

Flavor Release from ι -Carrageenan Matrix: A Quantitative Structure–Property Relationships Approach

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We carried out a QSPR (quantitative structure–property relationships) approach to evaluate the influence of the chemical structure of aqueous matrixes over the partition coefficient between the gas phase and the matrix. The determination of the partition coefficient of flavor ingredients was performed by headspace analysis at equilibrium for both saline solution and ι -carrageenan gel. Starting from an initial list of 90 descriptors, we selected 10 descriptors to perform equation generation by the GFA (genetic function approximation) method available in the Cerius² package. The best obtained equations involve only five descriptors, which encode electronic properties of charges repartition on the molecule (Jurs-RNCS and Dipole-Z) and molecules' shapes (PMI-Y, Shadow-XY, and RadOf-Gyration), both for saline solution and for ι -carrageenan gel. However, the best-fitting equation for carrageenan gel is obtained with a quadratic relation, suggesting that the effect of carrageenan polymers only modulates but does not change the interaction of aroma compounds with water molecules.

KEYWORDS: ι -Carrageenan; gels; aroma release; partition coefficient; interaction; headspace analysis; QSAR; QSPR; genetic function approximation

INTRODUCTION

The equilibrium flavor retention/flavor release depends to a great extent on the components of the food matrix and on the physicochemical properties of the flavor compound and influences flavor perception (1).

From a chemical point of view, some measures about aroma release and aroma interaction with matrix ingredients have been made, changing the aroma compounds in order to find out how the structure of the aroma compound might affect aroma release (2).

The effect due to the presence of proteins (3, 4) or fat (5, 6) is, if not definitely elucidated, at least already well-known. Despite of these efforts the influence of texturing agents is still rather unclear.

To study how aroma structure and viscosity affect flavor release from matrixes we have performed the determination of partition coefficient for aroma compounds in different matrixes. Previous studies showed the influence of texturing agents, such as carrageenans (7), on aroma release (1, 8). So we decided to determine the partition coefficient of 12 flavor compounds in salt solution and in ι -carrageenan gel. Some additional computational studies were carried out with the aim of evaluating the

effect of viscosity and checking the influence of the chemical structure over the aroma release.

Under thermodynamic conditions it is possible to estimate the impact of the composition of a matrix on the volatility of a flavor compound by means of the calculation of the partition coefficient between the gas phase and the matrix at equilibrium. There are few studies related to the quantitative structure–property relationships (QSPR) approach of partitioning coefficients of aroma compounds between the vapor phase and food matrixes (9–11). To evaluate the influence of the chemical structure on the partition coefficient we have decided to use a QSPR approach. Partition coefficient studies by means QSPR approaches are indeed within the origins of the concept of QSPR (12–16) most of them involving partition coefficients of octanol/water in order to establish the molecular basis of hydrophobicity.

QSPR methods, based in the quantitative structure–activity relationships (QSAR) approach (17), attempt to find relationships between the properties of molecules and an experimental response. The assumption is that changes in molecular properties elicit different responses. This can be expressed by means of a simple mathematical relationship, the QSPR equation:

$$ER = f(p_1, p_2, p_3, \dots, p_n) \quad (1)$$

where ER is the experimental response such as partition coefficient or, as in other research fields, the ADMET (“absorption, distribution, metabolism, excretion, and toxicity”) properties, $p_1 \dots p_n$ are molecular parameters or descriptors character-

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izing relevant properties of the molecules, and f is an unknown, in any case linear, or nonlinear, mathematically complex function. In general, QSPR approaches, such as the more-used QSAR ones, are usually carried out using supervised methods, where the model is trained using sets of compounds whose property values, to build the model, have been previously measured. Supervised methods used in QSPR models range from simple statistical regression methods such as multiple linear regression (MLR), principal components regression (PCR), or partial least-squares (PLS) through to more flexible ones as the hybrid methods including genetic algorithms with the preceding studies (GFA (genetic function approximation) coupled with PLS for instance) or even model-free methods such as neural networks.

The methodology selection depends on the problem to solve. In general, when molecular descriptors are well correlated with the property, simple statistical methods are good enough. Hybrid methods are useful when it is difficult to identify the molecular descriptors due to high correlation among them, and model-free methods are suitable when it is suspected that there is not a clear linear relationship between descriptors and the dependent variable. Nevertheless it is necessary to highlight that there are no formal guidelines for constructing a QSPR model, and some miscalculations, due both to data quality and to methodological problems, during the approach can be difficult to avoid (18).

