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Quantitative comparison of performance of isothermal and temperature-programmed gas chromatography

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Abstract

As a basic metric of separation for comparing isothermal and temperature-programmed GC (gas chromatography), we used the *separation measure*, *S* (defined elsewhere). We used this metric as both a measure of *separation* of any two peaks, and a measure of *separation capacity* of arbitrary intervals where peaks can potentially exist. We derived several formulae for calculation of *S* for any pair of peaks regardless of their shape and the distance from each other in isothermal and temperature-programmed GC. The formulae for isothermal GC can be viewed as generalizations of previously known expressions while, in the case of temperature-programmed GC, no equivalents for the new formulae were previously known from the literature. In all formulae for *S*, we identified similar key component-metrics (solute *separability*, *intrinsic efficiency* of separation, *specific separation measure*, *separation power*) that helped us to identify and better understand the key factors affecting the separation process. These metrics also facilitated the quantitative comparison of separation capacities and analysis times in isothermal and temperature-programmed GC. Some of these metrics can be useful beyond GC. In the case of GC, we have shown that, if the same complex mixture was analyzed by the same column, and the same separation requirements were used then isothermal analysis can separate more peaks than its temperature-programmed counterpart can. Unfortunately, this advantage comes at the cost of prohibitively longer isothermal analysis time. The latter is a well know fact. Here, however, we provided a quantitative comparison. In a specific example, we have shown that a single-ramp temperature program with a typical heating rate yields about 25% fewer peaks than the number of peaks available from isothermal analysis of the same mixture using the same column. However, that isothermal analysis would last 1000 times longer than its temperature-programmed counterpart. Using twice as longer column in the case of a temperature-programmed analysis, allows one to recover the 25% disadvantage in the number of separated peaks, while still retaining a 500-fold advantage in the speed of analysis.

Keywords: Gas chromatography; Separation measure; Separation power; Separability; Specific separation

1. Introduction

This study is a part of our continuing effort to find a theoretical solution to the problem of *optimal heating rate*, $R_{T,opt}$, in a temperature-programmed gas chromatography (GC). In a recent study [1] we formulated several criteria for the optimization, and experimentally found that, for the majority of typical cases, $R_{T,opt}$ lies somewhere around 10°C per void time. This result was in an agreement with the previously reported empirical findings [2–4]. We also

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found [1] that $R_{T,opt}$ increases by about a factor of 2 compared to its typical value when the column pressure drop, $p_{inlet}-p_{outlet}$, is low ($|p_{inlet}-p_{outlet}| \ll p_{outlet}$). On the other hand, $R_{T,opt}$ is about two times lower than its typical value if a method requires the maximum column pressure available in a given GC instrument.

In our view, a key step in search for a theoretical solution to the problem of optimum heating rate, is to find the metrics that allow quantitative comparison of separation-speed tradeoffs under different conditions in general, and as a function of heating rate in particular. An isothermal analysis can be viewed as a temperature-programmed one with zero heating rate, and, therefore, quantitative comparison of these techniques can be used as a test case of utility of these metrics.

It is well known [2,5–10] that temperature programming allows to greatly reduce the analysis time of a complex mixture compared to that available in an isothermal analysis. However, a rigorous quantitative evaluation of this difference as well as the difference in separation potential of these techniques is not known from the literature. Closing that void, as a step toward a theoretical solution of optimum heating rate in GC, is the main goal for this study.

Following are the highlights of the approach adopted in this study.

Let σ be (possibly, time-dependent) *standard deviation* [12] of a peak. All quantitative evaluations in this study are based on the metric known as the *separation measure* [11]:

$$S = \int_{t_a}^{t_b} dt/\sigma \tag{1}$$

that represents a number of all non-overlapping σ-wide subintervals (briefly, *σ-intervals*) within an arbitrary time interval (t_a, t_b) occupying a part or all of a chromatogram. Metric S incorporates some useful properties of *resolution* [13,14], R_s, *separation number* or *Trennzahl* [14–16], SN, and peak capacity [10,17–20], n, while providing a single measure (a number of σ-intervals) for both the separation of two peaks regardless of their shape and the distance between them, and the *separation capacities* of arbitrary intervals where peaks can potentially be present.

While the separation of a pair of peaks and the separation capacity of a time interval can be measured by the same metric, S, they change differently when method conditions change. For example, a change in method conditions might have different effects on specific solutes. As a result, this can cause a disproportional change in the peak separation or even a reversal of the elution order of some solutes. Because it greatly depends on the individual properties of the solutes, the separation of specific peaks is not suitable for the description of general separation potential of a column. That potential is better described by separation capacity, which only specifies the number of σ-intervals (reflective of the number of evenly separated peaks) in a designated interval while ignoring the possibility of the movement of the peaks relative to each other.

While the focus of this study is on GC, we maintain a general approach that can be used with other separation techniques, until the point where it becomes necessary to introduce concepts specific to temperature-programmed GC. In the general case, we use the following generic terms [21]. A separation process is *static* if (as in isothermal GC, isocratic LC) its parameters remain constant during the analysis time. Otherwise (as in temperature-programmed GC, gradient LC), the process is *dynamic*. A chromatographic medium is *uniform* if (as in GC with low column pressure drop where compressibility of the carrier gas can be ignored), at any time, its properties are the same for all locations along the migration path of the solutes. Otherwise (as in high pressure drop GC, gradient LC), the medium is *non-uniform*.

We also use several ways to express the relationship between the velocity of migration of a solute and that of the mobile phase. In addition to *retention factor* [14], k, (the ratio of the amount of the solute in the *stationary phase* to that in the *mobile phase*), we use the solute mobility factor [4,5,7,9,10,14,22,23], μ, (see Refs. [4,23] for the comments on terminology), and the solute interaction level [23], λ. The latter two are the fractions (with respect to the total) of the amount of the solute in the mobile and in the stationary phase, respectively. Quantities, k, λ and μ, relate as [23]:

$$\mu = \frac{1}{1+k} = 1-\lambda, \quad \lambda = \frac{k}{1+k} = 1-\mu,$$
$$k = \frac{\lambda}{1-\lambda} = \frac{1-\mu}{\mu} \tag{2}$$

We also use a *dimensionless heating rate* defined as [24]:

$$r = R_T t_M / \theta_{char} \quad (3)$$

where R_T is actual *heating rate* (in units of temperature/time), t_M is void time [14], and θ_{char} is *characteristic thermal constant* of a solute ($\theta_{char} = -dT/dk$ at $k=1$) – a quantity that is inverse of the slope in k vs. $-T$ function at $k=1$ [24].

