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Prediction of Retention Indices and Response Factors of Oxygenates for GC-FID by Multilinear Regression

Nils Kretzschmar, Markus Seifert , Oliver Busse  and Jan J. Weigand * 

Faculty of Chemistry and Food Chemistry, Technische Universität Dresden, 01062 Dresden, Germany

* Correspondence: jan.weigand@tu-dresden.de

Abstract: The replacement of fossil carbon sources with green bio-oils promotes the importance of several hundred oxygenated hydrocarbons, which substantially increases the analytical effort in catalysis research. A multilinear regression is performed to correlate retention indices (RIs) and response factors (RFs) with structural properties. The model includes a variety of possible products formed during the hydrodeoxygenation of bio-oils with good accuracy (R_{RF}^2 0.921 and R_{RI}^2 0.975). The GC parameters are related to the detailed hydrocarbon analysis (DHA) method, which is commonly used for non-oxygenated hydrocarbons. The RIs are determined from a paraffin standard (C5–C15), and the RFs are calculated with ethanol and 1,3,5-trimethylbenzene as internal standards. The method presented here can, therefore, be used together with the DHA method and be expanded further. In addition to the multilinear regression, an increment system has been developed for aromatic oxygenates, which further improves the prediction accuracy of the response factors with respect to the molecular constitution (R^2 0.958). Both predictive models are designed exclusively on structural factors to ensure effortless application. All experimental RIs and RFs are determined under identical conditions. Moreover, a folded Plackett–Burman screening design demonstrates the general applicability of the datasets independent of method- or device-specific parameters.

Keywords: response factors; retention indices; gas chromatography (GC); flame ionization detector (FID); detailed hydrocarbon analysis (DHA); oxygenated hydrocarbons; predictive modelling



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1. Introduction

The rising use of biogenic sources, beside fossil carbon sources, is an important strategy to face challenges on the route to a circular, CO₂-neutral chemical industry. These new carbon-source converting technologies evolve to deal with varying local accessibility and the high diversity of biotic and abiotic carbon sources. Catalytic processes remain the most economically viable processes in the chemical industry; hence, the development, characterization and evaluation of a wide range of catalytic systems is of major interest [1–8].

At first, it is important to establish and evaluate a setup for the necessary analytics. Depending on the research tasks, this can be challenging due to the rising complexity of the system and the declining availability of the reference compounds [9,10]. For large-scale industrial processes, such as Fluid Catalytic Cracking (FCC), standardized GC methods are available. The related detailed hydrocarbon analysis (DHA) method enables a precise analysis based on tabulated retention indices and empirical response factors [11–13]. The retention indices developed by Ervin Kovats in 1958 enable a device-independent standardisation of retention time [14]. Using the retention indices, only a calibration of a GC with a suitable paraffin standard is necessary to determine the retention times of a variety of other components and, thus, enables a qualitative analysis of the product spectrum. The quantitative analysis of the signal from a flame ionization detector (FID) is based on substance-specific response factors [15]. These are available through empiric formulas only, depending on the structural data of individual substances within the DHA standard [11–13].

However, the empirical formulas do not include compounds with oxygen-containing functional groups, as otherwise their content can be dramatically underestimated, as shown by Costa et al. for bio-oils [16]. An explanation was provided by Nicholson et al. [17] in 1980. They suggested that the response of a molecule depends on the time it needs to be reduced to CH_n radical species compared to other competitive reactions. The low response for oxygenates is, therefore, due to the structure-dependent low reaction rate to form CH_n compared to those that form CO or H_2CO . Starting from CH_n , CHO^+ fragments have been confirmed as the primary ions formed from oxygen functionalities at the FID [18,19].

To estimate the response factors, the more recent approaches rely on artificial neural networks [20] or multiple parameter regressions [21], but primarily focus on hydrocarbons. However, those complex approaches need detailed substance-specific data, such as polarizability, entropies, total one-center-one-electron repulsion energy and total hybridization of molecular dipoles [9,10,20–22]. For this reason, the identification and the determination of the response factors of oxygenated compounds are predominantly reperformed by scientists for each study [23–28].

