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Research on Thermodynamic Properties of Resveratrol Analogues Based on QSPR

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This paper selects 60 types of resveratrol analogues were selected and discusses the relationship between thermodynamic properties and the molecular descriptors, including the topological indexes of principal quantum number ($^0P_2$, $^0P_4$, $^0P_3$) and the sum total of them (Σ^0P). For the sake of simplicity, Σ^0P is confirmed as the fundamental variable for the models through comparative analysis. Based on the characteristics of sine series, sin($k\Sigma^0P$) (k=1, 2, 3, …) are incorporated into the models to eliminate the residuals, resulting in the maximization of adjusted coefficient of determination (R_{adj}^2). The introduction of sin(5Σ^0P) and sin(8Σ^0P) successfully eliminates the residuals and enhances the predictive power. The global correlation coefficients are greater than 0.99, and even close to 1. The stability and predictive power of each model are tested with additional resveratrol analogues other than the test samples by the cross-validation method. The test reveals that the QSPR model has a satisfactory stability and good predictive power.

1. Introduction

Resveratrol is a highly bioactive polyphenolic substance. Its chemical structure is shown in Figure 1.

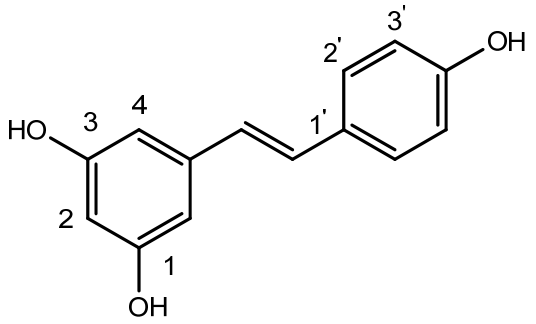

Figure 1: Chemical Structural Formula of Resveratrol

Resveratrol exists in many plants, ranging from the genus of Vitis (Vitaceae) to Polygonum (Polygonaceae). Resveratrol and its analogues has many biological functions, namely anti-inflammation, anti-tumortumor (Yuan et al., 2015), anti-oxidation (Farris et al., 2013), anti-bacteria and nerve protection (Han et al., 2012; Chen et al., 2015; Chen et al., 2015; Xia et al., 2014; Zhang et al., 2014). However, rarely any scholar has probed into the relationship between the structure and activity of resveratrol and its analogues. In light of the previous studies of structure-function relationship based on topological index (Qin, 2004), this paper explores the thermodynamic constitutive relationship (Du, 2014; Chen and Du, 2008; Xiao et al., 2015; He et al., 2015; Du, 2007; Du, 2010), aiming to disclose the properties of resveratrol analogues. The research results lay the theoretical basis for predicting the thermodynamic properties of the compounds.

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2. Section headings

2.1 Thermodynamic data

This study constructs the molecules of 60 types of resveratrol analogues with Chem3D software, using density functional B3LYP and 6-311++G(d, p) basis set optimization (Dunning and Hay, 1977; Liu et al., 2002), determines the stable configuration of molecules, and identifies the thermodynamic properties. Due to the limitation of space, only 39 results are given in Table 1.

