

Quantification in Gas Chromatography: Prediction of Flame Ionization Detector Response Factors from Combustion Enthalpies and Molecular Structures

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In a previous report, we validated the use of a database that compiled the relative response factors of flavor and fragrance compounds under standard GC conditions for a flame ionization detector. Here we investigate the prediction of unknown response factors from the molecular structure by using combustion enthalpies. In a first step, this enthalpy was well-predicted with either *ab initio* calculation or multiple linear regression based on the molecular formula. In a second step, good correlation was observed between these combustion enthalpies and experimental relative response factors, and so the response factors were predictable from only the molecular formula. With a database of 351 compounds, about 60% of them exhibited a difference of less than 5% between the predicted and experimental relative response factors and about 80% exhibited a difference of less than 10%.

The flame ionization detector (FID) has been widely used in gas chromatography because of its broad linear range response. The FID response of all hydrocarbons is generally considered to be roughly proportional to their molecular weight, i.e., to the number of carbons. But the signal of compounds containing heteroatoms is lowered due to the partial oxidation state of carbon atoms.¹ To account for this signal dependence, analysts use response factors such as the molar response factor (MRF, eq 1). The MRF is established by determining a ratio between the analyte peak area and the peak area of a standard compound added to the mixture in a known quantity. The MRF can be considered as a molecular property since it represents the relative molecular FID response. Dietz² used an expression for the response factor based on the masses of the compound and the internal standard (ISTD), instead of on their molarities (RF_D, Experimental Section, eq 2). A frequently used parameter is the relative response factor, RRF, also termed “multiplier response factor”³ because the relative quantities (in mass) of the compounds

are obtained by multiplying the FID area by this RRF (Experimental Section, eq 4).

Because they are dependent on the atomic composition of molecules, the response factors must be determined for each compound. To simplify the task, in many studies reporting the composition of a complex mixture (e.g., essential oils, flavors), analysts often consider the responses of all constituents in such a detector to be proportional to their molecular mass, and so when an ISTD is used, the RRFs are assumed to be equal to unity. In previous work, we showed that such an assumption can lead to determination biases in excess of 40%.⁴ However, the development of a rapid quantification method is a growing requirement. One major reason is that the recent European regulation, REACH, imposes registration of all chemicals sold in Europe.⁵ In the case of complex substances, such as essential oils, the number of samples to analyze and the number of their constituents are too large to consider individual determination of each response factor.

In our previous work, the use of an RRF database was validated under standard GC conditions. These compiled values save time when a laboratory faces numerous analyses of mixtures having a set of compounds in common. However, the RRF of compounds absent from the database must be individually determined, which can be a challenge when they are not commercially available. In this case, either the authentic compound must be synthesized to measure its RRF or the latter must be predicted. The first alternative is often very time-consuming and complex, e.g., for sesquiterpenes. For an unstable compound, this measurement is not even possible if it cannot be isolated in a pure state. The prediction can also be deduced by assuming that a compound exhibiting the same number of carbons and the same chemical functions will also have the same RRF.⁶ The second alternative consists of building a model based on calculated molecular properties, which is the approach considered in the present work.

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Table 1. Published Models Predicting FID Response Factors

factor and ref	N^a	R^2	SD ^b	parameters ^c	comment
RF _D Musumarra and Pisano (ref 7)	121	?	14.9%	18	focused on benzene- and N-heterocycles
RF _D Katritzky et al. (ref 8)	152	0.88	0.05	37 → 6	ECNs are of these 37 parameters
RF _D Lucic and Trinajstić (ref 9)	152	0.97	0.04	296 → 7	requires ECN calculation within the seven best descriptors
RF _D Jalali-Heravi and Garkani-Nejad (ref 10)	122	0.95	4%	77 → 58	neural network; requires a preliminary multiple linear regression
MRF Cao and Huo (ref 11)	23	0.94	5.8%	N^d	requires the calculation of an "inner molecular polarizability index"; focused on monosubstituted alkanes

^a Population of the training and prediction set of compounds. ^b Relative SDs when a % sign is added. ^c Number of parameters used in the model. An arrow indicates that the initial number was reduced to a smaller set of parameters. ^d Number of atoms in the compound chain (carbon + heteroatoms).