Consequently, the scope of this work is a fast and easy prediction of the retention indices and response factors for phenolic bio-oil compounds only from structural properties. A multilinear prediction model is created by the assignment of 99 oxygen-containing compounds, including alcohols, ketones and methylated oxygenated aromatics. Due to the high importance of aromatic oxygenates, an additional increment system has been developed for compounds with up to four substituents. Furthermore, a screening test plan (Plackett–Burman design) quantifies the impact of different method parameters on the response factors and retention indices using 2-methoxyphenol to confirm the general applicability of the prediction model.

2. Materials and Methods

2.1. Utilized Raw Materials and Consumables

The DHA paraffin standard (C5–C15) that was used for the determination of the retention indices was purchased from Restek. The pentanol and 1,3,5-trimethylbenzene used for the calibration were purchased from Thermo Fisher Scientific with a minimum purity of 99%. The absolute ethanol was delivered from VWR with a minimum purity of 99.9%. The other oxygenated hydrocarbons are summarized in Table S5 in the Supplementary Materials with their producers and their purity. No contamination was detected by the GC analysis. All chemicals were used without further purification. The gases, helium, hydrogen and synthetic air, used for the GC analysis, were purchased from PraxAir with a purity of 99.999%.

2.2. Preparation of the Standard Solutions

For the preparation of the standards, 30-mL disposable vials were used. Each standard solution consists of pentanol (solvent), the compound to be analyzed and two internal standards, ethanol and mesitylene. The substances were weighted on a precision balance (Ohaus[®] Corp., Parsippany, NJ, USA, Analytical Plus balance) with a 0.01 mg resolution. To ensure a homogeneous distribution and dissolution of the solid compounds, all samples were mixed in an overhead shaker. Afterwards, each solution was split into 10 GC vials. A further increase in the accuracy was realized by the preparation of two solutions with different concentrations of 10 and 25 mg/g for each substance.

2.3. GC Methods

A detailed comparison of the different parameters of the ASTM standards [7–9] with the method used [29] is displayed in Table S1. As an overview, Figure 1 illustrates the different temperature profiles.

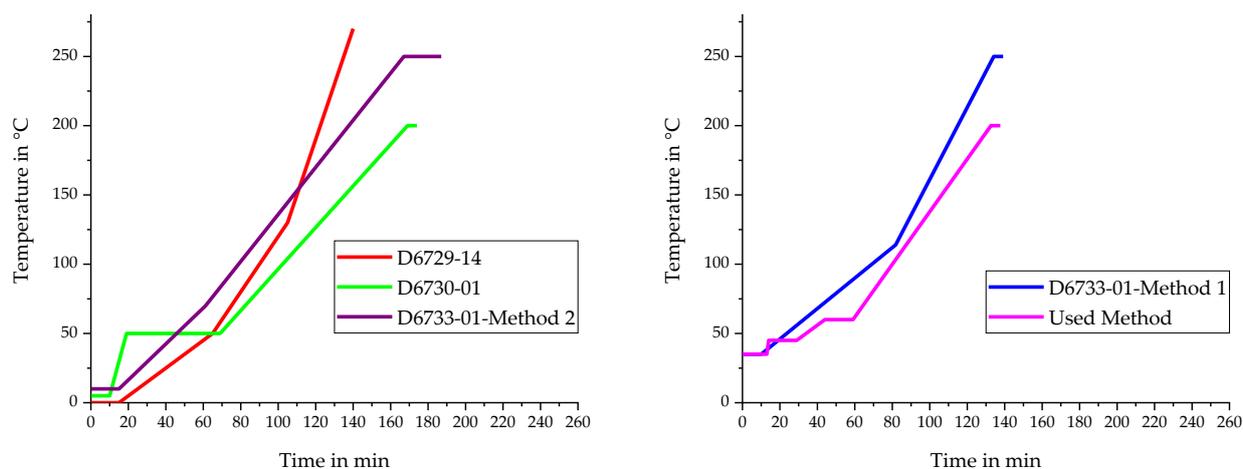


Figure 1. Comparison of the temperature profiles of the different ASTM standards for the detailed hydrocarbon analysis (DHA) method, including the applied method [11–13].