The mathematics involved in the detailed analysis of a temperature-programmed GC are complex [2,5]. The known results are approximate and depend on many minor details that obscure the main picture. Our major goal is to compare a general separation potential of isothermal and temperature-programmed GC rather than to evaluate specific details affecting the separation of particular peak pairs. To simplify the comparison, we concentrate only on the main picture while ignoring minor details. In order to do so, we make several idealizing assumptions listed below.

It is known that, even in static separation, a column *plate number*, N, can be different for different solutes. However, the changes are typically not significant [5], allowing one to treat N as being the same for all solutes.

Assumption 1a. In a static separation, plate number, N, remains the same for all solutes.

Habgood and Harris expanded the concept of the plate number, N, to a temperature-programmed analysis [5,6] (see also Appendix A). It is known from experimental data and from theoretical studies that, in a typical temperature-programmed analysis, N remains nearly the same for all solutes including those eluting during the heating ramps [5,6,25,26].

Assumption 1b. In a temperature-programmed analysis, plate number, N, remains the same for all solutes.

Generally, a solute can have lower or higher characteristic thermal constant, θ_{char}, compared to its predecessors eluting at a lower temperature, T [24,27]. An arbitrary difference between the θ_{char} values of the close elutants can cause an unpredictable reversal in their elution order if heating rate or other method parameters are changed. As we mentioned earlier, a possibility of the reversal of the elution order, and, hence, non-monotonic dependence of θ_{char} on T is out of the scope of this study.

Assumption 2. Characteristic thermal constants, θ_{char}, of the solutes monotonically depend on their elution temperatures.

Finally, in a recently developed theoretical analysis [23] confirmed by a computer simulation [24] we quantitatively described a well known experimental fact that all solutes that were substantially retained at the start of a long linear heating ramp, elute with roughly the same mobility factor, μ_e, that can be found as:

$$\mu_e = 1 - e^{-r} \quad (4)$$

where r is dimensionless heating rate described in Eq. (3). We have also shown [23] that, in a specially designed balanced single-ramp temperature program:

$$T = \begin{cases} T_{init}, & \text{when} \quad t \le t_{po} \\ T_{init} + (t - t_{po})R_T, & \text{when} \quad t > t_{po} \end{cases} \quad (5)$$

$$t_{po} = t_M/(1 - e^{-r}) \quad (6)$$

where T_{init} is initial temperature, t is time, and t_{po} is duration of isothermal temperature plateau preceding the ramp, *all* solutes, eluting during the ramp, elute with nearly the same mobility factors close to μ_e, Eq. (4).

Assumption 3. During a linear heating ramp, all solutes elute with the same mobility factors.

2. Theory

2.1. Thermodynamics of solute interaction with the column

In linear (non-overloaded) chromatography, retention factor, k, of an arbitrary solute can be expressed [2,5,10] as:

$$k = k_o \exp(G/(\mathcal{R}T)), \quad \text{or}$$
$$\ln k = \ln k_o + G/(\mathcal{R}T) \quad (7)$$

where k_o is retention factor of some a priori chosen

reference solute, $\mathcal{R} \approx 8.3144$ J/K/mol is *universal gas constant*, T is temperature, and G is an increment (relative to the reference solute) in *Gibbs free energy* of desorption of a given solute from a stationary phase. Quantity

$$g = G/(\mathcal{R}T) \tag{8}$$

is a convenient *dimensionless* measure of G. It allows to simplify Eq. (7) as:

$$\ln k = \ln k_o + g \tag{9}$$

Due to Eq. (2), one can also write:

$$\lambda = \frac{\lambda_o}{\lambda_o + (1-\lambda_o)\,e^{-g}},$$
$$\mu = \frac{\mu_o}{\mu_o + (1-\mu_o)\,e^{g}} \tag{10}$$

where $\lambda_o = k_o/(1+k_o)$, and $\mu_o = 1/(1+k_o)$.

It is somewhat unfortunate from a mathematical point of view (although it makes thermodynamic sense) that an unretained solute having $k_o = 0$ can not be chosen as a reference one because $\ln k_o$ in Eq. (9) approaches negative infinity when k_o approaches 0. In all subsequent examples of this study, we use as a reference another convenient alternative, $k_o = 1$, that leads to $\lambda_o = \mu_o = 0.5$.

2.2. Separability of two solutes

In order for two solutes to be separated in chromatography, there must exist a difference between their interaction with the column. This difference, measured at predetermined conditions for all solutes provides a convenient basis for comparison of performance of different chromatographic techniques (GC, LC, etc.) or different modes of the same technique (isothermal GC, temperature-programmed GC, etc.). In the latter case, we will assume that not only the dimensionless Gibbs free energies, g, in Eq. (9) are measured at the same conditions (the same temperature of a given column in GC, the same column and the same composition of mobile phase in LC, etc.), but also the same reference solute was used to supply the k_o values in all cases. It follows from Eq. (9) that, under these assumptions, k_o in Eq. (9) is a fixed quantity, and the difference between retention factors of two solutes, say ''a'' and ''b'', is a function of only the difference:

$$\Delta g = g_b - g_a \tag{11}$$

between their dimensionless Gibbs free energies, g_a and g_b. Because, within the scope of our study, Δg in Eq. (11) can be viewed as the root cause for the separation of two solutes, we will refer to it as the *separability* of the solutes. Quantity Δg ranges from zero for chemically identical (non-separable by a given column) solutes to about 10 (see Example 1) for a wide temperature range in a temperature-programmed GC.

In the forthcoming comparative study of performance of isothermal and temperature-programmed GC, we will compare these operational modes with regard to ***the same separability*** measured under ***the same conditions*** in both cases.

