MMPソフトウェアを用いたフレーバー＆フレグランスの分子デザイン

Designing Flavor and Fragrance Molecules with a Molecular Modeling Program

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Introduction

The prediction and classification of odor descriptors for flavor molecules is a difficult and complex problem. In the past researchers have correlated physical properties of the molecule such as structure, solubility, molecular shape and molecular energies to determine odor character. Using physiochemical properties, I described a force model based on molecular structure and thermodynamic properties to calculate odor and taste thresholds of small molecules in various liquid media. Recently, olfactory information has also been programmed into this model. A database (MMP Scent) of over 4000 compounds (75 descriptors) was used to compare much of the thermodynamic and other calculated parameters to the scent characteristics of the molecule. Three structural parameters were found to describe scent characteristics. These three parameters are called scent increments and are derived from the rotational/translational factor R_T, and from thermodynamics such as boiling point, number of atoms and critical properties[1].

The Force Model

- The primary stimulus of a receptor is assumed to be via mechanical and thermal energy mechanisms.
- Kinetic and rotational energy transfer is involved during impact and docking of odorant with a receptor.

The molar threshold force F_t (kinetic and rotational momentum) is defined by:

[1] $F_t = m_t\, \mathbf{g}_f$

where $\mathbf{g}_f$ is an acceleration factor depending only on the molecular properties of the odorant and m_t is the threshold molar concentration.

The model is obtained from five system variables: **1**. partition energy e_{12}, **2**. vapor pressure P_v, **3**. diffusivity D_{ab}, **4**. vapor density or liquid density r_v, r_l, **5**. molecular weight M_w. Let a*x be the activity of the molecule in solution then the acceleration factor $\mathbf{g}_f$ is the product of two groups:

$$G_f = \text{velocity group} * \text{frequency group} = \mathbf{(a*x*P_v / r_v)^{1/2} (e_{12}/ M_w * D_{ab})}$$

The variables are calculated for any molecule by applying standard equations used to describe transport phenomena in gases and liquids. Scaling mass with concentration of odorant in solution and multiplying by 10^6, the threshold concentration, $\mathbf{c_T}$ is calculated in mg per liter:

[2] $c_T = \mathbf{r_l * M_w}\, [G_f]\, [R_T/ I_0]$

Where $\mathbf{I_0}$ = molecular moment of inertia.

$\mathbf{[G_f]}$ = computable thermodynamic and transport properties[2]

$\mathbf{[R_T/ I_0]}$ = geometric and molecular dynamic properties

Functional groups, bonds and conformations contribute to the $\mathbf{R_T}$ factor.

Application to Off-Flavors

In some instances, it may be desirable to predict the threshold concentrations of undesirable flavors in foods. Sensory studies may not be possible if the chemicals are not available in pure form, toxic or are difficult to quantitate. The oxidation of limonene under acid conditions and heat yields oxidized reaction products, which were found to give off-flavors in stability studies during the development of a new citrus beverage. The oxidation involves addition of -OH groups across the double bond of the terminal C=CH2 group. The direction of this addition gives either terpineol or p-menth 1-en-9-ol. Further addition of water can give products that contain a phenol OH group on the ring. **Table 1** shows several potential, but not all reaction oxidation products for limonene.

Table 1- Thermodynamic, Dynamic and Functional Group Factors Required to Compute Odor and Taste Thresholds for a Model Citrus Beverage

Compound	Go	Gt	I(max)	Rt	den	MW
Limonene	8264.1	152643.9	167.1127	4.39397	0.848806	136.22
a-terpineol	1154.2	17530	227.4895	199.3439	0.89609	154.24
carvone	1355.69	18819.6	226.8109	42.16964	0.9684	150.20
menth-1-en-9 ol	333.687	4769.3	265.8303	199.3439	0.9002	154.24
trans menth-6-en-2,8 diol	37.498	597.07	297.2994	2100.975	0.98168	170.24
menth-6-en-8 ol	635.84	9065.4	248.313	26.10158	0.90942	154.24

Table 2- Calculated Odor (ppb), Taste (ppm) Thresholds in Water and Air (ppb)[3]. Fc values are the ratios of a 100-ppb concentration to the odor and taste thresholds relative to the ratio for Limonene