The investigations were performed on a Clarus 590 gas chromatograph with a wide-range FID from PerkinElmer. According to the used DHA method [29], a 100-m DB⁻¹ column with an inner diameter of 0.25 mm and a film diameter of 0.5 µm was used.

The analysis of the 0.1 µL of the sample was performed at a split ratio of 100:1 using the temperature profile from Table 1. The injector temperature was set to 290 °C, and the total time of each run was 253 min. Helium was used as a carrier gas at 37 psig constant pressure. The FID was operated at a temperature of 250 °C; the hydrogen flow was 34.5 mL/min; the oxygen flow was 400 mL/min, and the detector offset was 5 mV.

Table 1. Overview of the temperature profile used for the analysis.

Step	Temperature		Heating Rate [K/min]	Dwell [min]
	Starting [°C]	Final [°C]		
1	35	35	0	13
2	35	45	10	15
3	45	60	1	15
4	60	200	1.9	120

2.4. Computation

The evaluation was performed with the software TotalChrom from PerkinElmer. The noise threshold was set to 1; the area threshold was set to 500, and the bunching factor was set to 20. A statistical analysis was performed in JMP by the SAS Institute. Due to the limited number of 99 substances, no separation of the dataset into a training set and a validation set for the statistical analysis was applied, as it is commonly used in the field of big data [30,31]. Instead, the full dataset was used to build the models, and R² metrics were used as the basis of the model comparison and optimal model selection for assessing the overall performance of the regression models.

The retention indices, defined by Kovats [14], can be calculated according to Equation (1) from the ASTM D 6730 [12].

$$RI_i = 100 \cdot \left(n + \frac{\log(t_i) - \log(t_n)}{\log(t_{n+1}) - \log(t_n)} \right) \quad (1)$$

where

RI_i = retention index of the substance

n = carbon number of n-paraffin

t_i = retention time of the component
 t_n = retention time of the preceding n-paraffin
 t_{n+1} = retention time of the next n-paraffin molecule

Based on Equation (2), the retention times can be calculated from the specific retention indices.

$$t_i = t_n \cdot \left(\frac{t_{n+1}}{t_n} \right)^{\left(\frac{RI_i}{100} - n \right)} \quad (2)$$

The response factors of the hydrocarbons are normalized to n-heptane and calculated according to Equation (3) based on the ASTM D 6730 [12].

$$RF_i = \frac{0.83905 \cdot (C_{aw} \cdot N_C + H_{aw} \cdot N_H)}{C_{aw} \cdot N_C} \quad (3)$$

where

RF_i = relative response factor of the substance
 C_{aw} = atomic weight of carbon (12.011)
 N_C = number of carbon atoms in the substance
 H_{aw} = atomic weight of hydrogen (1.008)
 N_H = number of hydrogen atoms in the group

The response factors of the oxygenated hydrocarbons can be calculated according to Equation (4) by using the mass fractions corrected with the purity and the integrated FID signal areas. For each substance, the response factor was calculated in relation to both ethanol and 1,3,5-trimethylbenzene (mesitylene). As the components are a liquid and a solid, the response factors are standardised to n-heptane, as commonly applied for hydrocarbons. The procedure is based on the ASTM D 4626–95 [32].

$$RF_i = \frac{R_{M,Ref} \cdot RF_{Ref}}{R_{M,i}} = \frac{A_{Ref} \cdot w_i \cdot RF_{Ref}}{A_i \cdot w_{Ref}} \quad (4)$$

where

RF_i = relative response factor of the substance
 RF_{Ref} = relative response factor of the reference
($RF_{Ethanol} = 2.05$; $RF_{1,3,5-trimethylbenzene} = 0.9329$)
 $R_{M,i}$ = mass response factor of the substance
 $R_{M,Ref}$ = mass response factor of the reference
 A_i = area of the substance peak
 w_i = mass fraction of the substance corrected by the purity of the substance
 A_{Ref} = area of the reference peak
 w_{Ref} = mass fraction of the reference

2.5. Design of the Experiments

The investigation of the parameters influencing the response factors was carried out using a screening test plan in double determination. For this, guaiacol acts as a model substance due to its structural similarity to bio-oils. Due to the variation in the temperature profile, decane and undecane additionally functioned as internal standards for the screening tests to calculate the RI. The experimental design is based on the Plackett–Burman design and allows the investigation of 11 factors on two levels with 12 experiments, which are summarized in Table 2 [33]. However, of the 11 possible factors, 2 were declared as controls to evaluate the random experimental error.

