Method to study the separation of eight p-hydroxybenzoic esters by gas chromatography

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Abstract

A model to predict gas chromatographic retention indices from molecular structure and Derringer and Suich's approach were used to study the separation of eight p-hydroxybenzoic esters. The optimization method connects a general simplex method to a computer. A simplex difactor (column temperature/gas flow-rate) optimization–gas chromatography (SDO–GC) method was developed. More than half the number of experiments required in the general simplex method were omitted. Good agreement was obtained between predicted and experimental results.

Keywords: Simplex optimization; Computer simulation; Optimization; Desirability functions; Experimental design; p-Hydroxybenzoic esters

1. Introduction

In GC, computer simulations have begun to play an increasingly important role in the optimization of separation. Bautz et al. [1] described the performance of a computer method to predict the retention bandwidth and resolution for temperature-programmed GC separations with an average error of better than 10%. Dolan et al. [2] investigated the changes in bond spacing as a function of temperature through computer simulation. A simplex method was used to optimize selectivity for the separation of ten compounds by GC [3] and for the deconvolution of complex GC profiles [4]. Guillaume et al. [5] discussed the

prediction of GC retention times, column efficiency and resolution as a function of temperature and flow-rate for eight p-hydroxybenzoic esters.

In these optimization problems, there are usually several responses that must be considered. The aim of optimization is the selection, from a multiplicity of potential solutions, of the one that is the best with respect to certain well defined criteria [6]. The objective is to determine the best criteria to optimize separation in GC. There have been attempts to solve this problem using several different methods. Morgan and Deming's chromatographic response function [7–11] consists of a function related to a factor which describes the separation quality. This separation quality is expressed in terms of res-

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olution [12–14] or a discrimination factor [15]. Other methods of simultaneously optimizing different criteria have been proposed by Derringer and Suich [16], who used desirability functions [17]. This process has received little attention in GC. This paper analyses Derringer and Suich's desirability functions and reports the separation of eight p-hydroxybenzoic esters using Derringer and Suich's method with the simplex difactor optimization–gas chromatography (SDO–GC) program developed in our laboratory reducing the number of experiments.

2. Experimental

2.1. Reagents

The compounds chromatographed were p-hydroxybenzoic esters. The straight-chain esters, methyl to butyl (MeR, EtR, PrR, BuR), were purchased from Interchim (Montluçon, France). The branched-chain esters, isopropyl, isobutyl, *sec.*-butyl and *tert.*-butyl (IprR, IbuR, SbuR, TerR), were synthesized in our laboratory by an esterification reaction [18]. All the compounds were diluted in HPLC-grade methanol.

2.2. Apparatus

The analyses were performed using a Delsi (Suresnes, France) DI 200 gas chromatograph with a flame ionization detector and a Merck (Nogent-sur-Marne, France) D2500 chromato-integrator. An OV-17 capillary column was used with a stationary phase of poly(methylphenyl)siloxane (25 m × 320 μm I.D.) with a film thickness of 0.2 μm (Spiral, Dijon, France). The carrier gas was nitrogen with a flow-rate varying from 1.50 to 3 ml/min and the column temperature was varied from 145 to 170°C under isothermal conditions.

2.3. Desirability functions

The functions, first presented by Harrington [19] and developed by Derringer and Suich [16], convert the measured properties to a dimension-

less desirability scale for each criterion, so that values of several properties, obtained from different scales of measurements, may be combined. The desirability scale ranges between $d = 0$, corresponding to a completely undesirable level of quality, to $d = 1$, which indicates an ultimate level of quality beyond which further improvements would have no values. If Y_i^+ and Y_i^- are measures of the most desirable and undesirable values, respectively, of a response Y_i, then, if it is assumed that the desirability decreases linearly going from Y_i^+ to Y_i^-, the desirability contributed by this response is calculated as

$$d_i = 0 \qquad \text{if } Y_i \leqslant Y_i^-$$
$$d_i = +1 \qquad \text{if } Y_i \geqslant Y_i^+$$
$$d_i = \frac{Y_i - Y_i^-}{Y_i^+ - Y_i^-} \qquad \text{if } Y_i^- \leqslant Y_i \leqslant Y_i^+ \qquad (1)$$