Table 1: Thermodynamic Properties of Resveratrol Analogues

No	Molecules[a]	α (esu)	H^{Θ}(×10^{3}kJ.mol^{-1})[b]	E^{Θ}(kJ.mol^{-1})	C_V^{Θ}(J.mol^{-1}.K^{-1})	S^{Θ}(J.mol^{-1}.K^{-1})
1	3'-C4	234.98	-412.677	310.959	86.119	125.926
2	2,4-2C1-3'-C2	236.018	-412.685	309.022	94.504	128.562
3	2-C3-3'-C2	251.163	-515.848	388.417	109.956	155.925
4	2,4-C2-3'-C3	273.285	-722.194	544.33	154.151	206.543
5	3'-C5	247.757	-515.843	389.028	106.466	154.54
6	2-C1-4-C2	225.336	-309.51	232.346	69.375	94.918
7	2,3'-2C3	263.545	-619.012	466.809	129.963	183.87
8	2-C2-4-C3	250.927	-515.846	389.363	108.525	149.733
9	4-C1	199.643	-103.17	76.96	24.623	37.715
10	2-C1-4-C2-3'-C3	261.288	-619.012	465.315	135.239	185.385
11	2-C3-4-C4	275.639	-722.194	544.259	151.047	221.852
12	2-C2-4-C4	262.997	-619.012	467.185	129.014	181.012
13	4-C2	212.551	-206.336	155.402	44.514	61.417
14	2-C1-4-C3	238.701	-412.679	310.352	89.78	125.424
15	2-C7	280.362	-722.194	545.635	145.478	214.284
16	2-C2-4-C5	275.707	-722.194	544.866	149.649	220.309
17	4-C3	224.395	-309.505	233.643	64.576	88.63
18	2-C1	202.617	-103.175	76.822	25.15	38.748
19	2,3'-2C1-4-C3	250.11	-515.859	386.748	115.181	161.13
20	2-C3	228.835	-309.51	233.593	64.283	89.328
21	4-C4	236.505	-412.674	311.34	85.232	123.968
22	2-C3-4-C2-3'-C1	264.222	-619.012	465.391	134.285	181.895
23	2-C1-4-C3-3'-C2	260.374	-619.012	465.621	134.691	187.468
24	2-C1-3'-C4	248.818	-515.851	387.953	111.244	159.657
25	4-C5	249.041	-515.84	389.38	105.5	156.067
26	2,4-2C3-3'-C2	286.45	-825.35	622.408	173.983	239.095
27	2-C1-4-C4	250.885	-515.848	388.539	109.771	154.561
28	2-C1-3'-C5	261.25	-619.012	465.654	131.783	205.418
29	3'-C1	200.14	-103.178	76.354	25.397	34.158
30	2,4,3'-3C3	298.266	-928.532	699.711	195.351	279.265
31	2-C1-4-C5	263.426	-619.012	466.529	130.143	187.744
32	2,4-2C1-3'-C3	248.377	-515.856	386.786	114.663	164.456
33	3'-C2	210.521	-206.339	155.005	45.083	64.011
34	2-C4	241.598	-412.679	311.511	84.759	121.248
35	2-C2	215.533	-206.341	155.498	44.212	62.643
36	2,4-2C1-3'-C4	259.824	-619.012	464.96	135.57	189.226
37	3'-C3	223.257	-309.508	232.819	66.095	95.462
38	2,3'-2C4	287.551	-825.35	622.629	170.841	246.04
39	2,3'-2C2	238.552	-412.679	310.93	88.939	119.144

a. C1: methyl; C2: ethyl; 2C1: dimethyl; 3C1: trimethyl.
b. The values of H^{Θ}, E^{Θ}, C_V^{Θ} and S^{Θ} are relative to that of resveratrol.

2.2 Molecular descriptors

Whereas the thermodynamic properties of the molecules are related to the specific topological index of principal quantum number, the valence of the bond atom is defined as t_i:

$$t_i = m_i \left(n_i - 1 \right) + h_i \tag{1}$$

Where h_i is the number of the hydrogen atoms directly connected with atom i; m_i is the valence electrons of atom i; n_i is the principal quantum number of atom i, i.e. the number of electrons. The order is denoted as n:

$$^{n}\mathrm{P}=\sum\left(t_i t_{i-1} t_{i-2}\ldots\right)^{0.5} \tag{2}$$

Where i-1 is the atoms directly connected with atom i, and the other atoms. The 0 order and 1 order exponents are expressed by the formulas below:

$$^{0}\mathrm{P}=\sum t_i^{0.5} \tag{3}$$

$$^{1}\mathrm{P}=\sum\left(t_i t_{i-1}\right)^{0.5} \tag{4}$$

Since resveratrol analogues share a common parent structure, this paper focuses on the calculation of ^{0}P and ^{1}P of the alkyl. In view of the linear relationship between ^{0}P and ^{1}P , the ^{0}P values at the 2, 4 and 3' molecular positions are denoted as $^{0}P_2$, $^{0}P_4$ and $^{0}P_{3'}$, respectively.

3. Selection of model variables

3.1 Selection of basic independent variables

The thermodynamic properties of {$^{0}P_2$, $^{0}P_4$, $^{0}P_{3'}$} and {$\Sigma^{0}P$} are adopted to fit those of resveratrol analogues. For additional clarity, let $\Sigma^{0}P$ denote the ^{0}P value at each of the 2, 4 and 3 ' molecular positions of the alkyl, R^2, the determination coefficient, and R_{adj}^2, the adjusted coefficient of determination. R_{adj}^2 is expressed as:

$$R_{adj}=1-\frac{RSS/(n-k-1)}{TSS/(n-1)} \tag{5}$$

The result shows that the R_{adj}^2 value (with the addition of α) of $^{0}P_2$, $^{0}P_4$ or $^{0}P_{3'}$ is very close to that of $\Sigma^{0}P$. Hence, $\Sigma^{0}P$ is adopted to express the thermodynamic properties.