Table 2. Assignment of the examined factors and definition of the level settings + and –.

Abbr.	Parameter	Level “–”	Level “+”
A	Concentration of the substance	10 mg/mL	20 mg/mL
B	Reference to substance ratio	1	2
C	Control	-	-
D	Control	-	-
E	Injection volume	0.1 µL	0.2 µL
F	Split ratio	100	10
G	Hydrogen flow	34.5 mL/min	30.0 mL/min
H	Synthetic air flow	400 mL/min	350 mL/min
I	Temperature ramp	last ramp 1.9 K/min	last ramp 10 K/min
J	Detector temperature	250 °C	225 °C
K	Injector temperature	290 °C	250 °C

The original experimental design, which consists of 12 experiments, was extended by an additional 12 experiments with an inversion of the steps to separate the main effects from the double interactions. The result is a folded experimental design, which extends the resolution level from III to IV [34]. A detailed overview of the experimental plan is attached as Table S2.

3. Results and Discussion

3.1. Determination of the Retention Indices and Response Factors

As a benchmark to state-of-the-art analytics, the retention times of the DHA standard (C5–C15) are determined with high reproducibility due to the autosampler, as displayed in Table 3.

Table 3. Retention times of the components of the DHA-paraffin standard.

Substance	CAS-Number	Retention Time [min]
Pentane	109-66-0	10.097 ± 0.000
Hexane	110-54-3	15.197 ± 0.002
Heptane	142-82-5	25.842 ± 0.015
Octane	111-65-9	44.755 ± 0.015
Nonane	111-84-2	69.842 ± 0.011
Decane	124-18-5	86.627 ± 0.011
Undecane	1120-21-4	98.752 ± 0.013
Dodecane	112-40-3	108.677 ± 0.015
Tridecane	629-50-5	117.348 ± 0.012
Tetradecane	629-59-4	125.219 ± 0.012
Pentadecane	629-62-9	132.506 ± 0.009

In the first extension to the DHA method, mesitylene and ethanol were used as internal standards for the RF calculation. To prevent possible overlaps of the substances and standards and to increase the accuracy, we decided to use two internal standards at the same time. However, there was no overlap. Both standards eluted sufficiently far from each other. Pentanol was chosen as the solvent because all other components dilute well in it.

The second extension is illustrated in Table 4. It demonstrates the deviations of the experimentally determined response factors (RFs) of the selected oxygenates from those obtained by the calculations within this study, as well as from the reported DHA method.

Table 4. Comparison of (a) the experimentally determined response factors (RFs) with (b) the calculated RFs from this study and (c) the calculations from the reported DHA method.

Compound	RF _{measured}	RF _{this study}	RF _{DHA}
Methanol	2.8888	2.6713	1.1207
Phenol	1.3541	1.5104	0.9095
Cyclohexanol	1.2755	1.2070	0.9799

The regression was performed considering substance-specific characteristics such as boiling point, melting point, functional groups, presence of cyclic structures, aromaticity, chemical formulas and their interactions. Considering all of the factors, the R² values of 0.934 for the RF and 0.988 for the RI were achieved. In the third step, a backwards elimination was used to determine the significant description model, i.e., a stepwise elimination of the variables that possessed the lowest statistical confidence in the model. The aim was to develop a feasible formula with as few factors as possible that are significant and still provide a descriptive model with a high R². Table S2 in the Supplementary Materials provides an overview of the systematic elimination steps. Equation (5) results from the backward regression and enables the calculation of the RF for oxygenates.

