).

Genetic algorithms (GA) are optimization algorithms that mimic natural biological evolution. At each generation, a new set of approximations is created by the process of selecting individuals according to their level of fitness and breeding them together using genetic operators inspired by natural genetics, i.e. random mutation, crossover and selection procedures. This process leads to better models or solutions from an originally random starting population or sample^[24,25]. GA together with multiple linear regression (MLR) analysis has become an effective and powerful tool in selecting variables for QSARs. Thus GA-MLR technique in the BuildQSAR program^[26] was used in this work. Next, the optimal descriptor sets were used as the input files of SVM models.

The accuracy of a model was evaluated with the root-mean-square (rms) error, which can be expressed as

$$rms = \sqrt{\frac{\sum (f_i - y_i)^2}{N}} \quad (15)$$

where f_i is the calculated value, y_i is the experimental value for the i th monomer and N is the total number of samples used. The smaller the rms value, the more accuracy the model will be.

Results and Discussion

By analyzing the parameters u and v with respect to the 23 descriptors with the GA-MLR technique in the BuildQSAR program^[26], respective optimal subset of descriptors in the model of parameters u and v was obtained. The optimal subset of descriptors for the parameter u comprises the average molecular polarizability (α), the HOMO energy of alpha spin states ($E_{\alpha\text{HOMO}}$), and APT charge of C¹ atom (Q_{AC^1}). The optimal descriptor subset for the parameter v consists of Mulliken atomic charge of X³ (Q_{MX^3}), Mulliken atomic spin density of X³ (D_{MX^3}), and the energy gap between HOMO and LUMO of beta spin states ($E_{\beta g}$). The values of these descriptors are shown in Tables 1 and 2. The definitions and standardized coefficients of these descriptors in each MLR model are listed in Table 3. A larger absolute value of beta coefficients means the corresponding descriptor is more significant. Thus, $E_{\alpha\text{HOMO}}$ and $E_{\beta g}$ are the most significant descriptors in the models of parameters u and v , respectively.

The parameter u denotes the polarity of a monomer. A large u value means less polarity of a monomer. The frontier molecular orbital descriptors, such as E_{HOMO} , E_{LUMO} , and $E_g (= E_{\text{LUMO}} - E_{\text{HOMO}})$ play major roles in governing many chemical reactions^[17]. These descriptors were used widely in describing molecular reactivity, stability^[27,28], or polarity^[17]. According to the frontier molecular orbital theory of chemical reactivity^[17], E_{HOMO} describes the susceptibility of the molecule toward attack by electrophiles and thus is correlated with the ionization potential; and E_{LUMO} , characterizing the susceptibility of the molecule toward attack by nucleophiles, is directly related to the electron affinity. A higher E_{HOMO} value means the stronger electron-donating ability and the smaller electronegativity^[2], which results in a smaller electronic effect and molecular polarity. Thus $E_{\alpha\text{HOMO}}$ is positively correlated with the parameter u .

Local electron densities or charges are important in many chemical reactions and physicochemical

Table 3. Descriptors selected for models, meaning and beta coefficients.

Model	Symbol	Descriptor	Beta coefficients
u	α	The average molecular polarizability.	-0.193
	$E_{\alpha\text{HOMO}}$	The energy of HOMO for alpha spin states.	0.802
	Q_{AC^1}	Atomic polar tensor charges of C ¹ .	0.291
v	Q_{MX^3}	Mulliken atomic charges of X ³ .	0.265
	D_{MX^3}	Mulliken atomic spin densities of X ³ .	-0.279
	$E_{\beta g}$	The energy gap between HOMO and LUMO of beta spin states.	-0.419

properties of compounds. They are also used widely for the description of the molecular polarity of molecules^[7]. Molecular polarity is dependent on bond polarity and the molecular geometry. Generally, for vinyl monomers $C^1H_2=C^2HR^3$, the APT charge of C^1 , Q_{AC^1} is less than the charge of C^2 , Q_{AC^2} . A monomer with the larger descriptor Q_{AC^1} suggests that the polar bonds (i.e., the double bond in the monomer) is relatively evenly (or symmetrically) distributed, which results in a less molecular polarity. So it is easy to understand that the descriptor Q_{AC^1} is positively related to the parameter u . The last descriptor appearing in the model of u is α , i.e., the average polarizability. α increases with the size of the species either as a result of an increase with the number of electrons or by the expansion of the molecular radius. A large α indicates a large size of substituent group R^3 in a vinyl monomer, which may lower the molecular symmetry and lead to a large molecular polarity and a small parameter u . Therefore, α is negatively correlated with the parameter u .