2.4. Overall desirability

Harrington [19] suggested multiplying the desirability values. Therefore, if any one property is so poor that the product is not suitable for the application, then this product will not be acceptable, regardless of the other remaining properties. The mathematical model is the geometric mean of the component d values:

$$D = (d_1 d_2 \cdots d_k)^{1/k} \qquad (2)$$

where k is the number of desirability values and D is the overall desirability. It is clear that if one of d_i is zero, the associated D will also be zero. Further, D is strongly weighted by the smaller d_i values. Fig. 1 shows how D varies as a function of two d_i values.

2.5. Experimental design

In order to investigate the effects of two variables (gas flow-rate and column temperature) and their possible interaction on the response y, a composite central design was used [20,21]. Nine experiments repeated three times were carried out and the y values were determined. The y values were then fitted into a second-order polynomial:
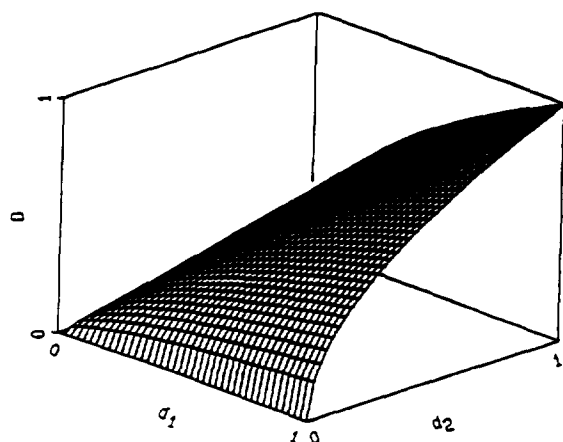
Fig. 1. Overall desirability D vs. desirability functions d_1 and d_2.

$$y = a_0 + a_1 x_1 + a_2 x_2 + a_{11} x_1^2 + a_{22} x_2^2 + a_{12} x_1 x_2$$

$$(3)$$

where x_1 and x_2 are the logarithm of the column temperature $T(°C)$ and of the gas flow-rate F (ml/min), respectively.

The values of a_0, a_1, a_2, a_{11}, a_{22} and a_{12} were determined from a matrix product:

$$y = MP \qquad (4)$$

where

$$
y = \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \end{pmatrix}
\quad
M = \begin{vmatrix}
1 & -1 & 1 & 1 & 1 & -1 \\
1 & -1 & -1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 & 1 & 1 \\
1 & 1 & -1 & 1 & 1 & -1 \\
1 & 0 & -\sqrt{2} & 0 & 2 & 0 \\
1 & 0 & +\sqrt{2} & 0 & 2 & 0 \\
1 & -\sqrt{2} & 0 & 2 & 0 & 0 \\
1 & +\sqrt{2} & 0 & 2 & 0 & 0 \\
1 & 0 & 0 & 0 & 0 & 0
\end{vmatrix}
$$

$$
P = \begin{pmatrix} a_0 \\ a_1 \\ a_2 \\ a_{11} \\ a_{22} \\ a_{12} \end{pmatrix}
$$

and $y_1, y_2, \ldots, y_9$ are the experimental values of the y value recorded for each pair of temperature and gas flow-rate (T_i, F_i). Matrix M, the composite central design, is given in reduced coordinates. The variables were coded to have a variation range from $-\sqrt{2}$ to $+\sqrt{2}$. The parameter vector P was calculated as

$$P = (M^t M)^{-1}(M^t y) \qquad (5)$$

where M^t is the transposed matrix of M.

2.6. Simplex optimization

To optimize the mathematical model y given by the experimental design, a simplex method was used (SDO–GC method). The y value was calculated for m sets of starting conditions, where m was given by the number of factors to be optimized plus 1. Therefore, in this case m was 3. The point corresponding to the lowest value of y was then reflected in relation to the curve defined by the two other points to give a fourth set of starting conditions. Once again, the point with the lowest value of y was reflected and the process repeated until the same column temperature and gas flow-rate continued to be selected.