The prediction of RRF has given rise to a modest number of papers for the help it can bring to the analyst (Table 1). The most investigated approach involves the use of the "effective carbon number" (ECN),¹² from which RRFs can be calculated³ (Experimental Section, eq 6). The ECN concept is based on the fact that the FID response of volatile organics is generally proportional to their number of carbons, with a lower contribution of partially oxidized carbons. Therefore, the structure of the considered compound must be divided into fragments that contribute to various extents to the global ECN, depending on the chemical functions of carbon and heteroatoms. The relative standard deviation of predicted versus experimental ECNs for a homologous series is in the range of a few percentage points,¹³ but to our knowledge no global relative standard deviation (RSD) has been calculated for a large data set. Some deviations were observed in the case of aromatic compounds,¹⁴ and the experimental conditions may have some impact on ECNs.¹⁵ However, such an approach allows prediction of the ECN only if the contribution of all fragments of the compound has previously been experimentally determined, which gives rise to additional papers from time to time to report the contribution of a given chemical function.^{1,3,13,16–18}

Several models are based on quantitative structure–property relationships (QSPRs, Table 1). The oldest one is focused on aromatics and N-heterocycles and uses an important number of descriptive parameters.⁷ Two models even start from a larger set of parameters from which the six to seven most significant parameters are selected. Notably, Katritzky's and Lucic's models involve quantum-chemical parameters and ECNs, respectively, which does not make their use very easy.^{8,9} Cao's approach is restricted to 23 monosubstituted alkanes and implies the preliminary calculation of an "inner molecular polarizability index", which is not justifiable.¹¹

RRFs have also been correlated with molecular structure descriptors by using a neural network, but a preliminary multiple

linear regression is necessary to build the linear models between RRF and descriptors.¹⁰

These published QSPR models are thus characterized by their complexity, a restricted training set, or the prior calculation of ECNs (Table 1). None of them is justified by the physical phenomenon that is assumed to really occur in the flame of the detector. Only the semiempirical ECN approach takes into account the initial oxidation state of carbon atoms, which requires significant experimental work. Therefore, the present study investigates whether the RRFs can be predicted from the thermodynamic characteristics of the combustion that occurs in the FID and then from the molecular formula.

EXPERIMENTAL SECTION

Definitions and Relationships. The MRF of a compound (eq 1) is defined as

$$\text{MRF} = \frac{(A_i)(\mathcal{M}_{\text{ISTD}})}{(\mathcal{M}_i)(A_{\text{ISTD}})} \quad (1)$$

with A_i , A_{ISTD} being peak area of the compound i and the ISTD, respectively, and \mathcal{M}_i , $\mathcal{M}_{\text{ISTD}}$ being molarities of the compound and the standard, respectively.

The Dietz response factor RF_D is defined by using masses:²

$$\text{RF}_D = \frac{(A_i)(m_{\text{ISTD}})}{(m_i)(A_{\text{ISTD}})} \quad (2)$$

with m_i , m_{ISTD} being mass of the compound and the ISTD, respectively.

It is related to MRF by

$$\text{RF}_D = \text{MRF} \frac{\text{MW}_{\text{ISTD}}}{\text{MW}_i} \quad (3)$$

where MW_{ISTD} and MW_i are the molar weights of the standard and the compound, respectively.

The RRF is defined as

$$\text{RRF} = \frac{1}{\text{RF}_D} = \frac{(m_i)(A_{\text{ISTD}})}{(m_{\text{ISTD}})(A_i)} \quad (4)$$

$$\text{RRF} = \frac{1}{\text{MRF}} \frac{\text{MW}_i}{\text{MW}_{\text{ISTD}}} \quad (5)$$

- (11) Cao, C.; Huo, P. *J. Chromatogr. Sci.* **2007**, *45*, 360–368.
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The relationship between RRF and the ECN is

$$\text{RRF} = \frac{(\text{MW}_i)(\text{ECN}_{\text{ISTD}})}{(\text{MW}_{\text{ISTD}})(\text{ECN}_i)} \quad (6)$$

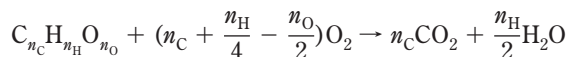
Ab Initio Calculation of Combustion Enthalpies. Over the past decade, the density functional theory (DFT) methods, and in particular the B3LYP functional (Becke—three parameters—Lee, Yang, Parr), have been shown to perform exceptionally well for the calculation of a wide range of structural, electronic, and thermochemical properties.^{19,20} The DFT (B3LYP/6-31G**) energies were calculated (after energy minimization) with the computer software Jaguar.²¹

Computation. All calculations and optimizations of regression equations were performed with Excel and the “solver” add-in (Microsoft, Redmond, WA).