$$\begin{aligned}
 RF_i = & 1.0719 \\
 & + (-0.0353) \cdot N_C + (-0.0142) \cdot N_H + 0.4318 \cdot N_O \\
 & + 0.2063 \cdot N_{OH} \\
 & + (-0.0729) \text{ for alcohols} \\
 & + (-0.0553) \text{ for phenols} \\
 & + (-0.1282) \text{ for else (aldehyde, ketone, ...)} \\
 & + (N_C - 7.0808) \cdot (N_H - 11.3737) \cdot (0.0264) \\
 & + (N_C - 7.0808) \cdot (N_O - 1.2828) \cdot (-0.0510)
 \end{aligned} \tag{5}$$

where

N_{OH} = number of hydroxyl groups in the substance

The RI follows from an analogous formula. Table 5 provides the variables, their p -values and the estimator for the RF and RI. For this, the estimators for the RF are replaced by those for the RI; for example, the intercept of 1.0710 by 117.796 and the multiplier for the carbon number of -0.0353 by 99.049.

In statistics, the p -value is an evidence measure for the credibility of the null hypothesis, i.e., low p -values near zero indicate a strong influence of the variable. Consequently, all factors considered are significant for the description model. As shown in Table 5, the two-way interactions of C–H and C–O result in a significant improvement of the description model for the RF but not for the RI. For this reason, the interactions can be neglected for the RI. Residuals by predicted plot for the RF and RI are shown in Figure 2.

The accuracy target for an R² of at least 0.90, comparable to Lučić et al. [21], is achieved for the RF (0.92) and is greatly exceeded for the RI (0.98). The experimental data (RI, RF and t_i) are available in a table (Table S4) and in a CSV file in the Supplementary Materials.

Table 5. Parameter estimates for the modeling of the response factor ($R^2 = 0.921$) and the retention index ($R^2 = 0.975$). A = alcohols; B = phenols; C = else (aldehyde, ketone, ether, etc.).

Dependencies on Elementary Composition				
Source	Response Factor (RF)		Retention Index (RI)	
	<i>p</i> -Value	Estimate	<i>p</i> -Value	Estimate
Intercept	-	1.0719	-	117.796
C	0.0104	-0.0353	0.0000	99.049
H	0.0260	-0.0142	0.0576	-4.160
O	0.0000	0.4318	0.0000	84.043
Dependencies on Functional Groups				
Source	<i>p</i> -Value	Estimate	<i>p</i> -Value	Estimate
Hydroxy groups	0.0001	0.2063	0.0000	157.068
Categorical(A/B/C)	0.0028	A = -0.0729 B = -0.0553 C = 0.1282	0.0000	A = -80.404 B = 23.134 C = 57.270
Two-Way Interactions C-H and C-O				
Source	<i>p</i> -Value	Estimate	<i>p</i> -Value	Estimate
(C-7.0808)·(H-11.374)	0.0000	0.0264	Not necessary	
(C-7.0808)·(O-1.2828)	0.0554	-0.0510		

The presence of many of the examined functional groups, such as aldehydes, ketones, ethers and alkyl groups, can be neglected because the molecular formulas and their interactions indirectly describe these factors. The same applies for the substance-specific properties, such as melting or boiling points. Finally, besides the chemical formula, only the number of hydroxyls and the distinction into alcoholic or phenolic groups are decisive for the accuracy of the model predictions.