The present study intends to perform a QSPR model able to explain the retention/release equilibrium of several aroma compounds between the vapor phase and carrageenan gel, or saline solution.

Insofar that currently there are not enough high-quality experimental data available to build such a model, this work anyhow does not intend to be a good quantitative model able to predict the partition coefficient of other aroma compounds. The QSPR approach can be a good method to approach such phenomenon since the QSPR searches for the best mathematical relationships between molecular properties and the physical experimental response to study. In that way, knowing molecular properties of aroma compounds involved in a retention phenomenon, we should be able to obtain an idea about those physicochemical interactions which are involved between aroma compounds and the matrix and chemical properties of the matrix whose influence are decisive. Our purpose is, in brief, to settle down the basis of an alternative research about aroma release mechanisms by means of the computational approach.

MATERIALS AND METHODS

Materials. Sodium chloride was purchased from Riedel-deHaën (Steinheim, Germany). *t*-Carrageenans were kindly supplied by Rhodia Food (Aubervilliers, France). All the flavor compounds used were obtained from Sigma-Aldrich (Saint Quentin Fallavier, France). Purity of the flavor compounds was evaluated by GC-MS (>95%).

Aroma Solutions and Polysaccharides Matrixes. The stock solution of the flavor compound was prepared in pure water.

The *t*-carrageenan gel is prepared in NaCl solution (0.34%). *t*-Carrageenans (1.03 g) were mixed with NaCl solution (89 g) at ambient temperature for 15 min. The mixture was then stirred and heated to 90 °C for 30 min. The mixture was left to cool at ambient temperature and then stored at 4 °C for 24 h. Before the aromatization, the *t*-carrageenan gel was heated at 60 °C for 30 min. Then 21 mL of the hot solution of *t*-carrageenan (1.15%) was mixed with 3 mL of the aroma solution. This gave a final aromatized gel concentration of 16 $\mu\text{L}\cdot\text{L}^{-1}$ for all aroma compounds, except for linalool, 200 $\mu\text{L}\cdot\text{L}^{-1}$, 0.3% sodium chloride, and 1% *t*-carrageenan.

The same procedure was applied to prepare saline solution for headspace analysis, in which the polysaccharide solution was replaced by an equal volume of NaCl solution. The final concentration of NaCl

is 0.3% (w/w), and the final concentration of aroma compound is 16 $\mu\text{L}\cdot\text{L}^{-1}$ for all aroma compounds.

Calibration Curve. A GC calibration curve of each aroma compound dissolved in dichloromethane was built. Calibration solutions were prepared in dichloromethane at known concentrations (5, 10, 15, 20, 30, and 50 $\mu\text{L}\cdot\text{L}^{-1}$). A volume of 1 μL of the calibration solutions was withdrawn and injected into an HP6890 gas chromatograph equipped with a DB-Wax column (J&W Scientific, i.d. 0.32 mm, length 30 m, film thickness 0.5 μm). The temperature of the injector and detector (FID) were, respectively, 250 and 260 °C. The helium carrier gas velocity was 35 $\text{cm}\cdot\text{s}^{-1}$. The FID signal was sampled every 50 ms using a PC-driven four-channel plug-in acquisition board developed in our laboratory (19). After analysis, the data were processed using software developed as well in our laboratory (20).

A linear regression was fitted to data of concentration of the flavor compound versus the FID response. The slope was used to the determination of the concentration of flavor compound in the matrix and in the vapor phase. The response of the GC-FID was assumed to be the same when injecting a liquid or gas sample.

Determination of Aroma Concentration in Saline Solution and Gel. The loss of aroma compound during the aromatization procedure was determined; the remaining amount of aroma compound was performed by dichloromethane extraction, according to Juteau et al. (21). Sample (1 g) was mixed with 3 mL of CH_2Cl_2 containing dodecane as external standard. For each sample (saline solution or gel), six samples were extracted. The variation coefficient for all extractions was less than 10%.

The extracts were injected in the same conditions programmed for the calibration curves. Quantification of the remaining aroma compound in the NaCl solution and in the *t*-carrageenan gels was then calculated using calibration curves.