Measurements of RRFs. The GC/FID instrument was an Agilent 6890 model (Agilent, Wilmington, DE), equipped with either a DB-1 or a DB-1MS column (60 m × 0.25 mm × 0.25 μm) from J&W Scientific (Agilent). The injector and FID temperatures were 250 °C. The test solutions (0.2 μL) were injected with a split ratio of 1:50. The carrier gas was helium. The oven program was held at 50 °C for 5 min and then increased at 3 °C/min up to 120 °C; then it was increased at 5 °C/min up to 250 °C and maintained for 5 min; and finally it was ramped at 15 °C/min up to 300 °C and maintained for 20 min. The H₂/air ratio was 9% and the air flow was set at 450 mL/min. All RRF measurements were relative to methyl octanoate as the ISTD. The training and the test sets of were made of 284 and 67 authentic compounds from the Firmenich collection, respectively. All together, these compounds represented most of the functional classes used in flavors and fragrances: hydrocarbons (18), alcohols (52), phenols (21), aldehydes (43), ketones (47), esters (96), lactones (13), ethers (40), sulfur compounds (32), nitrogen compounds (29), halogenated compounds (3), benzenic derivatives (80). The total was higher than the population of both sets because some compounds were polyfunctional.

RESULTS AND DISCUSSION

To our knowledge, the exact reaction occurring in the flame of a FID has not yet been completely clarified. However, the eluted organics are burnt, and at first glance, the reaction can be considered to be combustion. In the case of hydrocarbon, and assuming complete combustion, the formation of CO₂ and H₂O could be expected:

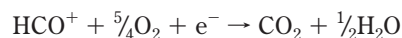


The FID signal depends on the number of carbon atoms in the compound, with a lower contribution for partially oxidized carbons (e.g., carbon of a carboxylic acid function).¹ This fact and the combustion reaction (reaction 1) suggest that MRF could be correlated with the combustion enthalpy (ΔH_{Comb}) of the compound.

However, the fully oxidized products resulting from their reaction (reaction 1) do not bear any electric charge, and so they are not detectable by the FID. It is often assumed that the signal is due to the primary ions of hydrocarbons in flames, HCO⁺,²² but no recent mechanistic study has been dedicated to the identification of the ions that are really responsible for the FID signal. However, if this transient species is assumed to be identical for all organics, i.e., HCO⁺, the effective enthalpy measured by the detector (ΔH_{Eff}) will be

$$\Delta H_{\text{Eff}} = \Delta H_{\text{Comb}} - n_{\text{C}}\Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2} \quad (7)$$

with $\Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2}$ the combustion enthalpy of HCO⁺ (reaction 2).



The present work aims at verifying the correlation of MRFs with ΔH_{Comb} and then at simplifying the prediction by using QSPR models. The possible impact of $\Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2}$ on this correlation will be investigated in the section “Estimation of MRF from ΔH_{Comb} ”.

Ab Initio Calculation of Combustion Enthalpies. For reaction 1, some experimental ΔH_{Comb} values exist in the literature, but very few correspond to the flavor and fragrance compounds of our database of experimental RRFs. DFT and ab initio methods have been developed to fit the thermochemical data^{21,22} and can be used to calculate the combustion enthalpy of organic compounds. As a first step, a set of 51 compounds with various chemical functions was selected from the literature,²³ as their combustion enthalpies can be directly determined from experimental data. These data refer to starting compounds in the gas or liquid state into CO₂, H₂O, N₂, SO₂, HF, HCl, Br₂, and I₂. For the present work, all starting ingredients were considered to be in the gas phase, in agreement with experimental conditions of the GC detector. The DFT energies were calculated for each of the starting and reaction compounds, and so the combustion enthalpy should be equal to the difference between the latter and the former, i.e., in the case of a simple compound of formula C_{*n_C*}H_{*n_H*}O_{*n_O*} corresponding to reaction 1:

$$H_{\text{Comb}} = E_{\text{Comp}} - n_{\text{C}}E_{\text{CO}_2} - \frac{n_{\text{H}}}{2}E_{\text{H}_2\text{O}} + \left(n_{\text{C}} + \frac{n_{\text{H}}}{4} - \frac{n_{\text{O}}}{2}\right)E_{\text{O}_2} \quad (8)$$

where E_{Comp} , E_{CO_2} , $E_{\text{H}_2\text{O}}$, and E_{O_2} are the energies of corresponding compounds.