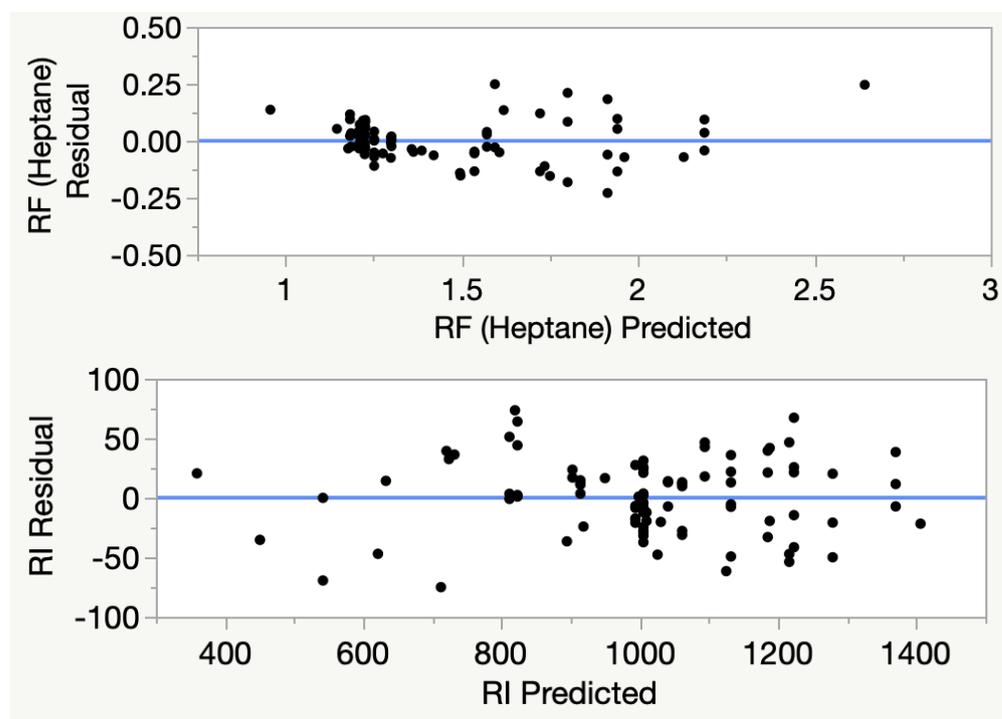


Figure 2. Residuals by predicted plot for the response factors (RF) (top; $R^2 = 0.921$) and retention indices (RI) (bottom; $R^2 = 0.975$). Each of the dots represents an investigated substance and its deviation from the prediction model.

3.2. Optimization for the Aromatic Oxygenates

In addition to the general multilinear regression, which also considers cyclic and acyclic alcohols and ketones, an increment system was developed specifically for aromatic oxygenates. The structure of the increment system is based on the IUPAC nomenclature and is depicted in Figure 3. The advantage of this increment system is a higher prediction accuracy due to the consideration of constitutional isomers as demonstrated from the residuals by a predicted plot, which is shown in Figure 4.

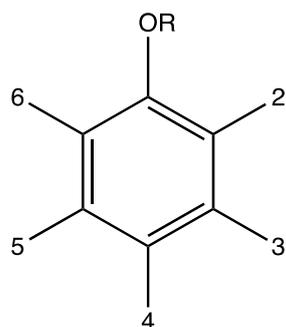


Figure 3. Schematic representation of the positions for modeling of aromatic oxygenates, with R = H or Me.

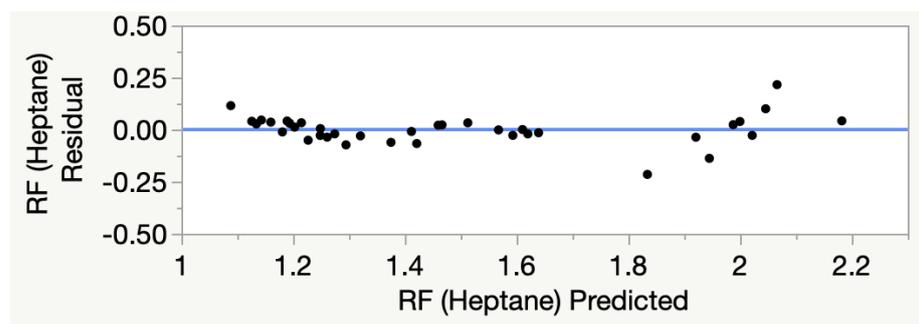


Figure 4. Residuals by a predicted plot for the response factors (RF) ($R^2 = 0.958$) for aromatic oxygenated hydrocarbons. Each of the dots represents an investigated substance and its deviation from the prediction model.

Due to the IUPAC-based nomenclature, the hydroxyl and methoxy groups at positions 5 and 6 are not considered, as well as the methyl groups and hydrogen at position 1, because the position numbers would change. Table 6 provides the variables and the estimator for the RF. The RF itself can be calculated based on the structure of the following equation:

$$RF_i = \text{Intercept} + \text{Position 1} + \text{Position 2} + \text{Position 3} + \text{Position 4} + \text{Position 5} + \text{Position 6} \quad (6)$$

Table 6. Parameter estimates for modeling of the response factor of aromatic oxygenated hydrocarbons ($R^2 = 0.958$).