3. Results and discussion

3.1. Compound retention time study

In chromatography, the temperature dependence of retention is given by

$$\ln k = -\frac{\Delta H°}{RT} + \frac{\Delta S°}{R} - \ln \beta \qquad (6)$$

where k is the retention factor of the solute:

$$k = \frac{t_R - t_0}{t_0} \qquad (7)$$

t_R is the retention time of the compound, t_0 the retention time of an unretained peak such as

methane, $\Delta H°$ and $\Delta S°$ are the enthalpy and entropy, respectively, of transfer of the solute from the carrier gas to the stationary phase, R is the gas constant, T is the column temperature and β is the phase ratio (volume of mobile phase divided by the volume of stationary phase). If χ^1 is the first Kier valency connectivity index of a p-hydroxybenzoic ester, it has been demonstrated [22] that $-\Delta H°$ and $-\Delta S°$ can be expressed as:

$$-\Delta H° = a + b\,^1\chi \qquad (8)$$

$$-\Delta S° = c + d\,^1\chi \qquad (9)$$

where a, b, c and d are constants [22].

In a recent paper [5], it was shown that the t_0 model can be written as the well known equation [23,24]

$$t_0 = \frac{\phi_1}{F} \qquad (10)$$

where ϕ_1 is a constant and F (ml/min) is the carrier flow-rate [5]. Combining Eqs. 6–10, the compound retention time of an ester was given [5] by the equation

$$t = \frac{\phi_1}{F}\left\{1 + \exp\left[\,^1\chi\left(\frac{\epsilon}{T} + \phi\right) + \frac{\gamma}{T} + \delta\right]\right\} \qquad (11)$$

where ϵ, ϕ, γ and δ are constants.

3.2. Eight-compound separation study using the SDO–GC method

This is an advanced simplex method connected to a computer. The principle is based on a special polynomial between the overall desirability D and the two factors considered. The desirability function was applied to the selection of a chromatogram with the most desirable combination of two types of response, namely separation quality represented by the lowest resolution value in the chromatogram ($R_{s_{min}}$) and the analysis time t_a. It was decided that $R_{s_{min}} < r_1$ was of no use and increasing $R_{s_{min}}$ beyond r_2 would bring no further gain. Therefore, $d_1 = 0$ for

$R_{s_{min}} < r_1$ and $d_1 = 1$ for $R_{s_{min}} > r_2$ and a value in between for $r_1 < R_{s_{min}} < r_2$ (Eq. 1). In the same way, if $t_a \leq t_1$, $d_2 = 1$ for $t_a \geq t_2$, $d_2 = 0$ and for $t_1 \leq t_a \leq t_2$, d_2 can be calculated using Eq. 1. In this application, r_1, r_2, t_1 and t_2 were chosen as 0.6, 2, 5 and 20 min, respectively. These quantities were chosen to give a D function that sharply discriminated manifestly unsatisfactory separations from better separations. The experimental D valves were calculated (Eq. 2) from the chromatograms. The experiments were repeated three times. The relative standard deviation of the D values was also less than 2%, indicating high reproducibility and good stability for the chromatographic system.

The results were processed by computer and the parameter estimates for the regression model of D are given in Table 1. The calculated and experimental D values are summarized in Table 2. The fitting of the model to the result is good (99.2%), with a Fisher Snedecor test equal to 384. Student's t-test was used to provide the basis for a decision as to whether the model coefficients were significant or not. The results of the test showed that no variable can be excluded from the model. This equation means that if x_1 and x_2 are known the overall desirability can be determined for the applied chromatographic conditions. The interest in the SDO–GC method is that it takes into account the analysis time t_a and the effects of the simultaneous variation of column temperature and gas flow-rate on the separation quality. The experimental design with the simplex method reduces the number of

Table 1
Estimates of regression parameters for the D model

Independent variable	Parameter term	D
Intercept	a_0	+0.530
x_1	a_1	+0.047
x_2	a_2	+0.059
x_1^2	a_{11}	−0.123
x_2^2	a_{22}	−0.035
$x_1 x_2$	a_{12}	−0.106