The parameter v describes the intrinsic reactivity of a monomer. A high reactive monomer, that has a large conjugative effect and a large v value, may lower the activation energy gained on adding the radical to the double bond of the monomer. Table 3 shows that v increases with decreasing $E_{\beta g}$. The reason is that a large $E_{\beta g}$ means high stability for the molecule in the sense of its lower reactivity in chemical reactions^[27]. A transition state species ($C^1H_3-C^2HR^3\cdot$ or $\cdot C^1H_2-C^2H_2R^3$) possessing a small $E_{\beta g}$ value suggests that the corresponding monomer is prone to forming a transition state structure and has a large parameter v value. As stated above, atomic charge descriptors can reflect molecular chemical reactivity (or intermolecular interactions)^[7]. A large Q_{MX^3} (Mulliken atomic charge of X^3) or small D_{MX^3} (Mulliken atomic spin density of X^3) implies that the monomer is relatively easy to form a transition state structure and has a large v value. Thus, both Q_{MX^3} and D_{MX^3} are related to the reactivity parameter v .

The program winSVM was used to develop SVM models for u and v . In order to get satisfactory models, the regularized constant C , the width of the non-penalized tube ϵ and the bandwidth parameter γ of the RBF kernel function should be selected properly^[22]. We take the training of SVM models of u as an example. Firstly, the training set of u (in Table 1) was selected as the input file to obtain 100 models after 100 iterations. The initial optimization results show that a model with SVM parameters of $C = 10$, $\epsilon = 10^{-4}$ and $\gamma = 1.0$ produced a low rms error. Thus, these SVM parameters were used for further optimization with the validation set. By training the SVM models of u with different γ values of 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, and 1.4 under the condition of $C = 10$ and $\epsilon = 10^{-4}$, the validation set produced the rms errors of 0.403, 0.353, 0.327, 0.345, 0.373, 0.390, and 0.405, respectively. Thus, the optimal γ corresponding to the minimal rms error (0.327) was set to 1.0. Subsequently, by applying $\gamma = 1.0$ and $\epsilon = 10^{-4}$, the second parameter C was optimized with C being equal to 7, 8, 9, 10, 11, 12, and 13. The validation set rms errors based on different C are 0.395, 0.362, 0.337, 0.327, 0.328, 0.334, and 0.343, respectively, so the optimal C was equal to 10. Similarly, the third parameter ϵ under the condition of C of 10 and

γ of 1.0, was optimized with $\epsilon = 10^{-6}$, $\epsilon = 10^{-5}$, $\epsilon = 10^{-4}$, $\epsilon = 10^{-3}$, $\epsilon = 10^{-2}$, and $\epsilon = 10^{-1}$. The validation set rms errors are 0.326, 0.326, 0.327, 0.327, 0.331, and 0.388, respectively. Thus, the optimal ϵ equals 10^{-5} .

In the end, the optimum ϵ -SVR model of u with the RBF kernel ($C = 10$, $\epsilon = 10^{-5}$ and $\gamma = 1.0$) was tested by the prediction set in Table 1. The u values calculated with the optimal SVR model are listed in Table 1 and depicted in Figure 1. For the SVM model of u , the rms errors for the training, validation and prediction sets are 0.220, 0.326 and 0.345, respectively. The mean rms error and correlation coefficient for 50 monomers are 0.272 and 0.972, respectively.