2.3. Peak separation in static chromatography

Let L and H be, respectively, the length and *apparent plate height* [28] of a column, and

$$N = L/H \tag{12}$$

be the column *plate number* [5,7,9,10]. In static chromatography, relationship between *standard deviation* [12], σ, of a peak and its *retention time*, t_R, can be expressed as [9,10]:

$$\sigma \approx t_R/\sqrt{N} \tag{13}$$

It is known [29–32] that, even in the most ideal static separation (uniform medium, infinitely sharp sample introduction, etc.) there is a slight difference between σ and $t_R/\sqrt{N}$ where N is defined as in Eq. (12). However, the difference (on the order of $1/N$) is negligible for practical purposes. Following a widely accepted practice, we will ignore the difference in the rest of this study. A notation

$$\mathcal{P} = \sqrt{N} \tag{14}$$

allows one to simplify Eq. (13) as:

$$\sigma = t/\mathcal{P} \tag{15}$$

Quantity $\mathcal{P}$ in Eq. (14) plays an important role in chromatography. Peak resolution and peak capacity in static chromatography are either proportional or

nearly proportional to $\mathcal{P}$ [5,7,9,10,18]. As shown below, separation measure in static and dynamic chromatography is proportional to $\mathcal{P}$ as well. The interpretation of these and other important relations in chromatography becomes more transparent if $\mathcal{P}$ is used instead of $\sqrt{N}$. Doing so, we will refer to $\mathcal{P}$ in Eq. (14) as to the *separation power* of the column. Coupled with Assumption 1a, Eq. (14) implies that $\mathcal{P}$ in Eq. (15) is a fixed number. Substitution of Eq. (15) in Eq. (1) yields for the *separation measure*, S, of an arbitrary time interval, (t_b/t_a):

$$S = \mathcal{P} \ln(t_b/t_a) \tag{16}$$

This expression is somewhat similar to a formula for a peak capacity in static chromatography [18], and provides one of the simplest ways to find S in a static analysis when the separation power, $\mathcal{P}$, of the column, and the retention times, t_b and t_a, of the peaks are known. However, Eq. (16) does not trace the separation measure, S, down to the basic principles, and, hence, can not be used for the comparison of separation in static and dynamic chromatography.

2.4. Specific separation measure in static chromatography

An arbitrary retention time, t, in static chromatography can be expressed [10] as:

$$t = L/\bar{u}_s = L/(\mu\bar{u}) \tag{17}$$

where $\bar{u}_s$ and $\bar{u}$ are, respectively, average velocities of the solute and mobile phase. Substitution of $t_a = L/\bar{u}_{s,a} = L/(\mu_a\bar{u})$ and $t_b = L/\bar{u}_{s,b} = L/(\mu_b\bar{u})$ in Eq. (16), yields:

$$S = \mathcal{P} \ln(\bar{u}_{s,a}/\bar{u}_{s,b}) = \mathcal{P} \ln(\mu_a/\mu_b) \tag{18}$$

A notation

$$\Delta s = \ln(\mu_a/\mu_b) \tag{19}$$

allows one to express Eq. (18) as

$$S = \mathcal{P}\Delta s \tag{20}$$

Eq. (18) suggests that, in static chromatography using a column with a given separation power, $\mathcal{P}$, the separation, S, of two solutes is a function of the difference between velocities, $\bar{u}_{s,a}$ and $\bar{u}_{s,b}$, of migration of the solutes along the column. This difference can be reduced to the difference between the mobility, μ_a and μ_b, of the solutes. According to Eq. (20), the effect of that difference on solute separation is proportional to the quantity Δs in Eq. (19). Because, according to Eq. (20), Δs can be viewed as the separation per unit of column separation power, $\mathcal{P}$, we will refer to Δs as to *specific separation* of two solutes. In other cases, when S is separation capacity of an arbitrary interval (not necessarily bound by two peaks), we will refer to Δs as to *specific separation capacity* of the interval. In both cases, we will also use for Δs a generic term, *specific separation measure*. Comparison of Eqs. (16) and (20) suggests that Δs can also be expressed as:

$$\Delta s = \ln(t_b/t_a) \tag{21}$$

While the separation, S, of two solutes can be expressed as a product, Eq. (20), of the specific separation, Δs, of the solutes and separation power, $\mathcal{P}$, of the column, neither is the cause of the separation. The latter can be traced to the separability, Δg, Eq. (11), of the solutes. Due to Eq. (2), one can write Eq. (19) as:

$$\Delta s = \ln(1 + (\alpha - 1)\lambda_a) \tag{22}$$

where parameter

$$\alpha = k_b/k_a \tag{23}$$

is known as *selectivity*, *relative retention*, and *separation factor* [9,14], of two solutes. Due to Eq. (9), α can be also expressed as:

$$\alpha = e^{\Delta g} \tag{24}$$

allowing one to write Eq. (22) as:

$$\Delta s = \ln(1 + (e^{\Delta g} - 1)\lambda_a) \tag{25}$$

where λ_a is interaction level of one of the solutes. Combining Eq. (20) with Eqs. (22) and (25), one can also write:

$$S = \mathcal{P} \ln(1 + (\alpha - 1)\lambda_a) = \mathcal{P} \ln(1 + (e^{\Delta g} - 1)\lambda_a) \tag{26}$$

One can view Eqs. (25) and (26) as expressions of specific separation, Δs, and separation measure, S, of an arbitrary solute and a given solute ''a''. These quantities are expressed via the interaction level, λ_a, of solute ''a'' and separability, Δg, of an arbitrary

solute and the solute ''a''. Both Δg and λ_a are basic properties of the solutes. In a special case of low separability of two solutes ($|\Delta g| \ll 1$), Eq. (26) becomes:

$$S = \mathcal{P}\lambda\Delta g, \text{ when } |\Delta g| \ll 1 \tag{27}$$

2.5. Intrinsic efficiency

Eqs. (25) and (20) show how a column transforms separability, Δg, of two solutes into their specific separation, Δs, and eventually – into their separation, S. A rate

$$E = \frac{\mathrm{d}s}{\mathrm{d}g} = \lim_{\Delta g \to 0} \frac{\Delta s}{\Delta g} \tag{28}$$

of transforming of small increments in Δg into small increments in Δs shows how efficient this transformation is. We will refer to E as to *intrinsic efficiency* of separation of the solutes. It follows directly from Eqs. (25) and (28) that

$$E = \lambda \tag{29}$$

As λ changes from 0 for an unretained peak to nearly 1 for the late elutants, Eq. (29) indicates that

in static chromatography, intrinsic efficiency, E, in the vicinity of a given solute is equal to interaction level, λ, of the solute, and changes from nearly zero for the early elutants to nearly unity for the later ones.

Due to Eq. (10), the intrinsic efficiency, E, Eq. (29), of separation of an arbitrary solute with a known separability, Δg, relative to a given solute ''a'' can be expressed as:

$$E(\lambda_a, \Delta g) = \frac{\lambda_a}{\lambda_a + (1 - \lambda_a)\, e^{-\Delta g}} \tag{30}$$

When, in Eqs. (25), (26) and (30), λ_a approaches unity (both solutes are well retained), these expressions converge to:

$$E = 1, \Delta s = \Delta g, \qquad S = \mathcal{P}\,\Delta g, \quad \text{well retained solutes} \tag{31}$$

Finally, Eq. (28) suggests that specific separation capacity, Δs, Eq. (25), of an interval (t_a, t_b) can be expressed as:

$$\Delta s = \int_{g_a}^{g_b} E\,\mathrm{d}g = \int_0^{\Delta g} E(\lambda_a, g)\,\mathrm{d}g \tag{32}$$

or, due to Eq. (29), as:

$$\Delta s = \int_{g_a}^{g_b} \lambda\,\mathrm{d}g \tag{33}$$

It can be verified by direct integration that, indeed, these integrals lead to Eq. (25).