Source	OH	OMe	Me	H
Position 1	0.0633	−0.0633	-	-
Position 2	0.4540	0.0475	−0.3309	−0.1705
Position 3	0.4300	0.1010	−0.3158	−0.2150
Position 4	0.5007	0.0654	−0.3061	−0.2600
Position 5	-	-	−0.0358	0.0358
Position 6	-	-	−0.0170	0.0170
Intercept		1.9507		

In general, hydroxyl and methoxy groups lead to an increase in the RF, as they result in a lower signal at the FID. Hydroxyl groups have a stronger influence than methoxy groups, which is explained by the higher bond dissociation energies of Ar–OH bonds (414 kJ/mol) compared to Ar–OMe bonds (356 kJ/mol) [4,35]. The former ones are more difficult to cleave. Furthermore, due to the structure-dependent low reaction rate of the reactions that form CH_n compared to those that form CO or H₂CO, a lower FID signal occurs. In contrast, methyl groups or even protons lead to a decrease in the RF, i.e., an increase in the signal at the FID [19].

Everything considered, the accuracy of the predictive model for the response factors of the substituted and aromatic oxygenated hydrocarbons is still high ($R^2 = 0.96$), as illustrated in Figure 4.

3.3. Influence of the Method-Specific Factors by Design of the Experiments

The investigation of the method-specific factors influencing the response factors and response indices is carried out using the example of 2-methoxyphenol (guaiacol) and the principles of experimental design. Using a folded Plackett–Burman design [33,34], the main effects and interactions of nine parameters are determined in a screening experiment. In addition, two factors are used as control factors to determine the experimental variation. An overview of all experimental step sizes (+/–) is already listed in Table 2. For these experimental series, Table 7 shows the *p*-values and the influence of the investigated device parameters for the response factor and the retention index.

Table 7. Parameter estimates for the folded Plackett–Burman design to quantify the impact of the method parameters for GC analysis with FID.

Source	Response Factor (RF)		Retention Index (RI)	
	<i>p</i> -Value	Estimate	<i>p</i> -Value	Estimate
Intercept	-	1.452	-	1066.7
Concentration of substance	0.0157	0.033	0.0022	0.1
Reference to substance ratio	0.1782	0.018	0.8619	0.0
Control	0.3051	0.014	0.2048	–0.1
Control	0.9833	0.000	0.9997	0.0
Injection vol.	0.7100	0.005	0.0008	0.2
Split ratio	0.0090	–0.036	0.0000	0.4
Hydrogen flow	0.2425	0.015	0.4433	0.0
Syn. air flow	0.2334	0.016	0.1805	0.1
Temp. ramp	0.6384	0.006	0.0000	2.4
Detector temp.	0.2090	0.017	0.8356	0.0
Injector temp.	0.2777	0.014	0.9963	0.0

In statistics, the *p*-value is an evidence measure for the credibility of the null hypothesis, i.e., low *p*-values near zero indicate a strong influence of the variable. Consequently, due to the low *p*-value, only the factors “concentration of the substance” and “split ratio” are significant for the response factor, which is consistent with the literature [36–39]. However, their influence (estimate < 0.05) is negligible compared to those determined in the multilinear regression (see Table 5), which can be explained by technical improvements, e.g., the use of a wide-range FID [40]. For the retention index, the factors “concentration of substance”, “injection volume” and “temperature ramp” are more prominent. A larger amount of the substance leads to a peak broadening and, thus, to a slight shift of the signal to a higher

retention time. The chromatograms of three exemplary runs, which are shown in Figure 5, illustrate the apparently high deviations. However, the total span of the variation is still low (estimate = 0.3). Based on Equation (2), a deviation of the retention time by 0.025 min results in a high concentration. Only the temperature profile has a considerable but small influence on the retention indices (estimate = 2.4). Based on the standard temperature profile, the deviation for both retention indices (1066.7 and 1069.1) is 0.298 min. Consequently, the response factors are stable for all device parameters in the investigated range. For the retention indices, it is recommended to use the proposed temperature profile; nevertheless, a variation also results in an acceptable accuracy (RI +2.4). However, it should be noted that a higher heating rate reduces the separation efficiency, which limits the minimum time for the GC analysis.