When the energies directly obtained from the DFT calculation were used for the estimation of combustion enthalpies, the calculated values were systematically lower than the experimental values. This was assumed to be inherent in the lack of precision that led to a systematic error in the energy calculation of small compounds with this method. Therefore, the energies of O₂ and

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Table 2. Original and Corrected Energies of O₂ and Combustion Products Used for the Calculation of the Combustion Enthalpy^a

	DFT energy	corrected energy
H ₂ O(g)	-76.41971	-76.43597
CO ₂	-188.58093	-188.58299
O ₂ triplet	-150.31613	-150.31202
N ₂	-109.52411	-109.53234
SO ₂	-548.58753	-548.62274
HF	-100.42745	-100.44751
HCl	-460.80080	-460.80705
Br ₂	-26.30981	-26.31501
I ₂	-22.77042	-22.78512

^a Energies are given in hartree (1 hartree = 627.5 kcal/mol).

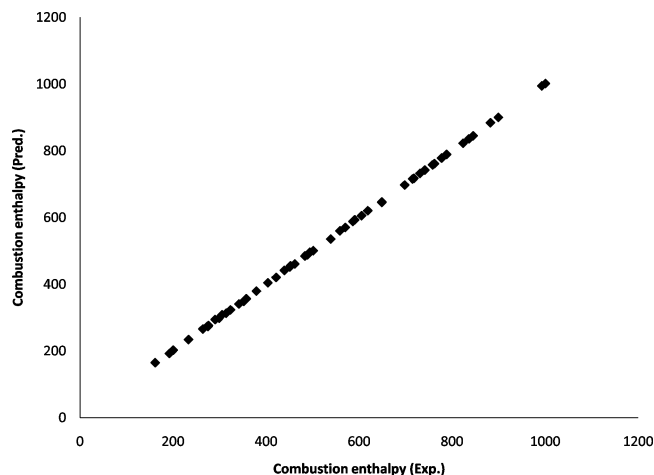


Figure 1. Calculated vs experimental combustion enthalpies (in kcal/mol). $R = 0.999$, $S = 1.66$ kcal/mol, $N = 51$.

combustion products were optimized by minimizing the squared difference between experimental values and those calculated using eq 8 (Table 2).

The resulting correction of DFT energies was minor as a relative value, but it significantly improved the prediction of ΔH_{Comb} . A very good precision was obtained for the set of 51 compounds, with a standard deviation of 1.66 kcal/mol for values ranging between 150 and 1000 kcal/mol (Supporting Information, Table S-1, column ΔH_{Comb} from DFT, and Figure 1). These corrected values were used in this report to predict ΔH_{Comb} .

Calculation of Combustion Enthalpies from Molecular Formulas. The enthalpy formation of oxygen and the combustion products could be expressed as a linear combination of the energy of their atoms; therefore, the whole combustion enthalpy should itself result from a linear combination of the compound energy and its atom number.

$$\Delta H_{\text{Comb}}^{\text{DFT}} = eE + c(n_{\text{C}}) + h(n_{\text{H}}) + o(n_{\text{O}}) + n(n_{\text{N}}) + s(n_{\text{S}}) + f(n_{\text{F}}) + \text{cl}(n_{\text{Cl}}) + \text{br}(n_{\text{Br}}) + i(n_{\text{I}}) \quad (9)$$

with E being the DFT energy of the compound and n_{C} , n_{H} , etc. being the number of carbon, hydrogen, oxygen, ..., atoms in the compound.