3.2 Residual analysis of a single independent variable

Without loss of generality, the model with the lowest adjusted coefficient of determination (R_{adj}^2) is identified as: $S^{\ominus}$=3.35+12.1$\Sigma^{0}P$. Figure 2 shows its residual distribution.

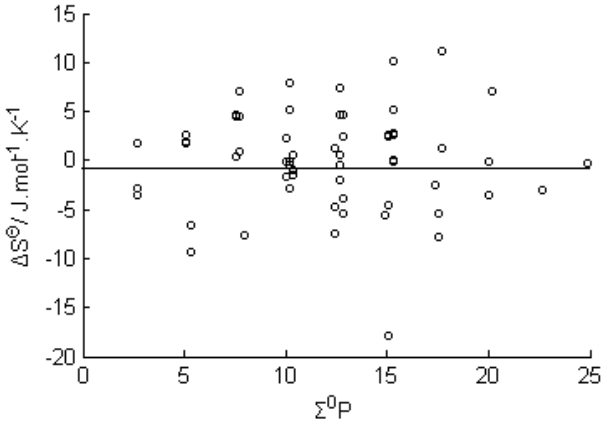

Figure 2: The residual distribution of $S^{\ominus}$

As shown in Figure, the residual is roughly evenly distributed in the $\Delta S^{\ominus}$ and has nothing to do with the linear.

3.3 Introduction to sine series

If a variable is introduced to improve the accuracy of the model without significantly changing the variable coefficient of the original model, the new variable should have the same degree of independence with the original variable. Therefore, the present study introduces the {sin($k\Sigma^{0}P$)} (k=1, 2, 3…) to decompose the residual.

The sine series is characterized by:
(1) {sin($k\Sigma^0P$)} randomly appears on both sides of the ΔY=0 (Y=α, H^Θ, E^Θ, $C_V{}^\Theta$ and S^Θ), and bears residual distribution characteristics;
(2) If {$k\Sigma^0P$} changes continuously, then adopt {sin($k\Sigma^0P$)} for the orthogonal series to minimize the number of multiple linearly independent variable.

3.4 Determination of independent variable

Because {$k\Sigma^0P$} is a discrete variable, it is necessary to investigate the multiple linearly independent variables. In this study, the variance inflation factor (VIF) is introduced to investigate the linear independence of the independent variables:

$$VIF=1/(1-R^2) \quad (6)$$

Where R is the correlation coefficient between a variable and the other variables. Due to the limitation of space, only the k≤9 case is taken into consideration. The result indicates that none of {Σ^0P, sin($k\Sigma^0P$), sin($2\Sigma^0P$), sin($9\Sigma^0P$)} is linearly independent. In pursuit of the minimum number of variables, this study determines the variables according to the following steps:
(1) Introduce one of the variables to the calculation model of the R_{adj}^2.
(2) After introducing the variable, compare the R_{adj}^2 value of each model, find the maximum, and determine the corresponding variable as the independent variable.
(3) On the premise that all VIFs are smaller than 10, repeat the above steps until the R_{adj}^2 value of the model reaches the maximum.

3.5 Determination of combined independent variables

Following the steps in Section 3.4, introduce sin($5\Sigma^0P$) in the case of k ≤9 (continue to introduce sin($8\Sigma^0P$) to the structural model), add (α), and express the other thermodynamic properties by{Σ^0P, sin($5\Sigma^0P$)}. The expression is more accurate than the expression of the results on {$^0P_2$, $^0P_4$, $^0P_3$}.

4. Model analysis

Formulas (7)~(11) present the five quantitative structure–property relationships models (QSPR) and the final results.

$$\alpha=189.541+4.869\sum{}^0P-2.709\sin(5\sum{}^0P), \ (SD=1.742,\ R^2=99.51\%,\ R_{adj}^2=99.50\%) \quad (7)$$

$$H^\Theta=0.143-41.054\sum{}^0P+10.520\sin(5\sum{}^0P), \ (SD=1.362,\ R^2=100.00\%,\ R_{adj}^2=100.00\%) \quad (8)$$

$$E^\Theta=-0.419+30.966\sum{}^0P-9.305\sin(5\sum{}^0P), \ (SD=1.444,\ R^2=99.99\%,\ R_{adj}^2=99.99\%) \quad (9)$$

$$C_V{}^\Theta=0.447+8.578\sum{}^0P+3.653\sin(5\sum{}^0P), \ (SD=0.942,\ R^2=99.95\%,\ R_{adj}^2=99.95\%) \quad (10)$$

$$S^\Theta=6.017+11.919\sum{}^0P-3.013\sin(5\sum{}^0P)+1.757\sin(8\sum{}^0P), \ (SD=5.022,\ R^2=99.32\%,\ R_{adj}^2=99.28\%) \quad (11)$$

For the five QSPR models, the adjusted coefficients are all above 0.98, signifying high correlation. The estimated results are in good agreement with the theoretical results.