Headspace Analysis. Headspace vials (24 mL of sample in a 100 mL Schott vial) were equilibrated in a water bath at 30 °C until thermodynamic equilibrium was reached (4 h). For each sample (saline solution and gel) six vials were made. Only one sampling per flask was made. Vapor phase samples (1 mL) were taken with a gastight syringe (1 mL, SGE) and injected onto the GC-FID, under the same conditions programmed for the calibration curve. The variation coefficient for all headspace analyses was less than 10%. The concentration of flavor compound in the vapor phase was also calculated using calibration curves.

Determination of the Partition Coefficient. All the concentrations obtained were converted into $\text{mol}\cdot\text{L}^{-1}$ (densities and weights were taken from sigma-aldrich.com), and eq 2 was applied to calculate the partition coefficient of retention.

The partition coefficient (PC) of the flavor compound *A* retained by the matrix is defined with the following eq 2:

$$\text{PC} = \frac{[A]_{\text{matrix}}/C_0}{P_A/P^0} \quad (2)$$

where $[A]_{\text{matrix}}$ is the concentration of the flavor compound *A* in the matrix phase, $C_0 = 1 \text{ mol}\cdot\text{L}^{-1}$, P_A is the partial pressure of the flavor compound *A* in the vapor phase, and P^0 is the total pressure (10^5 Pa).

In this way, we can determine the concentration in both the vapor phase and the liquid phase. Partial pressure is calculated from the ideal gas equation: $PV = nRT$, where P is the pressure in the headspace (Pa), V is the volume of the headspace (m^3), and n is the number of moles of flavor compound *A*.

Therefore, the partition coefficient $\text{PC}_{\text{retention}}$ is calculated with the following eq 3:

$$\text{PC}_{\text{retention}} = \frac{[A]_{\text{matrix}}/1}{[A]_{\text{vapor}}RT/10^5} \quad [A]_{\text{vapor}} (\text{mol m}^{-3}) \quad (3)$$

and noted PC_{Sal} and PC_{Gel} to express the partition coefficient of aroma compound between the saline solution and the carrageenan gel, respectively.

QSPR. The two-dimensional molecular structures of the 12 aroma compounds (see Table 2) were drawn using ChemDraw Ultra 7.0, and

Table 1. List of Descriptors

descriptor	information
Dipole-Z	dipole moment in the dimension Z
RadOfGyration	radius of gyration
Jurs-DPSA-3	difference in atomic charge weighted surface area
Jurs-RNCS	relative negative charge surface area
Jurs-TASA	total hydrophobic surface area
Shadow-XY	area of molecular shadow in the XY plane
Shadow-nu	ratio of largest to smallest dimension
Shadow-Xlength	length of molecule in the dimension X
PMI-Y	principal moment of inertia in the dimension Y
CHI-1	Kier and Hall connectivity index order one

Table 2. Partition Coefficient for the Aroma Compounds

no.	compound	MW	PC _{Sal}	PC _{Gel}
1	3-methyl-2-pentanone	100.16	15.64 ± 0.41	14.09 ± 0.92
2	4-methyl-2-pentanone	100.16	14.41 ± 1.05	11.74 ± 0.68
3	5-methyl-2-hexanone	114.19	11.88 ± 0.72	7.76 ± 0.26
4	5-methyl-3-heptanone	128.21	8.68 ± 0.40	6.84 ± 0.45
5	butyl pentanoate	158.24	5.40 ± 0.31	4.21 ± 0.42
6	ethyl butanoate	116.16	6.38 ± 0.13	5.34 ± 0.13
7	ethyl heptanoate	158.24	10.82 ± 0.9	7.25 ± 0.41
8	ethyl hexanoate	144.21	7.01 ± 0.28	3.17 ± 0.33
9	ethyl pentanoate	130.19	5.28 ± 0.16	3.81 ± 0.17
10	ethyl propionate	102.13	10.05 ± 0.29	7.19 ± 0.15
11	3-methylbutyl acetate	130.19	5.11 ± 0.34	3.99 ± 0.24
12	2-methylpropyl 3-methyl butanoate	158.24	2.31 ± 0.18	3.05 ± 0.15

three-dimensional conversions were carried out using the Chem 3D program. Conformational analysis was performed within Catalyst 4.9 software (Accelrys, Inc.) running on SGI-O2, creating a collection of conformers which were thereafter evaluated in a range of energies. Each compound got similar conformations, about 5 kcal·mol⁻¹ above the local minimum found, which happens to be an extended one, for the description calculation.