The parameters resulting from the optimization of eq 9 by using the experimental and predicted values were as follows: $e =$

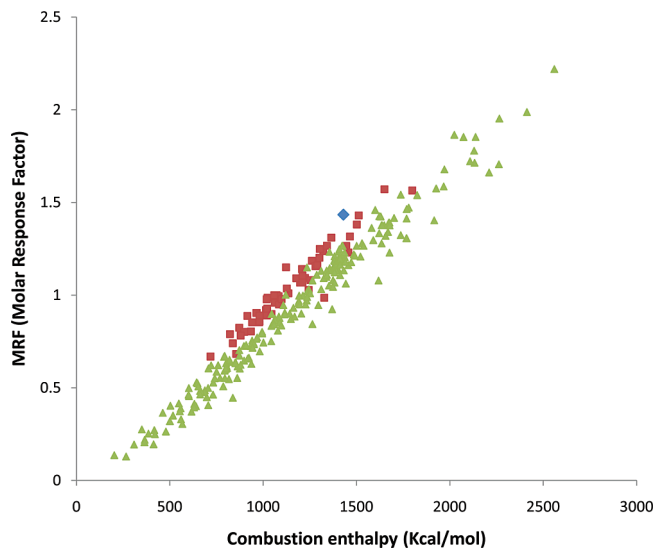


Figure 2. MRF vs ΔH_{Comb} calculated from the DFT energy (eq 8 or 9) (in green, red, blue: zero, one, and two benzenic ring(s), respectively).

627.5; $c = 24015.0$; $h = 401.6$; $o = 47160.4$; $n = 34365.8$; $s = 249940.0$; $f = 62629.2$; $\text{cl} = 288754.8$; $\text{br} = 8256.3$; $i = 7148.8$ (ΔH_{Comb} being expressed in kcal). This equation is equivalent to the calculation based on the optimized energies for O₂ and the combustion product and, consequently, gives exactly the same result ($R = 0.999$, $\text{SD} = 1.66$ kcal/mol, $N = 51$).

Because DFT calculations are not always available in all laboratories, the term related to this energy (eE) was omitted in eq 9 to calculate the combustion enthalpies directly from the molecular formula ($\Delta H_{\text{Comb}}^{\text{MF}}$). The parameters were optimized to minimize the squared difference between calculated and experimental values (eq 10). The results were expected to be less accurate than those based on the DFT energies; however, the statistical parameters of this regression ($R = 0.999$, $\text{SD} = 6.68$ kcal/mol, $N = 51$) were still good and can be used instead of $\Delta H_{\text{Comb}}^{\text{DFT}}$.

$$\Delta H_{\text{Comb}}^{\text{MF}} = 11.06 + 103.57n_{\text{C}} + 21.85n_{\text{H}} - 48.18n_{\text{O}} + 7.46n_{\text{N}} + 74.67n_{\text{S}} - 23.57n_{\text{F}} - 27.44n_{\text{Cl}} - 11.90n_{\text{Br}} - 2.04n_{\text{I}} \quad (10)$$

Relationship between MRF and ΔH_{Comb} . As mentioned in the introduction, the GC/FID signal is expected to mainly depend on the combustion enthalpy of detected compounds. Using calculated ΔH_{Comb} values based on the DFT energies (eq 8), we found a good correlation with the MRF. However, the compounds exhibiting a benzene ring were all shifted from the global correlation line (Figure 2, red and blue points). This suggests that MRF could be estimated by using the calculated ΔH_{Comb} combined with a descriptor that counts the number of benzenic rings, n_{Benz} , in the chemical structure.

The benzenic derivative's shifts could possibly be explained by the specific behavior of such compounds in a flame. Using benzene, Nicholson and Swingler report that, rather than CHO^+ , cyclopropyl ions can become predominant in some region of

the flame.²⁴ If this mechanism was favored for benzene derivatives, the combustion of these cyclopropyl ions could take place instead of reaction 2, and then the shift of $\Delta H_{\text{Effective}}$ from ΔH_{Comb} in eq 7 would be $n_C \Delta H_{1/3 \text{C}_3\text{H}_3^+ \rightarrow \text{CO}_2}$ instead of $n_C \Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2}$, which suggests a greater value for C_3H_3^+ than for CHO^+ .