2.6. Separation in dynamic chromatography

In dynamic chromatography, the standard deviation, σ, of a peak can be found as [5,6] (see also Appendix A):

$$\sigma = t_{R,I}/\mathcal{P} \tag{34}$$

where $\mathcal{P}$ is separation power defined in Eq. (14), $t_{R,\,I}$ is elution time of the solute in a ***static*** analysis conducted under conditions existing at the actual time, t_R, of elution of the same solute in the actual ***dynamic*** analysis. Obviously, for an isothermal analysis, Eq. (34) becomes Eq. (14).

Quantity $t_{R,I}$ in Eq. (34) can be expressed as:

$$t_{R,I} = t_M/\mu_e \tag{35}$$

where μ_e is (actual) solute mobility at the actual time, t_R, of its elution from the column, and t_M is void time measured under ***static*** conditions existing at t_R in the (actual) ***dynamic*** analysis. Substitution of Eq. (35) in Eq. (34) yields:

$$\sigma = t_M/(\mu_e\mathcal{P}) \tag{36}$$

This allows one to express the separation measure, S, Eq. (1), in dynamic chromatography as:

$$S = \int_{t_a}^{t_b} \frac{\mu_e\mathcal{P}}{t_M}\,\mathrm{d}t \tag{37}$$

When, in dynamic chromatography, quantity $\mu_e\mathcal{P}/t_M$ does not change with time, Eq. (37) becomes $S = (\mu_e\mathcal{P}/t_M)(t_b - t_a)$.

2.7. Separation in temperature-programmed GC

Temperature-programmed GC is a special case of dynamic chromatography. It follows from Assumption 1b and Eq. (14) that separation power, $\mathcal{P}$, in temperature-programmed GC is the same for all peaks. This allows us to write Eq. (37) as Eq. (20) where, in the case of temperature-programmed GC,

$$\Delta s = \int_{t_a}^{t_b} \frac{\mu_e}{t_M} dt \tag{38}$$

To solve the integral in Eq. (38), we notice that, when Assumption 3 is in effect, μ_e is a fixed number that, according to Eq. (4), depends only on dimensionless heating rate, r, Eq. (3). On the other hand, due to the temperature-dependence of gas viscosity, t_M depends on T. For helium, hydrogen and nitrogen, this dependence can be approximately expressed as [4,33,34] $t_M = t_{M,a}(T/T_a)^{1-\xi}$ where, $t_{M,a}$ is void time at the elution temperature, T_a, of peak ''a'', and $\xi \approx 0.3$. Taking these facts into account, replacing t with T as $dt = dT/R_T$, where R_T is heating rate, and utilizing Eq. (3) in the form $r = R_T t_{M,a}/\theta_{char,a}$ where $\theta_{char,a}$ is characteristic thermal constant [24] of solute ''a'', transforms Eq. (38) into:

$$\Delta s = \frac{1 - e^{-r}}{r\theta_{char,a}} \cdot \int_{T_a}^{T_b} (T/T_a)^{\xi - 1}\, dT \tag{39}$$

This, after the integration and the substitution in Eq. (20), yields:

$$S = \phi \mathcal{P} \mu_e \cdot \frac{T_b - T_a}{\theta_a} = \phi \mathcal{P} \cdot \frac{1 - e^{-r}}{r} \cdot \frac{T_b - T_a}{\theta_a} \tag{40}$$

where

$$\phi = \frac{(T_b/T_a)^{\xi} - 1}{(T_b/T_a - 1)\xi}, \quad \xi \approx 0.3 \tag{41}$$

is a factor, Fig. 1, gradually decreasing from 1 for closely eluting peaks to around 0.75 for wide temperature ranges.

Eq. (40), while allowing one to find S from easily measurable elution temperatures, T_b and T_a, of two peaks (assuming that r, θ_a and $\mathcal{P}$ are known parameters), does not express the dependence of S on the basic parameters affecting the separation, and, hence, does not facilitate the comparison of S in isothermal and temperature-programmed GC (see similar comment after Eq. (16)). To make that comparison possible, we, similarly to the isothermal case of Eqs. (25) and (26), express Δs and S via the separability, Δg, of the solutes at ***the same temperature***).

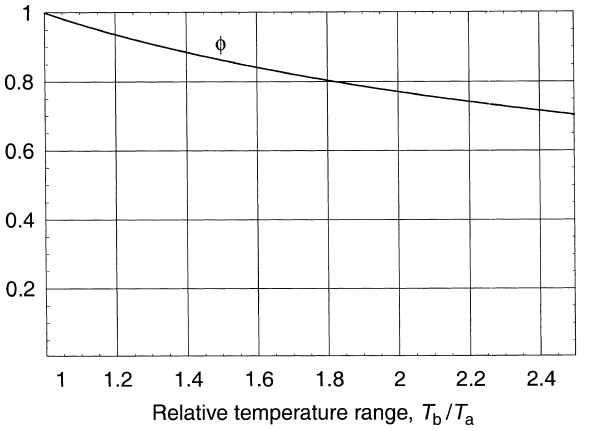

Fig. 1. Factor, ϕ, Eq. (41). If the difference, $T_b - T_a$, between elution temperatures of two peaks is relatively small ($|T_b/T_a - 1| \ll 1$) then $\phi \approx 1$ indicating that S in Eq. (40) is nearly proportional to $T_b - T_a$. However, the increase in S with the increase in $T_b - T_a$ is slightly slower than proportional because ϕ gradually declines with the increase in $T_b - T_a$. For example, $\phi \approx 0.77$ when $T_a = 300$ K, $T_b = 600$ K. In this case, S reaches only 77% of the level where it would have been if it was proportional to $T_b - T_a$.