Compound	ct (odor) ppb	ct (taste) ppm	ct (air) ppb	Fc(odor)	Fc(taste)	Taste/odor
Limonene	25.1242	0.4641	1.4167	1.00	1.00	citrus/lemon
a-terpineol	139.7885	2.1231	10.3127	0.18	0.22	floral/woodsy
carvone	36.6624	0.5089	2.6973	0.69	0.91	spearmint
menth-1-en-9 ol	34.7435	0.4966	3.0478	0.72	0.93	fruity/herbal
trans menth-6-en-2,8 diol	44.2860	0.7052	4.6754	0.57	0.66	fruity/herbal
menth-6-en-8 ol	9.3751	0.1337	0.8685	2.68	3.47	pine/camphorous

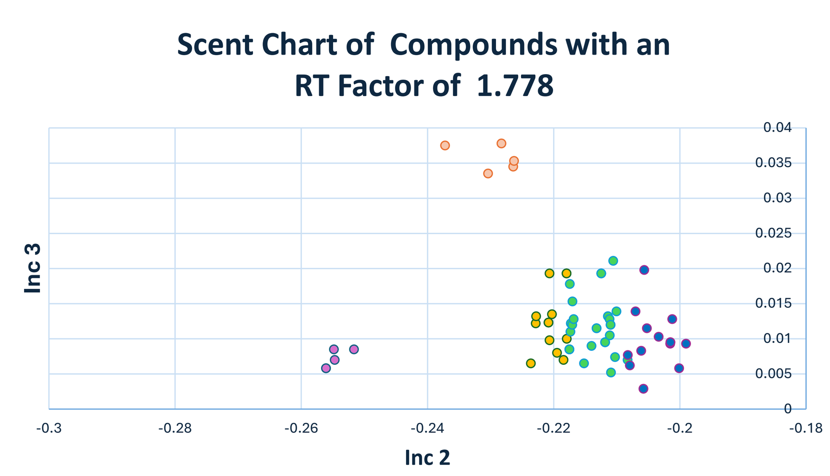
The conversion to these reaction products results in a lowering of flavor threshold for at least one of these products by a factor of 3. (**Table 2**) All these products can have a major impact on flavor contribution. The flavor contribution (Fc) can be given as the concentration in the beverage (100 ppb)/ threshold concentration. As can be seen from the table the reaction products result in a significant change in flavor profile. Significant changes indicated by the last off-flavor may explain development of an unpleasant medicinal taste to the beverage.

Scent Increments and Odor Character and Design

The force model assumes that three parameters called scent increments (Inc) can be used to estimate the odor properties of any molecule based on structure. The model is not based on neural networks nor A. I. but only on molecular properties that engineers and chemists have been able to calculate for decades.

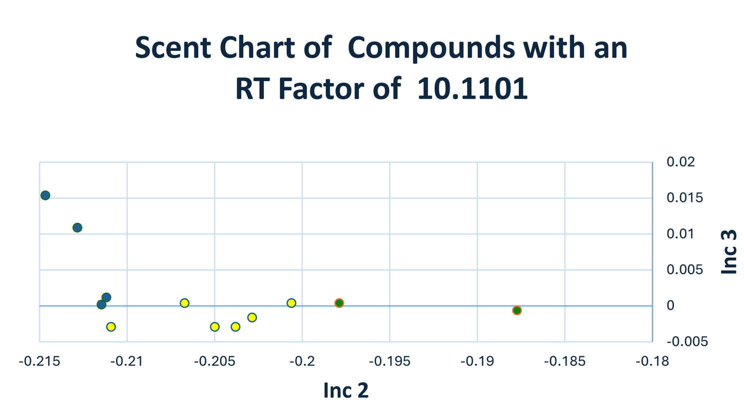
Increment 1~ R_T Increment 2 ~ Temperature variable Increment 3~ Pressure variable

The R_T factor has a range of 10^{18} from sulfurous (0.007) to odorless 10^{15}. As an example, our database contains 70 compounds with R_T =1.778. Below is a Scent Chart with colors showing separation of these compounds into 5 scent groups using the variables inc 2 and inc 3.