Estimation of MRF from ΔH_{Comb} . If the regression to generate a linear equation is directly applied between MRF and ΔH_{Comb} , the sum of the squared differences between the measured and the predicted response factors will be minimized. The objective of this work being to achieve the best possible quantification of analytes, the regression equation was optimized by minimizing the error between the calculated and the measured analyte concentrations. Therefore, the following error, based on molarities, was minimized for the training set comprising 284 compounds.

$$\text{error} = \sum_i \left(\frac{\mathcal{M}_i^{\text{calc}} - \mathcal{M}_i^{\text{meas}}}{\mathcal{M}_i^{\text{meas}}} \right)^2 \quad (11)$$

From eq 1

$$\mathcal{M}_i^{\text{calc}} = \frac{(A_i)(\mathcal{M}_{\text{ISTD}})}{(\text{MRF}_i^{\text{calc}})(A_{\text{ISTD}})} \quad (12)$$

and

$$\mathcal{M}_i^{\text{meas}} = \frac{(A_i)(\mathcal{M}_{\text{ISTD}})}{(\text{MRF}_i^{\text{meas}})(A_{\text{ISTD}})} \quad (13)$$

Then

$$\text{error} = \sum_i \left(\frac{\text{MRF}_i^{\text{meas}}}{\text{MRF}_i^{\text{calc}}} - 1 \right)^2 \quad (14)$$

The following prediction equation of MRFs from the ΔH_{Comb} values based on DFT energies (eq 9) was obtained ($R = 0.986$, $\text{SD} = 0.063$, $N = 284$):

$$\text{MRF} = -0.071 + 8.57 \times 10^{-4} \Delta H_{\text{Comb}}^{\text{DFT}} + 0.127 n_{\text{Benz}} \quad (15)$$

The correlation between calculated and predicted MRFs is shown in Figure 3. To test the possible impact of the incomplete combustion into HCO^+ , we added the term $n_C \Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2}$ to eq 15, and this latter was reoptimized with eq 14. The statistics of this optimization remained unchanged compared with those of eq 15, which suggests that $\Delta H_{\text{HCO}^+ \rightarrow \text{CO}_2}$ does not significantly influence the prediction of response factors.

The prediction validity of this model was checked by applying eq 15 to a test set made of 67 compounds, which gave a slightly lower precision compared with the result obtained for the training set ($R = 0.981$, $\text{SD} = 0.0988$). However, these results demonstrate that the above hypothesized relationship between the response coefficient and ΔH_{Comb} indeed exists.

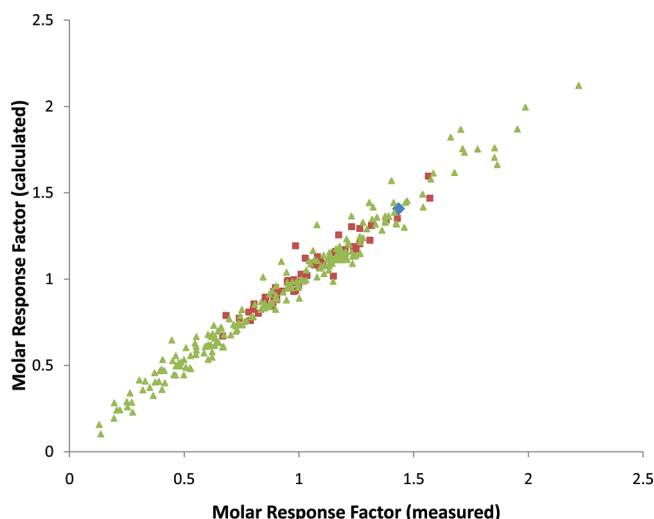


Figure 3. Calculated (eq 8) vs experimental MRF for the training set (in green, red, blue: zero, one, and two benzenic ring(s), respectively).

Table 3. Comparison of MRF and RRF Predictions from ΔH_{Comb} and Molecular Formulas^a

	from $\Delta H_{\text{Comb}}^{\text{DFT}}$		from $\Delta H_{\text{Comb}}^{\text{MF}}$	
	<i>R</i>	SD	<i>R</i>	SD
MRF (training set)	0.986	0.063	0.987	0.061
MRF (test set)	0.981	0.099	0.982	0.095
RRF (both sets)	0.925	0.125	0.936	0.116

^a Training and test sets comprised 284 and 67 compounds, respectively.