It can be shown (see Appendix B) that, due to Assumption 2 and Assumption 3, Eqs. (38) and (20) can be expressed as:

$$\Delta s = E\Delta g, S = \mathcal{P}\Delta s = \mathcal{P}E\Delta g \tag{42}$$

$$E = \frac{\mu_e}{r} = \frac{1 - e^{-r}}{r} \tag{43}$$

The dependence of E on a dimensionless heating rate, r, is shown in Fig. 2. Combining Eqs. (42) and (43), one has:

$$\Delta s = \frac{1 - e^{-r}}{r} \cdot \Delta g, \quad S = \frac{1 - e^{-r}}{r} \cdot \mathcal{P}\Delta g \tag{44}$$

It can be also shown (see Appendix B) that:

$$\frac{dg}{dT} = \frac{1}{\theta_{char}} \tag{45}$$

$$S = \mathcal{P} \cdot \frac{1 - e^{-r}}{r} \cdot \int_{T_a}^{T_b} \frac{dT}{\theta_{char}} \tag{46}$$

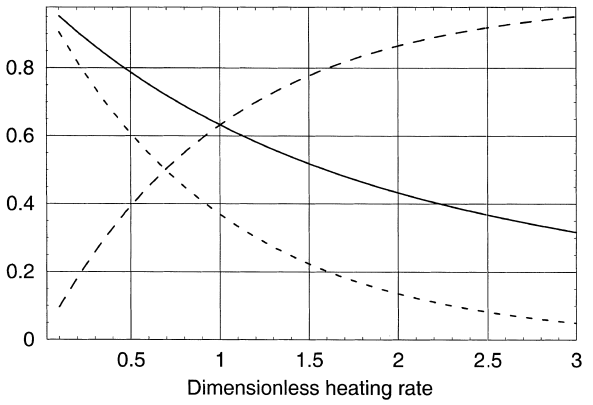

Fig. 2. Intrinsic efficiency, E, Eq. (43), (———) vs. dimensionless heating rate, r, Eq. (3), in a temperature program described in Eqs. (5) and (6). Shown for comparison are interaction levels, $\lambda_e = e^{-r}$ [23] (- - -), and mobility factors, $\mu_e = 1 - \lambda_e$, Eq. (4), (– – –) of the solutes eluting during the same ramp.

where dg/dT is the rate of growth of separability of the eluting solutes from the reference solute. Eqs. (45) and (46) show that,

during a linear heating ramp, each θ_{char}-wide temperature span corresponds to $\Delta g = 1$

Example 1. Consider a case where $\mathcal{P} = 300$ (i.e. $N = 90\,000$ as in, e.g., a 10 m × 100 μ column), $r = 0.5$, $\theta_{char} = 30°C$. Let also $S_{min} = 6$ be the lowest acceptable separation. It follows from Eq. (43) that $E \approx 0.8$. Furthermore, according to Eqs. (42) and (45), each 30°C temperature span corresponds to separability $\Delta g = 1$, which, due to $E \approx 0.8$, yields specific separation capacity $\Delta s \approx 0.8$ and separation capacity $S = \mathcal{P}\Delta s \approx 300 \times 0.8 = 240$. This separation capacity provides a peak capacity [11] $n = S/S_{min} \approx 240/6 = 40$ peaks (realistically though, no more than about $40/e \approx 15$ peaks can be randomly distributed within this space [10,11,35]). A 300°C wide temperature span corresponds to $\Delta g = 300°C/\theta_{char} = 10$ that yields $\Delta s \approx 8$, has separation capacity $S \approx 2400$, and provides the space for up to $n \approx 2400/6 = 400$ nominally separated peaks, although, as before, no more than about $400/e \approx 150$ peaks can be randomly distributed within this space. □

When r approaches 0 (very low heating rate), Eqs. (42)–(44) converge to:

$$E = 1,\ \Delta s = \Delta g,\ S = \mathcal{P}\Delta g,\ \text{low heating rate} \qquad (47)$$

implying that an isothermal analysis can be viewed as a temperature-programmed one that has zero heating rate.

3. Discussion

In the theoretical section, we derived several formulae for calculation of the *separation measure* [11], S, in isothermal and temperature-programmed GC. As shown elsewhere [11], S is a number of σ-wide intervals (briefly, *σ-intervals*) between two designated points, t_a and t_b, on the time axis, and can be used as a measure of *separation* of two peaks having retention times t_a and t_b, as well as a measure of *separation capacity* of an arbitrary time interval (t_a, t_b) regardless of the presence of peaks at t_a and/or t_b. As a measure of separation capacity, S relates to the *peak capacity* [10,11,17,35,36], n, of the same interval as $n = S/S_{min}$ where S_{min} is the lowest acceptable separation of two neighboring peaks [11]. The latter relation makes S a convenient metric for the evaluation of a separation performance of a column in different operational modes such as isothermal and temperature-programmed GC.

3.1. Parameters affecting the separation

To better expose the meaning of the newly derived expressions for S, and to facilitate the comparison of the separation performance of isothermal and temperature-programmed GC, we identified several component-metrics the formulae for S. In order to do so, we transformed in the formulae for S to the form $S = \mathcal{P}\Delta s$, Eq. (20), where, Eq. (32), $\Delta s = \int_0^{\Delta g} E\,dg$. The latter, when E is a fixed number (see below), becomes $\Delta s = E\Delta g$. A block-diagram, Fig. 3, of a column as an information processing device highlights the meaning and the interaction of these metrics. These were briefly outlined along with the introduction of each metric in the theoretical section. Here we provide more useful details.

Among other useful features of S is its direct

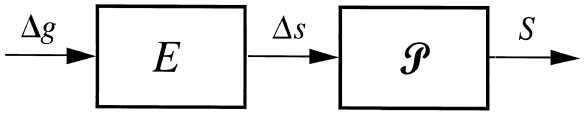

Fig. 3. Block-diagram of a column as an information processing device that transforms the separability of the solutes, Δg, (input information) into the separation, S, of the corresponding peaks. The first stage of the device transforms Δg into specific separation, $\Delta s = S/\mathcal{P}$, where $\mathcal{P} = \sqrt{N}$ is the separation power of the column. The efficiency of that transformation is E. The second stage transforms Δs into the separation, S. The separation power, $\mathcal{P}$, can be viewed as the gain of the second stage.

connection with a simple interpretation of the column *separation power*, $\mathcal{P} = \sqrt{N}$, Eq. (14), where N is the column *plate number*. Quantity $\mathcal{P}$ has a more straightforward interpretation that N. In isothermal GC, $\mathcal{P}$ is the increment in S for each e-fold increment ($e \approx 2.72$ is base of natural logarithm) in the analysis time. This means that, during an isothermal analysis, for any time, t, after the void time, t_M, there always are $\mathcal{P}$ σ-intervals between t and et. During a slow heating ramp ($|r| \ll 1$ where r is dimensionless heating rate, Eq. (3)) in a temperature-programmed analysis, $\mathcal{P}$ is the increment in S per each θ_{char}-wide temperature span where θ_{char} (typically, 30–50°C) is *characteristic thermal constant* [24,27] of the solutes in a given column. For example (see also Example 1), if $\theta_{char} = 30$°C then, during a slow heating ramp, S increases by $\mathcal{P}$ for each 30°C increment in the column temperature. These and other interpretations of $\mathcal{P}$ (see below) allow to view it as a *gain factor*, Fig. 3, in the process of solute separation, and, because the difference between its values in isothermal and temperature program GC is typically insignificant [5] (see also Appendix A), one can exclude $\mathcal{P}$ from the studies where isothermal and temperature-programmed GC is compared, and deal with *specific separation* $\Delta s = \mathcal{P}/S$, Eq. (20), Fig. 3, that is independent of column dimensions.