5. Model verification

5.1 Robustness test

This section tests the robustness of the model. From Formulas (7)~(11), it is observed that S^Θ has the lowest adjusted coefficient of determination. For example, out of the 60 molecues in Table 1, remove molecues 1, 5, 9...57 and take the remaining ones as a training set; similarly, remove molecues 2, 5, 10...58 and take the remaining ones as another training set. In this way, a total of four training sets are constructed. The independent variable is determined by the steps in Section 3.4. See Table 2 for the modeling results, where Q stands for the cross-validation correlation coefficient.
Table 2 shows that the best variable obtained by the model based on each training set is consistent with the original sample (the 4th set is the control group). The main variables of Σ^0P, sin($5\Sigma^0P$) and sin($8\Sigma^0P$) are expressed by S^Θ. The cross-validation correlation coefficient (Q) of each set is greater than 0.97, an evidence to the good stability of the QSPR model.

5.2 Predictive power

To verify the predictive power of the proposed model, 7 samples are randomly selected in addition to those in Table 1, and are processed by the formulas (7)~(11). According to the results, the predicted thermodynamic parameters values are fairly close to the theoretical values. The maximum error for S^{Θ} appears in 2-C3-4-C1-3 'C3 resveratrol (-2.50%). Overall, the relative error between the predicted results and the theoretical values is less than 5%. Thus, the proposed model is proved to have excellent predictive power.

Table 2: Regression Results of Molecular Descriptors and S^{Θ}

No.	Model	R^2/%	R_{adj}^2/%	VIF_{max}	Q
	$S^{\Theta} = 0.616 + 12.223\sum {}^0P$	99.00	98.98	1.000	0.9877
1	$S^{\Theta} = 4.598 + 12.025\sum {}^0P - 3.432\sin(5\sum {}^0P)$	99.11	99.07	1.236	0.9823
	$S^{\Theta} = 4.069 + 12.033\sum {}^0P - 4.181\sin(5\sum {}^0P) + 3.272\sin(8\sum {}^0P)$	99.26	99.21	1.280	0.9780
	$S^{\Theta} = 3.172 + 12.071\sum {}^0P$	98.81	98.78	1.000	0.9973
2	$S^{\Theta} = 4.230 + 12.035\sum {}^0P - 1.524\sin(5\sum {}^0P)$	98.83	98.78	1.041	0.9980
	$S^{\Theta} = 5.558 + 11.912\sum {}^0P - 2.121\sin(5\sum {}^0P) + 1.961\sin(8\sum {}^0P)$	98.89	98.81	1.215	0.9981
	$S^{\Theta} = 4.304 + 12.026\sum {}^0P$	99.33	99.31	1.000	0.9888
3	$S^{\Theta} = 5.750 + 11.954\sum {}^0P - 1.788\sin(5\sum {}^0P)$	99.35	99.32	1.159	0.9899
	$S^{\Theta} = 6.557 + 11.926\sum {}^0P - 2.679\sin(5\sum {}^0P) + 2.029\sin(8\sum {}^0P)$	99.39	99.35	1.305	0.9918
	$S^{\Theta} = 3.927 + 12.013\sum {}^0P$	99.53	99.52	1.000	0.9693
4	$S^{\Theta} = 6.102 + 11.886\sum {}^0P - 2.431\sin(5\sum {}^0P)$	99.57	99.55	1.270	0.9707
	$S^{\Theta} = 6.228 + 11.880\sum {}^0P - 2.574\sin(5\sum {}^0P) + 0.332\sin(8\sum {}^0P)$ [a]	99.57	99.55	1.421	0.9717

a. In the 4th training set, the model with Σ^0P, $\sin(5\Sigma^0P)$ and $\sin(8\Sigma^0P)$ has a greater VIF_{max} than the model with Σ^0P and $\sin(5\Sigma^0P)$, indicating that the former has no better regression results than the latter.

6. Conclusions

Taking the topological indexes of principal quantum number $\{{}^0P_2, {}^0P_4, {}^0P_3\}$ and the sum total of such indexes $\{\Sigma^0P\}$ as molecular descriptors and the basic model variables, this paper introduces sine series to construct the thermodynamic structure-activity relationship model for resveratrol analogues, and proposes an adjustment judgment coefficient to obtain the satisfactory results. It is proved that the model has good stability and predictive power.

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