In eq 15, the MRF of a given compound was predicted from $\Delta H_{\text{Comb}}^{\text{DFT}}$, whereas the combustion enthalpy was also predictable from the molecular formula ($\Delta H_{\text{Comb}}^{\text{MF}}$). Therefore, the MRF predictions resulting from both approaches were compared. When applied to the training set, the correlations were very similar and even slightly better by using the combustion enthalpies based on molecular formula ($\Delta H_{\text{Comb}}^{\text{MF}}$, eq 10) than by using the DFT model ($\Delta H_{\text{Comb}}^{\text{DFT}}$, eq 9) (Table 3).

Estimation of RRF and Accuracy of the Prediction. The RRF values were calculated from MRF by using eq 5 and both predictions of combustion enthalpies, $\Delta H_{\text{Comb}}^{\text{DFT}}$ and $\Delta H_{\text{Comb}}^{\text{MF}}$. The correlation (Figure 4) was again slightly better by using the combustion enthalpies based on the molecular formula than by using the DFT model (Table 3). The two outliers were polar short-chain compounds (acetic acid and ethyl bromide). However, other polar short-chain compounds were better correlated and attempting to correlate the deviations with the polarity as represented by the linear retention index on a polar column was unsuccessful.

To evaluate the accuracy of the RRF estimation, we investigated the distribution of their bias versus the values of the database (Figure 5). Regardless of the calculation of the combustion enthalpy, $\Delta H_{\text{Comb}}^{\text{DFT}}$ or $\Delta H_{\text{Comb}}^{\text{MF}}$, almost 60% of the RRFs were predicted at $\pm 5\%$ and 80% were calculated at $\pm 10\%$. In the case of RRFs equal to unity, only 37% of them were within this range of $\pm 10\%$.

However, the estimation of predicted RRF biases with the database values does not provide information about the quantification accuracy of a mixture of analytes. As it is not possible to

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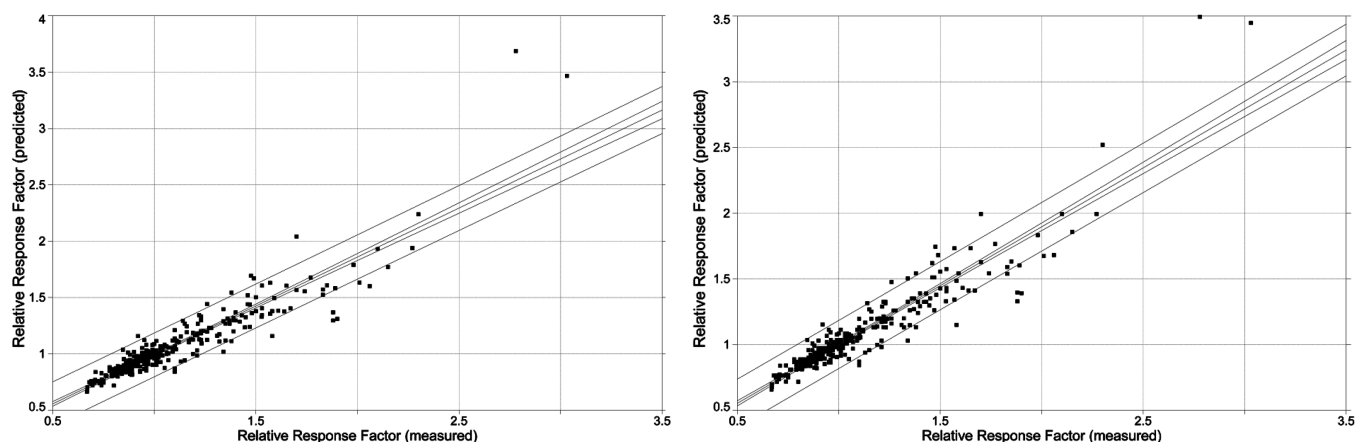


Figure 4. Predicted vs experimental relative response factors, with their confidence and prediction intervals at a level of 90%, for the training and the test sets ($N = 381$), using $\Delta H_{\text{Comb}}^{\text{DFT}}$ (left) and $\Delta H_{\text{Comb}}^{\text{MF}}$ (right).