Generally, Δs can be found, Eq. (32), as $\Delta s = \int_0^{\Delta g} E\,dg$ where Δg is *separability* of two solutes, and E is *intrinsic efficiency* of the column, Fig. 3.

The separability, Δg, of two solutes is the difference, Eq. (11), between dimensionless Gibbs free energies, Eq. (8), of the solute desorption from stationary phase. We treat Δg as a root cause for the solute separation in the column. In the block-diagram of Fig. 3, this is reflected in treating Δg as an input for the separation process.

The separability of two solutes, say, ''a'' and ''b'', relates to their *relative retention* [9,14], $\alpha = k_b/k_a$, (also known as *separation factor*, and *selectivity* [14]) as $\alpha = e^{\Delta g}$, Eq. (24). Because of one-to-one relation between Δg and α, these parameters represent two alternative ways of expressing the same thing – the difference in Gibbs free energies of two solutes. However, using Δg has several advantages over using α.

First, quantity Δg is logically closer than α to the first principles (while Δg is the difference between Gibbs free energies of two solutes, $\alpha = e^{\Delta g}$ is the exponent of that difference). Second, in many important cases, the separation of two peaks is proportional to Δg (i.e. to $\ln\alpha$). These include the case, Eqs. (27) and (31), of low separability ($|\Delta g| \ll 1$) and/or well retained ($k \gg 1$) solutes in isothermal GC, and all cases, Eq. (44), of separation during a linear heating rate in the temperature program described in Eqs. (5) and (6). Some of these cases also supply additional convenient interpretations for the separability, Δg, and separation power, $\mathcal{P}$. Thus, Eq. (31) for the separation, S, of well retained solutes in isothermal GC, and Eq. (47) for S in temperature-programmed GC with a slow heating ramp ($|r| \ll 1$) indicate that $\mathcal{P}$ is an increment in S per unity increment in Δg.

It is also worth mentioning that, a familiar expression [7]:

$$R_s \approx (\alpha - 1) \cdot \frac{k}{1+k} \cdot \frac{\sqrt{N}}{4}, \quad |\alpha - 1| \ll 1 \tag{48}$$

for the resolution, R_s, of *Gaussian* peaks in *isothermal* GC is valid *only* when $|\alpha - 1| \ll 1$. This implies $\alpha - 1 = e^{\Delta g} - 1 \approx \Delta g$, and one can write:

$$R_s \approx \frac{\sqrt{N}}{4} \cdot \frac{k}{1+k} \cdot \Delta g, \quad |\Delta g| \ll 1 \tag{49}$$

exposing a simpler and more straightforward proportional dependence of R_s on Δg compared to R_s being proportional to $\alpha - 1$, but not to α. In view of Eqs. (2), (14) and (27), one can further simplify the latter expression writing it as:

$$R_s \approx \frac{\mathcal{P}}{4} \cdot \lambda\, \Delta g = \frac{S}{4}, \quad |\Delta g| \ll 1. \tag{50}$$

which is in line with the previously established relations $R_s = S/4$ for Gaussian peaks of not very different width [11].

Returning to block-diagram in Fig. 3, we notice that three parameters – the separability, Δg, of the solutes, the intrinsic efficiency, E, of separation, and the separation power, $\mathcal{P}$, of the column – affect the separation. We already discussed the roles of the last and the first of these parameters. The intrinsic efficiency, E, Eq. (28), of separation is the rate of transforming the separability, Δg, of two solutes into their specific separation, Δs. This means that, specific separation, Δs, (and, eventually, the separation, S) of the same solutes by two different methods utilizing the same column boils down to the difference in intrinsic efficiencies in these methods. In isothermal GC, E, according to Eq. (29), is equal to the interaction levels, λ, of the solutes, and, hence, gradually increases, Fig. 4a, from 0 for unretained solutes to 1 for the highly retained solutes. During a linear heating ramp, E, after some transition, Fig. 4a, converges to the level $E = (1 - e^{-r})/r$, Eq. (43), that depends only on dimensionless heating rate, r, Eq. (3). Previously [1] we established that, for the best speed/resolution tradeoff in the most typical cases, r is about 0.4. In this case, Eq. (43) leads to $E \approx 0.8$.

3.2. Isothermal and temperature-programmed GC

To compare isothermal and temperature-programmed GC, we used a single-ramp temperature program, Eqs. (5) and (6), that starts at the same initial temperature, T_{init}, as the temperature in its isothermal counterpart. The ramp is preceded by the t_{po}-long temperature plateau. The intrinsic efficiency, E, of the separation during this plateau is the same as that in the isothermal analysis, Fig. 4a. The duration, t_{po}, or the plateau depends, Eq. (6), on the heating rate in the following ramp. In all cases, the plateau lasts until the elution of the solute whose isothermal interaction level, λ, is the same as the stable interaction level, $\lambda_e = e^{-r}$, for the ramp. This reduces the duration and the degree of the transitional departure of E, from its stable level $E = (1 - e^{-r})/r$, Fig. 4a.