We have selected some descriptors highly influenced by the molecular alignment, so we have made an alignment based in the superimposition of chemical groups, with Sybyl 6.9 (Figure 1).

All the structures were exported to Cerius² (version 4.10, Accelrys, Inc., running on SGI-O2), and the module QSAR⁺ was used for generating the descriptor collection, equation construction, and validation. Despite of the hundreds of molecular descriptors already published, we have chosen only 90 within the classical groups of descriptors (conformational, electronic, spatial, structural, thermodynamic, and topological descriptors).

- Conformational: energy (Mopac AM1).

- Electronic: apol (sum of atomic polarizabilities), dipole (dipole moment), HOMO (highest occupied molecular orbital energy), LUMO (lowest unoccupied molecular orbital energy), Sr (superdelocalizability).
- Spatial: RadOfGyration (radius of gyration), Jurs descriptors (Jurs charged partial surface area descriptors; there are 30 Jurs descriptors; we selected solvent accessible surface area, partial charged surface area, relative positive and negative charges, and relative polar and apolar surfaces). Shadow indices (surface area projections descriptors), area (molecular surface area), density (density), PMI (principal moment of inertia), V_m (molecular volume).
- Structural: MW (molecular weight), Rotlbonds (number of rotatable bonds).
- Thermodynamic: AlogP98 (Ghose and Crippen AlogP, parameters 1998), MolRef (Ghose and Crippen molar refractivity).
- Topological: kappa indices (molecular shape kappa indices, which are a family of graph-based structure descriptors that represent shape), PHI (molecular flexibility index), Chi indices (Kier and Hall Chi connectivity indices represent molecular structure by encoding significant topological features of whole molecule), SubGraphCount indices (Kier and Hall subgraph count indices, theoretical indices), Wiener, log Z, Zagreb.

It is noteworthy as well that within such kind of studies which are not based in a structural behavior, like ligand receptor ones, it is not useful to use more sophisticated techniques—as, for instance, the 3D-QSPR approaches—since it is not clear whether the structure can affect the behavior or is based in more general molecular properties. Indeed, finding out in aroma release a kind of pharmacophoric or related approach is useless.

Actually normal statistical methods such as PLS or MLR are not suitable due to the relatively high correlation between chosen descriptors, so an evolutionary approach gives better choices to find a suitable descriptors set. The equation generation was performed by GFA, a statistical method associated with the genetic algorithm available in the Cerius² package.

In GFA, equation models have a randomly chosen proper subset of the independent variables (22). Starting from a first population of random equations, the GFA allows selection of the best models to offspring through the crossover generation to provide an optimal model.

In the GFA analysis, the fitness of each equation is scored by a lack-of-fit (LOF) measure:

$$\text{LOF} = \text{LSE} / \{1 - [(c + dp)/m]\}^2, \quad \text{with } \text{LSE} = \sum_{i=1}^{\text{test}} (y_i - \hat{y}_i)^2$$

where y_i and \hat{y}_i are, respectively, the observed and predicted values of the dependent variable, c is the number of basis functions, d is the smoothing parameter (defaulted to 1.00), p is the total number of features contained in all basis functions, and m is the number of