Table 2
Calculated (D_c) and experimental (D_e) overall desirability functions

Experiment No.	Temperature (°C)	Flow-rate (ml/min)	D_c	D_e	ΔD (%)
1	148.00	1.70	0.165	0.166	0.60
2	166.00	1.70	0.468	0.476	1.68
3	148.00	2.70	0.479	0.481	0.41
4	166.00	2.70	0.375	0.372	0.80
5	145.00	2.16	0.235	0.229	2.55
6	170.00	2.16	0.342	0.338	1.18
7	157.00	1.55	0.397	0.401	0.99
8	157.00	3.00	0.543	0.549	1.10
9	157.00	2.16	0.534	0.538	0.74

Table 3
Results of the simplex process

Experiment No.	Flow-rate (ml/min)	Temperature (°C)	D
1	145	1.55	0.000
2	150	1.60	0.192
3	155	1.65	0.394
4	160	1.66	0.471
5	162	1.70	0.482
6	160	1.72	0.483
7	159	1.73	0.481
8	158	1.75	0.479
9	164	1.76	0.498
10	166	1.76	0.475
11	171	1.80	0.368
12	165	2.10	0.474
13	163	2.31	0.493
14	160	2.52	0.531
15	159	2.44	0.541
16	158	2.29	0.542
17	157	2.01	0.510
18	157	2.39	0.540
19	154	2.46	0.545
20	155	2.63	0.556
21	155	2.75	0.558
22	154	2.88	0.560
23	154	2.71	0.552
24	154	2.59	0.548
25	154	2.90	0.560
26	154	2.89	0.560
27	150	2.91	0.555

experiments needed. The highest value of D was used as a criterion of separation.

The SDO–GC method was applied to carry out this optimization procedure. Two initial experiments were required. These can be selected from the nine preliminary experimental runs needed to use the simplex process. Twenty-seven iterative processes were performed by the computer and the results are given in Table 3. The maximum $D = 0.56$ was the highest D value. The optimum conditions were a gas flow-rate of 2.90

Table 4
Comparison of observed (t_o) and predicted (t_p) retention time for the eight esters with flow-rate = 2.90 ml/min and column temperature = 427 K

Compound[a]	t_p (min)	t_o (min)	Δt (min)	Δt (%)
MeR	3.84	3.76	0.08	1.89
EtR	5.18	5.03	0.15	2.94
PrR	6.74	6.62	0.12	1.80
BuR	8.86	8.43	0.43	4.83
IprR	6.37	6.26	0.12	1.94
IbuR	8.18	7.86	0.32	3.95
SbuR	8.54	8.19	0.35	4.08
TeR	7.55	7.33	0.22	2.89

[a] MeR = methyl, EtR = ethyl, IprR = isopropyl, PrR = n-propyl, TerR = $tert.$-butyl, IbuR = isobutyl, SbuR = $sec.$-butyl and BuR = n-butyl p-hydroxybenzoate.

ml/min and a column temperature of 154°C with an analysis time calculated to be 8.40 min. The response surface generated for the D model is given in Fig. 2. The chromatogram of these eight esters under these optimum conditions is given in Fig. 3. Table 4 compares predicted (Eq. 11) and measured retention time for the solute molecules. The relative error was less than 10%. This optimum chromatogram best fulfils the postulated requirements of the shortest analysis time with efficient separation. This rapid optimization method takes into account the simultaneous variation of several properties (analysis time, resolution) thanks to a single mathematical equation (Eq. 2). It consequently presents advantages

compared with the use of programmed column temperature, for which commercial programs are already available.