The three SVM parameters (C , ϵ and γ) of the model v were tuned with the same method. Learning parameters of $C = 10$, $\epsilon = 10^{-4}$ and $\gamma = 1.0$ were selected after initial optimization. Then the different parameters γ (0.9, 1.0, 1.1, 1.2, 1.3, and 1.4), C (5, 10, 15, 20, 25, 30, 35, and 40), and ϵ (10^{-6} , 10^{-5} , 10^{-4} , 10^{-3} , 10^{-2} and 10^{-1}), were tested successively. Respective validation set rms errors are 0.271, 0.254, 0.242, 0.236, 0.254, and 0.272 for different γ values ($C = 10$ and $\epsilon = 10^{-4}$); 0.337, 0.236, 0.214, 0.206, 0.206, 0.216, 0.241, and 0.289 for different C values ($\gamma = 1.2$ and $\epsilon = 10^{-4}$); and 0.206, 0.206, 0.206,

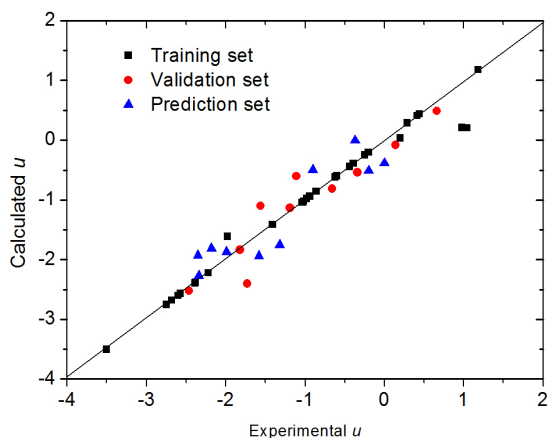


Figure 1. Plot of the experimental versus calculated u values.

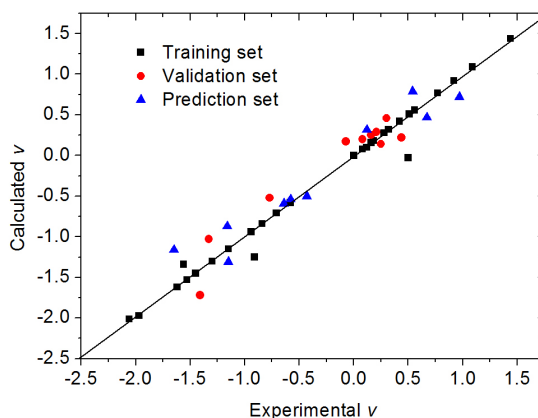


Figure 2. Plot of the experimental versus calculated v values.

0.206, 0.212, and 0.254 for different ϵ values ($C = 20$ and $\gamma = 1.2$). Thus, the optimal SVM parameters for v should be $C = 20$, $\gamma = 1.2$ and $\epsilon = 10^{-4}$.

The optimal ϵ -SVR model for v produced rms errors for the training set of 0.123, the validation set of 0.206 and the prediction set of 0.238. The mean rms error and correlation coefficient for the parameter v of 50 monomers are 0.170 and 0.981, respectively, which are comparable to the values of existing models^[12]. The calculated v values from the optimal SVR model are listed in Table 2 and depicted in Figure 2.

It should be noted that there are significant experimental errors for reactivity parameters such as Q , e , u , and v . For example, as long as the correlation coefficient R between the experimental and calculated e values is greater than 0.876 (rms = 0.326), then a good fit has been achieved^[12,12]. This means these QSAR models of reactivity parameters (u and v) are acceptable if their correlation coefficients are close to or above 0.9. Our models in this paper have correlation coefficients of 0.972 for u and 0.981 for v , denoting that our results for the model e are satisfactory and acceptable.

Conclusions

QSAR models of the reactivity parameters u and v in the U-V scheme used for the prediction of reactivity ratios and transfer constants for vinyl monomers in radical copolymerization were developed, by applying GA and SVM techniques. Quantum chemical descriptors used to build SVR models, were calculated from transition state species with structures $C^1H_3-C^2HR^3\bullet$ or $\bullet C^1H_2-C^2H_2R^3$, formed from vinyl monomer $C^1H_2=C^2HR^3 + H\bullet$. The models were proved to be accurate with mean rms errors of 0.272 ($R = 0.972$) for u and 0.170 ($R = 0.981$) for v , which demonstrate that calculating descriptors from transition state structures to develop SVM models for reactivity parameters u and v is feasible.

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