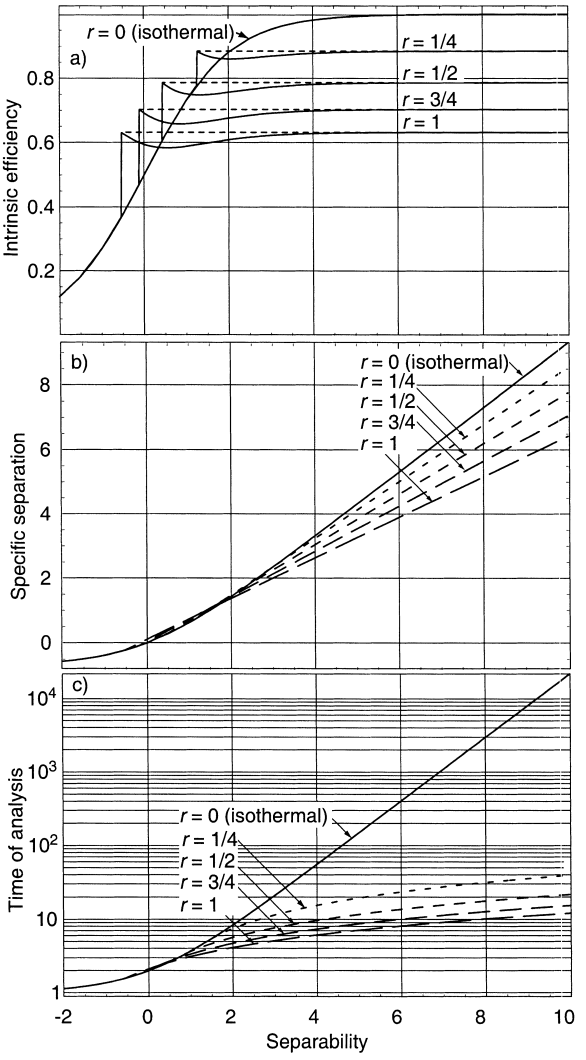

Fig. 4. Intrinsic efficiency, E, the net specific separation (from the unretained solute), Δs, and dimensionless analysis time, t/t_M vs. separability, Δg, in a temperature program, Eqs. (5) and (6), with different dimensionless heating rates, r, and in isothermal analysis at $T = T_{init}$. Quantity Δg is counted from the solute that, in the isothermal analysis, elutes with $t = 2t_M$ (i.e. $\Delta g = 0$ corresponds to $t = 2t_M$, and, also, to $k = 1$ and $\lambda = \mu = 0.5$, see comments to Eq. (9)). In (a), solid lines (———) result from computer simulation [40] of E based on numerical solution of elution integral [4] with k described in Eq. (B.1), dashed lines (– – –) represent flat E values, Eq. (43), used to generate the graphs in (b) and (c). Quantity Δs was calculated as $\Delta s = \ln 2 + \int_0^{\Delta g} E(0.5, g)\, dg$. The offset, ln2, added to Δs in Eq. (32), accounts for Δs, Eq. (21), of the solutes isothermally eluting at $t = 2t_M$ and at $t = t_M$. This addition allows to count the net Δs from $t = t_M$ while Δg is counted from $t = 2t_M$.

Previously (see Example 1) we have shown that a 10-unit wide range of Δg in Fig. 4 corresponds to a heating ramp covering about 300°C temperature range. The higher (compared to its temperature-programmed counterpart) intrinsic efficiency, E, of an isothermal analysis within this wide range of separability, Fig. 4a, leads to higher specific separation capacity, Fig. 4b, of the entire analysis of the same mixture. The difference depends, Fig. 2, on the heating rate. For the same column, this corresponds to proportionally higher separation capacity, and, hence, to proportionally larger number of equally separated peaks. In the final analysis, the slower the heating rate (up to the zero rate of an isothermal analysis) the higher the specific separation capacity, Δs, and, hence, the higher the separation capacity, S, and the larger the number of equally separated peaks can be achieved for the same range, Δg, of separability, and for the same separation power. In other words,

for the same column analyzing the same complex mixture, isothermal GC provides the highest separation capacity

Unfortunately, this is not the whole story. Fig. 4c shows that the time required to cover the same Δg in isothermal analysis could be several orders of magnitude longer than that in its temperature-programmed counterpart.

Example 2. According to Fig. 4c, it takes about 1000 times longer to isothermally elute the solutes with $\Delta g = 10$ range compared to that in respective temperature program with $r = 1/2$.

The speed advantage of temperature-programmed GC is so large that it provides ample room for the compensation of its disadvantage in separation capacity while still retaining a large advantage in the speed.

Example 3. Under the conditions of Example 2, Δs in the isothermal run is about 25% larger than that in its temperature-programmed counterpart. This, according to Eq. (20), corresponds to 25% larger separation capacity, S, for the same column. In order to attain a 25% increase in S for the temperature-programmed run and to reach the parity in S with the isothermal run, one could use a column with 25% greater separation power, $\mathcal{P}$. This could be achieved by using about 56% longer column ($1.25^2 \approx 1.56$) while keeping the same stationary phase type and thickness, the same carrier gas type and its flow-rate, and translating [4,37] the temperature program accordingly. This would lead to an increase in the analysis time. In a typical case, an x-fold increase in $\mathcal{P}$ using this scheme causes a x^3-fold increase in the analysis time [1,38,39]. Therefore a 25% increase in $\mathcal{P}$ for a temperature-programmed analysis would lead to almost a 2-fold increase in its analysis time ($1.25^3 \approx 1.96$). Nevertheless, the temperature-programmed analysis would still remain about 500 times shorter compared to its isothermal counterpart with the same S.

4. Conclusion

We derived several new formulae, Eqs. (16), (26), (40) and (44) and others, for the separation measure, S, in isothermal and temperature-programmed GC. The formulae for isothermal GC can be viewed as generalizations of previously known expressions for the resolution and the peak capacity while the formulae for temperature-programmed GC have no previously known equivalents. We also identified several key metrics describing specific aspects of the separation process. Among them were:

- *separation power*, $\mathcal{P} = \sqrt{N}$, of a column where N is the column plate number (typically, nearly the same in isothermal and temperature-programmed GC)
- *separability*, Δg, of two solutes – a measure of the solute thermodynamic difference in respect to a given column, and the root cause of their separation
- *specific separation measure*, $\Delta s = S/\mathcal{P}$ – a metric representing the separation measure per unit of separation power of the column
- *intrinsic efficiency*, E, of separation of two solutes – the rate of transformation of Δg into Δs

Using these metrics, we have shown that the difference in the separation capacity of isothermal

and temperature-programmed GC boils down to the difference in their intrinsic efficiencies, E. In the analysis of the same complex mixture, isothermal analysis has higher E for all highly retained solutes compared to E for the same solutes in the temperature-programmed analysis. We also found how E declines with the increase in the heating rate.

Unfortunately, the higher separation capacity of isothermal GC comes at the expense of its prohibitively longer analysis time. In a particular example, we have shown that, using the same column, the isothermal analysis can yield about 25% higher separation capacity than its temperature-programmed counterpart. However, this advantage comes at the expense of about 1000 times longer analysis time. Using a two times longer column in the temperature-programmed analysis, allows to compensate for its disadvantage in separation capacity while still retaining about 500 times shorter analysis time.