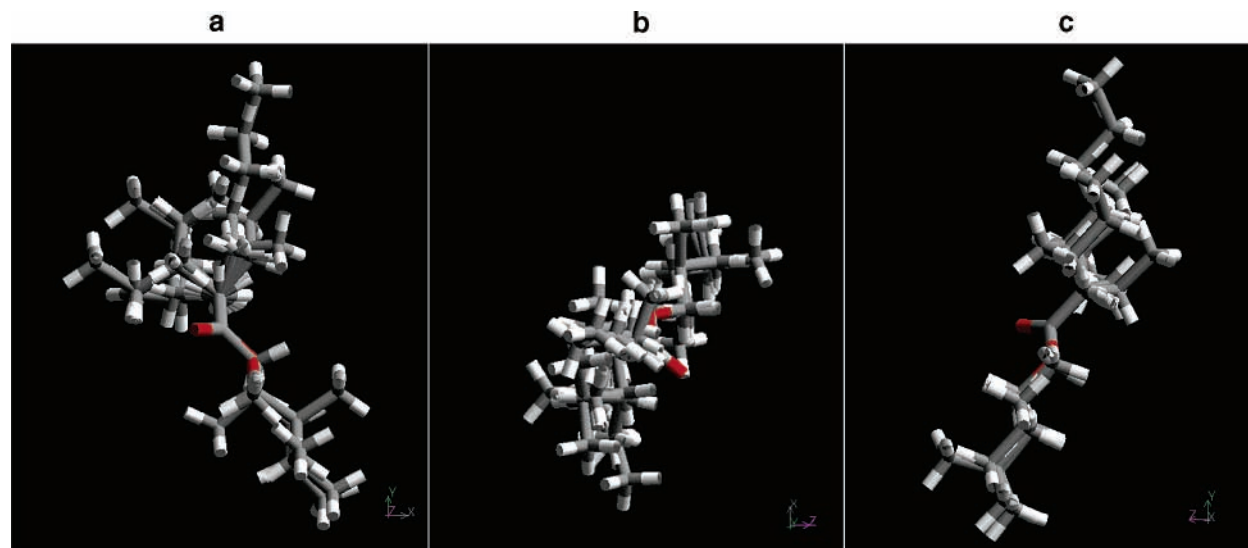
**Figure 1.** Alignment of the aroma compounds used in the present work: (a) in the XY plane, (b) in the YZ plane, and (c) in the XZ plane.

Table 3. Values of Used Descriptors

compound	Dipole-Z	RadOfGyration	Jurs-DPSA-3	Jurs-RNCS	Jurs-TASA	Shadow-XY	Shadow-nu	Shadow-Xlength	PMI-Y	CHI-1
3-methyl-2-pentanone	-2.524	2.299	59.660	8.507	239.39	37.028	1.371	7.873	37.869	3.181
4-methyl-2-pentanone	-2.787	2.432	58.758	7.824	227.81	38.348	1.753	9.219	54.874	3.126
5-methyl-2-hexanone	-3.068	2.756	65.878	8.140	265.72	45.073	1.959	10.475	96.156	3.626
5-methyl-3-heptanone	-2.199	2.940	63.825	4.248	297.15	49.085	2.067	10.804	107.814	4.202
butyl pentanoate	-0.919	3.915	89.576	1.067	365.92	59.305	2.558	14.354	264.446	5.308
ethyl butanoate	-0.920	2.994	72.978	2.224	271.51	41.564	2.176	11.073	99.709	3.808
ethyl heptanoate	-1.238	3.937	87.816	1.619	366.21	56.081	2.708	14.771	303.672	5.308
ethyl hexanoate	-1.154	3.622	82.614	1.779	335.36	50.976	2.567	13.520	218.283	4.808
ethyl pentanoate	-0.992	3.295	77.608	1.976	302.77	45.866	2.343	12.368	149.573	4.308
ethyl propionate	-0.704	2.593	64.022	3.527	239.77	35.625	1.854	9.849	59.294	3.308
3-methylbutyl acetate	-0.093	3.083	76.234	2.325	277.17	48.386	2.164	11.560	142.544	4.126
2-methylpropyl 3-methyl butanoate	-1.205	3.546	78.975	0.788	348.72	57.240	2.268	12.317	207.622	5.020

Table 4. Correlation Matrix of Partition Coefficients and Used Descriptors

	PC _{Sal}	PC _{Gel}	Dipole-Z	RadOfGyration	Jurs-DPSA-3	Jurs-RNCS	Jurs-TASA	Shadow-XY	Shadow-nu	Shadow-Xlength	PMI-Y	CHI-1
PC _{Sal}	1											
PC _{Gel}	0.955	1										
Dipole-Z	-0.731	-0.698	1									
RadOfGyration	-0.652	-0.727	0.521	1								
Jurs-DPSA-3	-0.658	-0.720	0.624	0.972	1							
Jurs-RNCS	0.866	0.868	-0.852	-0.828	-0.834	1						
Jurs-TASA	-0.605	-0.661	0.393	0.973	0.912	-0.758	1					
Shadow-XY	-0.623	-0.658	0.319	0.916	0.845	-0.674	0.954	1				
Shadow-nu	-0.650	-0.770	0.546	0.957	0.928	-0.830	0.886	0.819	1			
Shadow-Xlength	-0.616	-0.723	0.528	0.985	0.962	-0.811	0.931	0.869	0.986	1		
PMI-Y	-0.523	-0.609	0.441	0.981	0.950	-0.741	0.965	0.917	0.919	0.966	1	
CHI-1	-0.647	-0.699	0.459	0.982	0.929	-0.796	0.995	0.961	0.905	0.946	0.972	1

compounds in the training set. The evolved equation population is sorted by decreasing LOF values.