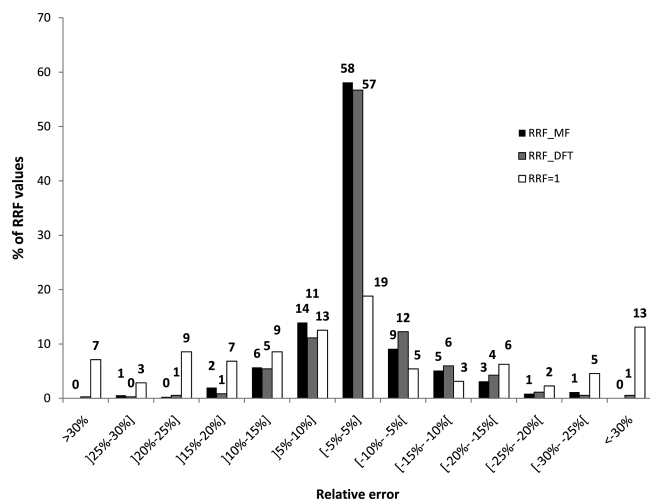


Figure 5. Distribution of the relative errors of predicted vs measured RRFs ($N = 351$) (black, RRF^{MF} ; gray, RRF^{DFT} ; white, $\text{RRF} = 1$).

quantify a mixture made of all database constituents, the model mixture used in our previous determination of the database accuracy was used⁴ (Table 4). The concentration biases of individual constituents were all below 8.2%, such as those resulting from the use of the RRF database. The mean biases were very similar when predicting the RRFs from $\Delta H_{\text{Comb}}^{\text{DFT}}$ or $\Delta H_{\text{Comb}}^{\text{MF}}$. On the basis of these mean biases, the predicted RRFs, as expected, led to less accurate quantification than did those compiled in the database but were much more accurate than RRFs taken as unity.

CONCLUSION

By using a database of compounds that exhibited a variety of chemical functions, we have obtained good RRF estimations from a single parameter, the combustion enthalpy, with an adjustment for benzenic derivatives. This model includes chemicals of formula $\text{C}_{n_{\text{C}}}\text{H}_{n_{\text{H}}}\text{O}_{n_{\text{O}}}\text{N}_{n_{\text{N}}}\text{S}_{n_{\text{S}}}\text{F}_{n_{\text{F}}}\text{Cl}_{n_{\text{Cl}}}\text{Br}_{n_{\text{Br}}}\text{I}_{n_{\text{I}}}$, which covers almost all compounds used in the flavor and fragrance domain and refers to methyl octanoate as an ISTD. The prediction is achieved in two steps: at first ΔH_{Comb} is calculated from the molecular

Table 4. Individual Deviations from the Real Model Mixture Composition (w/w %) and Mean Biases Resulting from a Full Internal Standardization (Measured RRFs), Predicted and Database RRFs, and a Semiquantification ($\text{RRF} = 1$)

compound	measured RRFs (%)	RRF database (%)	predicted RRFs (MF) (%)	predicted RRFs (DFT) (%)	RRF = 1 (%)
isoamyl acetate	0.82	0.44	0.76	2.73	19.74
eucalyptol	0.01	1.55	5.07	2.05	8.73
linalool	0.24	0.50	6.08	5.46	12.36
4-methylacetophenone	1.70	5.49	6.18	3.13	11.15
anisaldehyde	0.63	0.90	5.15	6.03	14.60
citronellol	1.27	0.91	0.31	1.41	7.51
eugenol	1.18	1.88	1.79	1.50	3.90
coumarin	2.34	7.34	7.97	4.87	2.79
ethyl decanoate	0.46	0.21	3.02	1.02	0.28
β -caryophyllene	5.16	4.93	5.55	2.52	41.79
methyl isoeugenol	2.59	1.92	7.51	8.17	7.48
pentadecane	0.13	1.20	1.79	0.26	29.07
hedione	1.01	2.33	0.19	1.75	12.43
mean bias	0.50	0.71	1.61	1.63	4.88

formula and eq 9 or 10, depending on the availability of software to calculate DFT energies, and then response factors are obtained by using eq 15 (and eqs 3 and 4 for RF_d and RRF, respectively). This simple approach is based on the phenomenon occurring in the FID, in contrast to existing models that involve a variety of parameters without justification of their role in the combustion. However, the resulting RRF predictions well-compete with models that use more sophisticated descriptors. As the combustion enthalpies can be estimated directly from molecular formulas, the implementation of this method is easy.

SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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