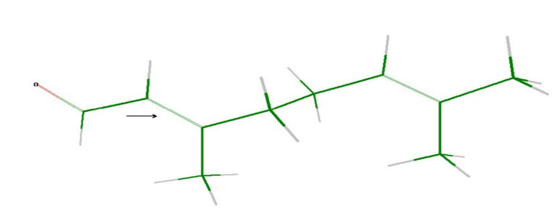
inc2 0.256 to 0.252 inc3 0.005 to 0.02	jasmine		
inc2 0.24 to 0.22 inc3 0.03 to 0.04	balsamic	wood	musk
inc2 0.223 to 0.217 inc3 0.01 to 0.019	tobacco	caramellic	sweet
inc2 0.217 to 0.208 inc3 0.01 to 0.008	mint	camphor	
inc2 0.208 to 0.199 inc3 0.007 to 0.019	green	camphor	jasmine

I will now demonstrate how a new flavor molecule can be designed and engineered from these Scent Charts. Below are compounds with R_T = 10.1101. Yellow represents citrus/lemon odors bounded by green odors to the right and aldehydic odors to the left.

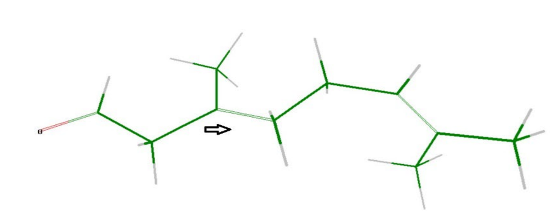


inc2 0.211 to 0.214 inc3 0.002 to 0.015	aldehydic	floral
inc2 0.210 to 0.200 inc3 0.004 to - 0.003	citrus	lemon
inc2 0.187 to 0.198 inc3 0.0004 to - 0.0006	green	

Citral at inc 2 = 0.2006 and isocitral at 0.1978
Mol files as drawn with MMP Flavor Plus.

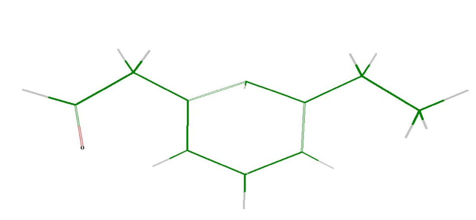


Citral (3,7 dimethyl 2,6 Octadienal)



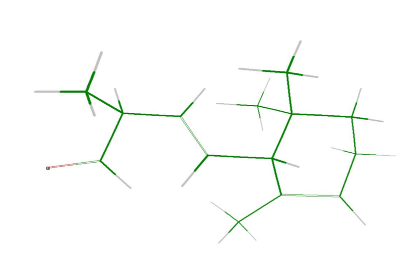
Isocitral (3,7 dimethyl 3,6 Octadienal)

When designing scent character, it is important to keep scent increment 1 nearly constant or equivalent to the original molecule. Changes in the value of scent increment 1 correlate to functionality and to hydrophobic and hydrophilic properties of the molecule. Several options available are changing positions of the double bonds or adding a ring. Below is a molecule designed by cyclization of 6 carbons of isocitral ($C_{10}H_{16}O$) and keeping the aldehyde functional group.



"Citrional"
ODT= 1.07 ng/M[3]

Increments calculated for designed "Citrional" ($C_{10}H_{14}O$) are inc 1=10.1101, inc 2=0.2189,inc 3 = 0.0106. Scent character is determined from a match of these three parameters in our database. Note that inc 2 falls in the blue(aldehydic) region of the scent chart.



Methyl Ional
ODT= 0.24 ng/M[3]

The compound methyl ional ($C_{14}H_{22}O$) is found as the **best** match with inc 1 = 10.1101, inc 2 = 0.2181, and inc 3 = 0.0124. This compound is found in the region of the scent chart describing aldehydic and specifically woody and **orris**, a rare and expensive scent found in perfumery.

Conclusion

A force model is presented for predicting olfactory and taste thresholds and scent character of flavor and fragrance molecules. Chemical functionality, thermodynamic, geometric and structural information can be quantitated for any molecule. This study views a molecule as a stimulus and how design classifies its odor response.

参考文献

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2. Richard Turk, Addi Fadel, Grant Mudge, US Patent 7446079, Perfumes for Rinse-off Systems, November 4, 2008
3. Abraham, M.H., Sánchez-Moreno, R., Cometto-Muñiz, J. E., An Algorithm for 353 Odor Detection Thresholds in Humans, *Chemical Senses* **37**:207-18, 2012

The authors have no conflicts of interest associated with this poster. 私は今回の演題に関連して、開示すべき利益相反はありません。