GFA was performed on a starting population of 100 equations over 5000 evolutions. As a result of MLR on each model, the best ones become the next generation and two of them produce an offspring. This process was repeated until no improvement was observed in the model. We chose restricting equation components from one to three independent variables in each equation, to avoid meaningless, but amazingly well-fitted, equations.

There are some descriptors highly correlated, but leaving aside one of them there is no chance to build a model. Indeed cross-variation of the descriptors and transposition of the variables was performed to check it, rendering a poor fitting.

The reliability and significance of the equations was estimated by r^2 and bootstrap r^2 (BS r^2) values. For equations obtained with three independent variables, validation was carried out by Y -randomization at the 99% confidence level (99 randomized trials) and by means of a leave-many-out (LMO) method, leaving aside two compounds; selecting more would not be adequate due to the low number of training compounds.

RESULTS

Descriptor selection is always one of the limiting steps for QSPR methodology, so for descriptor selection, the higher correlation with the property and the lower between those selected was sought; indeed the final number of descriptors to be used in the equation generation was 10 (Table 1). Anyway, the correlation between the entire chemical properties candidates to become a molecular descriptor within this work is usually between 0.5 and 0.9. This value is really high, but descriptors were not really well correlated with the experimental partition coefficients. AlogP98 descriptor, which corresponds to the octanol/water partition coefficient and is related to the hydrophobicity of the aroma molecule, was not retained because of

poor correlation with PC_{Sal} ($r^2 = 0.203$, $F = 2.55$) and PC_{Gel} ($r^2 = 0.246$, $F = 3.26$).

The partition coefficients obtained for the different flavor compounds tested are shown in Table 2. Globally the partition coefficients were quite similar for both NaCl solution and ι -carrageenan gels; thus, ι -carrageenans seem to have a little influence over the partition coefficient, as was likely to be expected from the bibliography.

Among the group of 10 descriptors that got better fitness with the partition coefficients we have performed a GFA in order to find out the best set of descriptors for constructing the QSPR. Descriptor values and the correlation matrix of the partition coefficient are reported in Tables 3 and 4, respectively.

We have systematically increased the number of factors for the equation from one to three. This process has rendered the following equations.

With one factor:

$$PC_{Sal} = 4.08202 + 1.22628Jurs-RNCS \quad (4)$$

LOF = 5.436, $r^2 = 0.748$, $r = 0.866$, $F = 30.080$, BS $r^2 = 0.750$.

$$PC_{Gel} = 2.50532 + 1.07553Jurs-RNCS \quad (5)$$

LOF = 4.110, $r^2 = 0.754$, $r = 0.868$, $F = 30.609$, BS $r^2 = 0.754$.

With two factors:

$$PC_{Sal} = 71.8593 + 0.146367PMI-Y - 27.1106RadOfGyration \quad (6)$$

LOF = 7.264, $r^2 = 0.787$, $r = 0.887$, $F = 16.591$, BS $r^2 = 0.788$.

$$PC_{Gel} = 58.711 + 0.114105PMI-Y - 22.0745RadOfGyration \quad (7)$$

LOF = 4.812, $r^2 = 0.815$, $r = 0.903$, $F = 19.884$, BS $r^2 = 0.815$.

With three factors:

$$PC_{Sal} = 17.7111 + 0.053342PMI-Y + 1.5186Jurs-RNCS - 0.477052Shadow-XY \quad (8)$$

LOF = 4.730, $r^2 = 0.922$, $r = 0.960$, $F = 31.452$, BS $r^2 = 0.924$.

Confidence level: 99%, mean value of r from random trials = 0.534450, CV $r^2 = 0.906$.

$$PC_{Gel} = 49.9212 - 18.8845RadOfGyration + 0.09784 PMI-Y - 0.812408Dipole-Z \quad (9)$$

LOF = 7.307, $r^2 = 0.842$, $r = 0.918$, $F = 14.251$, BS $r^2 = 0.846$.

Confidence level: 98%, mean value of r from random trials = 0.542833, CV $r^2 = 0.805$.