5. Nomenclature

Symbol	Description	Measured in units of
E	intrinsic efficiency	1
G	Gibbs free energy	energy/mole
g	dimensionless Gibbs free energy, Eq. (8)	1
Δg	separability, Eq. (11)	1
H	plate height	length
k	retention factor	1
L	column length	length
N	plate number, Eq. (12)	1
$\mathcal{P}$	separation power, Eq. (14)	1
r	dimensionless heating rate, Eq. (3)	1
R_s	resolution	1
R_T	heating rate	temperature/time
S	separation measure	1
Δs	specific separation measure, Eq. (20)	1
T	temperature	temperature
t	time	time
T_{char}	characteristic elution temperature	temperature
T_{init}	initial temperature of a heating ramp	temperature
t_M	void time	time
t_{po}	duration of matching temperature plateau, Eq. (6)	time
t_R	retention time	time
$t_{R,I}$	isothermally measured retention time in a temperature program	time
$\bar{u}$	gas velocity	length/time
$\bar{u}_s$	solute velocity	length/time
α	relative retention Eq. (23)	1
λ	interaction level, Eqs. (2)	1
μ	mobility factor, Eqs. (2)	1
θ_{char}	characteristic thermal constant	temperature
σ	standard deviation of a peak	time
ϕ	a factor, Eq. (41)	1

Subscript ''e'' indicates the value of a solute parameter at the time of its elution.

Appendix A

Plate number in a temperature-programmed GC

A concept of a plate number, N_T, in a temperature-programmed GC was introduced by Habgood and Harris [5,6] (term ''column efficiency'' was actually used). Unfortunately, we were unable to find more recent sources (except for our own [4]) where this concept was utilized. A brief description of the concept is provided below.

For a given solute in a temperature-programmed analysis, N_T can be measured in two steps.

1. The standard deviation, σ_T, of a peak corresponding to the solute in a ***temperature-programmed*** analysis is measure. Also recorded are all conditions (column temperature, T_T, inlet pressure $p_{i,T}$, etc.) existing at the time of the solute elution from the column.
2. The experiment is repeated ***isothermally*** under the previously recorded conditions ($T=T_T$, $p_i=$

$p_{i,T}$, etc.), and retention time, $t_{R,I}$, of the peak corresponding to the same solute is measure.

Quantity N_T is calculated as:

$$N_T = t_{R,I}^2/\sigma_T^2$$

One can also measure the isothermal, σ_I, standard deviation of the peak corresponding to the same solute and calculate a conventional isothermal plate number, N_I, as:

$$N_I = t_{R,I}^2/\sigma_I^2$$

Habgood and Harris have shown theoretically and experimentally that the difference between N_I and N_T is practically insignificant. Recently, we have also theoretically and experimentally shown that, in a pneumatically optimized column, N_T for all peaks eluting during a heating ramp should and actually is nearly the same [25,26].

Appendix B

Derivation of E vs. r

First, we derive the relationship between ΔT and Δg for two arbitrary solutes where Δg is separability of the solutes (the difference between their dimensionless Gibbs free energies measured at ***the same temperature***) and ΔT is the temperature difference necessary for these solute to elute with ***the same Gibbs free energy***.

In the vicinity of a solute elution temperature, its retention factor, k, as a function of temperature, T, can be expressed as [24]:

$$\ln k = (T_{char} - T)/\theta_{char} \tag{B.1}$$

where $\theta_{char} = -dT/dk$ at $k=1$ (inverse of the slope in k vs. $-T$ at $k=1$) is *characteristic thermal constant* of a solute, and T_{char} is its *characteristic elution temperature* (the temperature at which the solute elutes with $k=1$). Eq. (B.1) together with Assumption 2 indicates that, in the vicinity of their elution temperatures, the difference between two closely eluting solutes having the same characteristic thermal constant, θ_{char}, is completely described by the difference in their characteristic elution temperatures, T_{char}. Eq. (B.1) allows to express the difference in *retention factors*, k_a and k_b, of two solutes as:

$$\ln k_b - \ln k_a = \left[(T_{char,b} - T_b) - (T_{char,a} - T_a)\right]/\theta_{char} \tag{B.2}$$

Consider, first, a ***fixed temperature***, i.e. $T_b = T_a$. From Eqs. (9) and (B.2), one has for the separability, Δg, of the solutes:

$$\Delta g = \ln k_b - \ln k_a = (T_{char,b} - T_{char,a})/\theta_{char} \tag{B.3}$$

On the other hand, a ***fixed Gibbs free energy***, implies according to Eq. (9), that $\ln k_b = \ln k_a$. As a result, Eq. (B.2) yields for two different solutes:

$$\Delta T = T_b - T_a = T_{char,b} - T_{char,a} \tag{B.4}$$

Substitution of $T_{char,b} - T_{char,a}$ from Eq. (B.4) into Eq. (B.3) yields $\Delta T = \theta_{char}\Delta g$ or

$$dT/dg = \theta_{char} \tag{B.5}$$

Now we can derive an expression for the intrinsic efficiency E. Comparison of Eqs. (38) and (32) suggests that, during the heating ramp, quantity E in Eq. (32) can be expressed as:

$$E = \frac{\mu_e}{t_M} \cdot \frac{dt}{dg}, \tag{B.6}$$

where dt/dg is the inverse of a temporal rate of increase in separability of the solutes during the heating ramp. For the heating ramp with the rate R_T, dt can be expressed as $dt = dT/R_T$. Eq. (B.6) becomes:

$$E = \frac{\mu_e}{t_M R_T} \cdot \frac{dT}{dg} \tag{B.7}$$

and, due to Eq. (B.5), can be further rearranged as $E = \mu_e\theta_{char}/(t_M R_T)$ which, using dimensionless heating rate, Eq. (3), becomes:

$$E = \mu_e/r \tag{B.8}$$

It should be noted, that void time, t_M, in Eqs. (B.7) and (3) is measured at the elution temperature, T, of each particular solute. Because of the temperature dependence of gas viscosity [33,34], η, void time changes with T in proportion with η. On the

other hand, characteristic thermal constants, θ_{char}, of the solutes tend to increase with the increase in their elution temperature. This trend is also proportional to η [27]. As a result, the increases in t_M and in θ_{char} in Eq. (3) for r cancel out, and r in Eq. (B.8) remains constant for any linear (constant R_T) heating ramp.

Substitution of Eq. (4) in Eq. (B.8) yields Eq. (43) in the main text, and, because E remains constant during a linear heating ramp, Eq. (32) can be expressed as Eq. (42) in the main text. Also, combining Eqs. (B.5) and (B.6), one can write $(\mu_e/t_M)dt=(E/\theta_{char})dT$. For a fixed $\mathcal{P}$, this allows to rewrite Eq. (37) as Eq. (46) (main text).

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