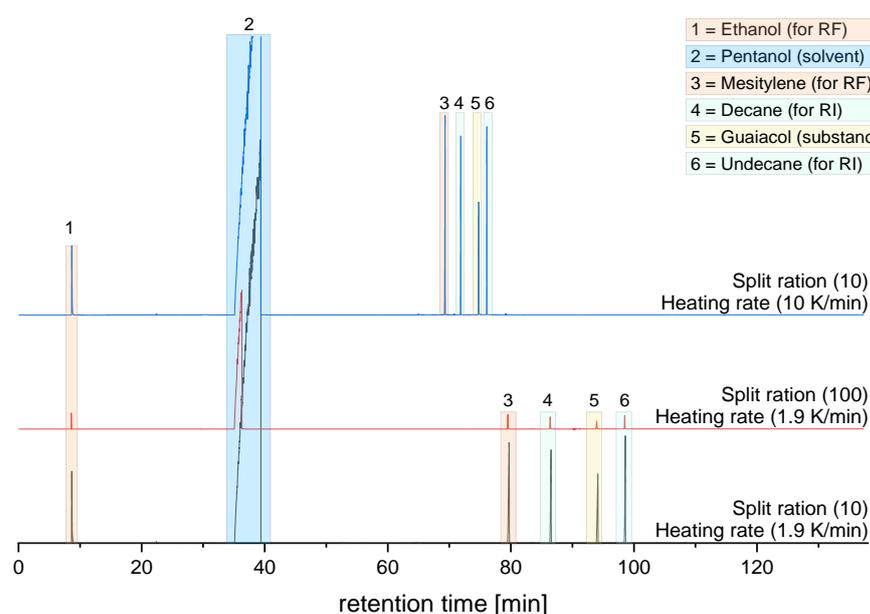


Figure 5. Comparison of three different chromatograms for the Design of Experiments with obviously different shapes. The chromatograms differ in their temperature profiles at the last heating rate and in the split. Nevertheless, similar response factors (RFs) and retention indices (RIs) are obtained. Ethanol and mesitylene are used for the determination of the RFs of the model substances guaiacol, decane and undecane for the determination of the RIs. Pentanol serves as a solvent.

4. Conclusions

In this study, the response factors (RF) and retention indices (RI) are predicted for a variety of possible products that can be formed during the hydrodeoxygenation of phenolic model substances for bio-oils using a GC with a wide-range FID. A multilinear regression combined with a systematic selection of a minimum number of parameters based on structural properties results in a high degree of accuracy for the RFs and RIs ($R^2 \geq 0.921$ and 0.975). As aromatic oxygenated hydrocarbons are particularly important for studies on the conversion of lignocellulosic biomass, an increment system is developed, especially for phenols and methoxylated compounds. By considering the constitution, it is possible to improve the accuracy of the response factor prediction without complicated formulas and further tabulated constants ($R^2 \geq 0.958$). An experimental design confirms the almost negligible dependence of the RF and RI from device or method specific parameters, such as injection volume or carrier gas flow. Based on the described procedure and the experimental data, an extension to further substance groups, as well as the application to other analytical methods is possible. Everything considered, the work reduces the analytical effort for research in the field of bio-oil conversion towards new sustainable technologies by a robust procedure that is ready for application.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/data7090133/s1>; Table S1: Additional materials and methods; Table S2: Backward regression; Table S3: Design of Experiments; Table S4: Database for response factors and retention indices; Table S5: Database of substances used for the calibration and their producers, including purity; database-csv.txt; PerkinElmer Methodefile.meth.

Author Contributions: Conceptualization, N.K.; methodology, N.K.; validation, N.K., M.S., O.B. and J.J.W.; formal analysis, N.K.; investigation, N.K.; resources, J.J.W.; data curation, N.K.; writing—original draft preparation, N.K.; writing—review and editing, M.S., O.B. and J.J.W.; visualization, N.K.; supervision, M.S., O.B. and J.J.W.; project administration, J.J.W.; funding acquisition, N.K. and J.J.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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