With the use of three factors, all the models for the carrageenan gel were completely unsatisfactory, so we have tried a nonlinear fitting with it. The best equation of all is the following:

$$PC_{Gel} = 13.6191 + 0.00031PMI-Y^2 + 0.053638Jurs-RNCS^2 - 0.116672PMI-Y \quad (10)$$

LOF = 1.963, $r^2 = 0.942$, $r = 0.979$, $F = 60.307$, BS $r^2 = 0.959$.

Confidence level: 99%, mean value of r from random trials = 0.751625, CV $r^2 = 0.912$, where r^2 is the r square and r the simple correlation coefficient. All equations are considered as statistically significant since probability values are <0.05 , and therefore, F is statistically significant.

DISCUSSION

It is a matter of fact that in every single QSPR, or more generally in every QSAR approach, there are some points to consider carefully before starting. First of all is the quality of the experimental data, but such problem is circumvented by the fact that we have performed our own measures of the experimental property, where experimental conditions and procedures has been carefully fixed. In this way the problem derived from the lack of data homogeneity appears to be solved.

Another source of problems in QPSR approaches is the descriptors selection. It has become common place in such a kind of work to say that a QSPR is as good as the descriptors used are, and it is fairly true, not only for the intrinsic quality of the descriptors used, which must be taken for granted, but

mainly for the accuracy of the relationship between the set of descriptors chosen and the experimental fact to be described. Nowadays it is quite normal to find the calculation of hundreds of descriptors in order to search within the better ones, so likely, it could be surprising using in this work a so-reduced starting number of molecular descriptors. We have decided upon this strategy because of the absence of knowledge about the chemical features which might influence aroma release. Such lack of knowledge makes it mandatory to search different molecular features in order to obtain a better scope of the process, but such features have to be reliable. From our point of view the more common molecular descriptors are the best choice because they are more independent from the software since the algorithms used to calculate them are already well-known and are highly reproducible. It is possible that more descriptors, either in number or sophistication, would render better results, but for early stages of QSPR development where the aim is being focused more in unveiling the molecular properties involved than in the model's performance, we reckon this is the best choice. Nowadays it is rather common indeed to find differences, sometimes even huge differences, in descriptors values calculated with different versions of the very same program, a fact that can lead to a wrong perception of the molecular properties involved within aroma release. For the same reasons we have discarded the use of molecular fragments descriptors since they cannot give an adequate insight of the physical mechanism of the problem.

Except for eqs 8 and 10 all models are statistically poor; even eq 10 is indeed not particularly good (**Figure 2**). Despite this weakness, some remarks should be formulated.

There are only five descriptors used in the seven equations: Jurs-RNCS (in eqs 4, 5, 8, 10), PMI-Y (in eqs 6–10), RadOfGyration (in eqs 6, 7, 10), Shadow-XY (in eq 8), Dipole-Z (in eq 9).

Jurs-RNCS and Dipole-Z encode electronic properties of charges repartition on the molecule.

Jurs-RNCS is a spatial Jurs descriptor, which encodes the relative negative charge surface area (23). More precisely, it is equal to the value of the solvent accessible surface area of the most negative atom, divided by the charge of the most negative atom divided by the total negative charges:

$$Jurs-RNCS = \frac{\text{solvent accessible surface area of most negative atom}}{\frac{\text{charge of most negative atom}}{\text{total negative charge}}}$$

The dipole moment descriptor Dipole-Z is a 3D electronic descriptor that indicates the strength and orientation behavior of a molecule in an electrostatic field. For the present alignment, the magnitude and the components of the dipole moment about

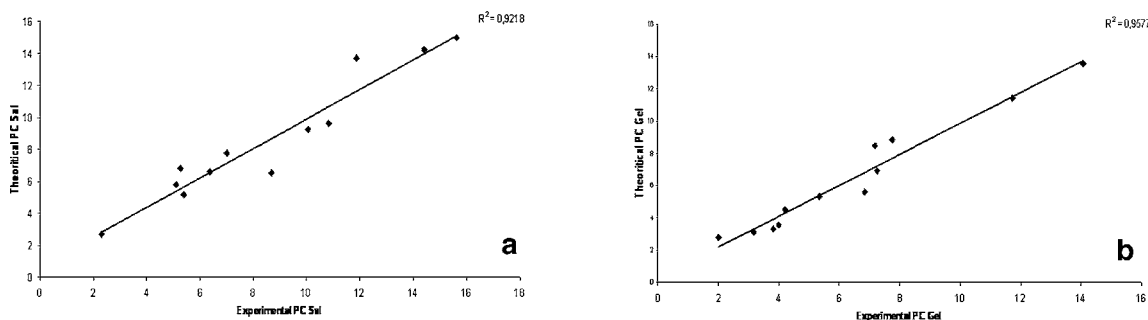


Figure 2. Relationships between observed and calculated PCs for eqs 8 (a) and 10 (b).