4. Conclusion

For a convenient range of gas flow-rates and column temperatures, the SDO–GC method both reduces the number of experiments needed to be carried out and provides a suitable retention model. Using this procedure, the separation for the p-hydroxybenzoic esters required nine experiments instead of 27 with the general simplex method. This optimization procedure
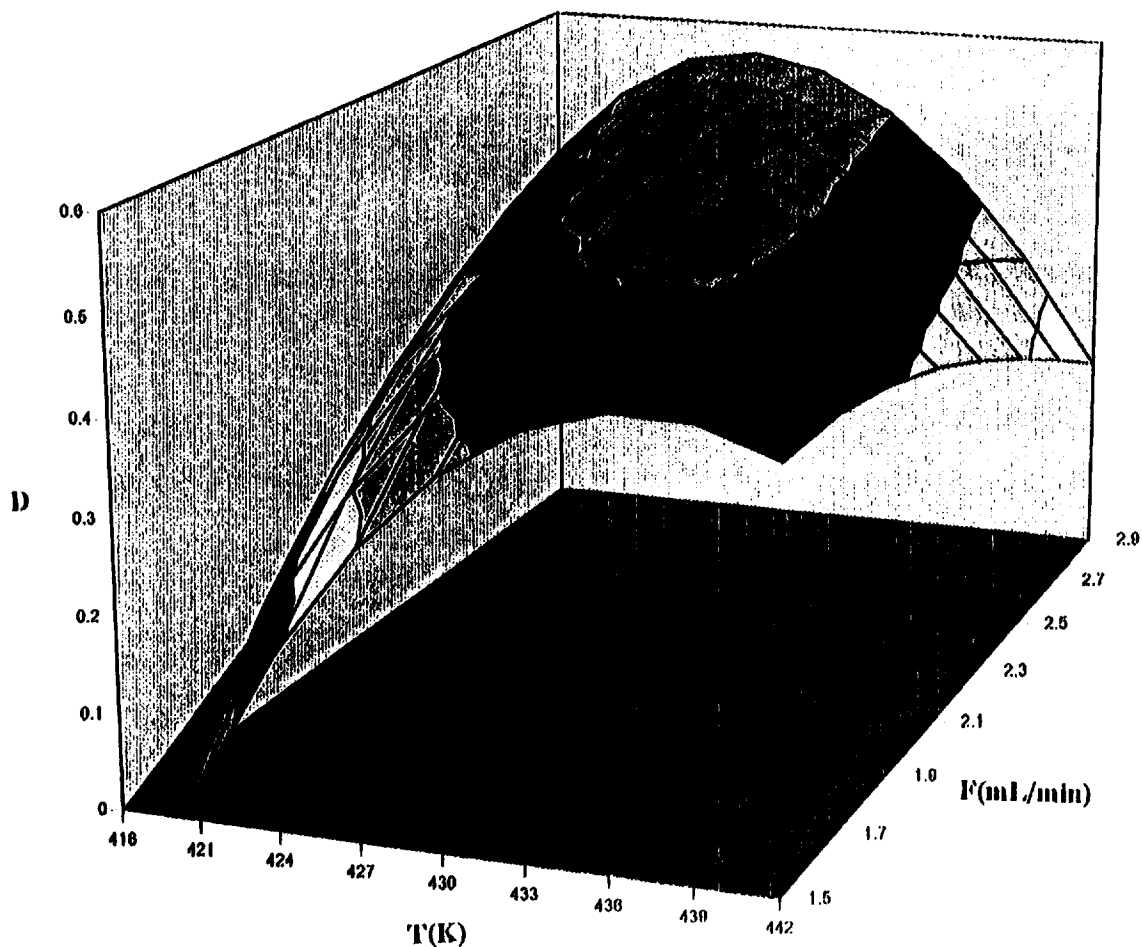

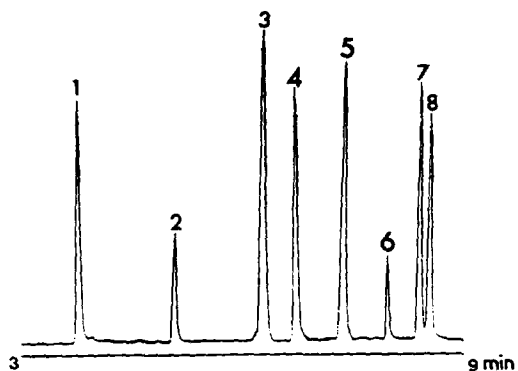Fig. 2. Response surface for D vs. T and F.

Fig. 3. Chromatogram of *p*-hydroxybenzoic esters obtained with optimum conditions of carrier gas flow-rate 2.90 ml/min and column temperature 427 K.

could be of interest to industrial processes and control engineers as it both reduces the analysis time and improves separation.

Acknowledgements

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