the *Z* axis correspond to the carbonyl bond (**Figure 1**). In this way, the significance is the same as Jurs-RNCS.

PMI-Y, Shadow-XY, and RadOfGyration help to characterize the shape of the molecules.

The descriptor PMI-Y calculates the principal moments of inertia about the principal axes *Y* (**Figure 1**). An object's moment of inertia depends on its shape and the distribution of mass within that shape: the greater the concentration of material away from the object's centroid, the larger the moment of inertia.

The descriptor Shadow-XY is calculated by projecting the molecular surface on the perpendicular plane *XY* (**Figure 1**). As PMI-Y, this descriptor depends not only on conformation but also on the orientation of the molecule.

The radius of gyration is a parameter characterizing the size of a particle of any shape; it provides the distance that would be found if the entire mass of the object were all packed together at only that radius. For molecules, the RadOfGyration value depends only of the molecule's size (chain length, branching, conformation), but at the opposite of PMI-Y and Shadow-XY, this descriptor is independent of orientation.

Equations 4 and 5 in the first hand, and eqs 6 and 7 in the second hand, involve the same descriptors for expression of PC_{Sal} as well as PC_{Gel} . If we look carefully at the descriptors that appear in both three factors of eqs 8 and 9, the same molecular properties are represented: a measure of the molecular shape (represented by the Shadow XY index, radius of gyration, and the principal moment of inertia along the *Y* axis). In eq 8, the molecular charge is represented in both equations by the Jurs descriptor RNCS, positively correlated. Even eq 9 uses the same kind of descriptors changing the RNCS by the dipole moment, which is, at the end, another measure of molecular charge separation. PMI-Y and Jurs-RNCS are the used descriptors in both linear eq 8 and in nonlinear eq 10.

The small number of compounds and the different weight of the chemical functionality within the compounds set used in this work prevent searching for a predictive model. Nevertheless, those results show some remarkable features that are worth mentioning.

The equation obtained for PC_{Sal} and PC_{Gel} involves the same descriptors, respectively, using one, two, and three factors. Jurs descriptor RNCS and the absolute value of Dipole-*Z* are positively correlated with the partition coefficient, indicating the major role of water, as well in saline solution and in carrageenan gel. In the present case of molecules orientation and alignment, the greater the chain length and moderate the branching, the larger the values of the three shape descriptors (RadOfGyration, PMI-Y, and Shadow-XY). Such results show that the higher the charge the more retention, and the more globular form or the more ramifications within the molecule the less retention for esters and ketones. Such behavior is consistent with the nature of water with a high ionic force, where hydrophobic compounds, usually highly branched and/or with long aliphatic chains, are barely soluble.

In this way, the effect of carrageenan polymers only modulates but does not change the interaction of aroma compounds with water molecules and can be considered as an important clue that texturing agents are not a key factor within phase partitioning. Indeed, the fact that the best-fitting equation is nonlinear, despite the high correlation between the partition coefficient values for both water and carrageenan gel matrixes, seems to indicate a possible change in the mobility of small molecules. Further experiments on a larger set of compounds and measurement of the diffusion coefficient by NMR-DOSY

(diffusion order spectroscopy) (24) are actually in progress with the aim to confirm this hypothesis.

A complete list of descriptor values and details of GFA calculations is available at anne.tromelin@dijon.inra.fr.

ABBREVIATIONS USED

ADMET, absorption, distribution, metabolism, excretion, and toxicity; BS r^2 , bootstrap r^2 ; DOSY, diffusion order spectroscopy; GFA, genetic function approximation; LMO, leave-many-out; LOF, lack-of-fit; LSE, least-squares error; PC, partition coefficient; QSAR, quantitative structure–activity relationships; QSPR, quantitative structure–property relationships.

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