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Pressure-regulating fluid interface and phase behavior considerations in the coupling of packed-column supercritical fluid chromatography with low-pressure detectors

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Abstract

Packed-column supercritical fluid chromatography is usually performed with flow control on the upstream side of the column and pressure control on the downstream side. This arrangement is compatible with detectors that can be operated at column-outlet pressure and placed between the column outlet and a pressure-regulating device. However, mass transfer problems may arise when low-pressure detectors like a mass spectrometer or evaporative-light-scattering detector are used with downstream pressure regulators or programmable nozzles. These problems can be avoided by replacing the regulator or nozzle with a tee delivering a pressure-regulating make-up fluid from a pressure-controlled pump. Parameters are chosen to avoid the liquid–vapor two-phase regions of the phase diagram for the resulting mixture. We demonstrate this approach and show how to use phase diagrams and their pressure–temperature projections for setting operating conditions.

Keywords: Detection, SFC; Pressure-regulating fluid interface

1. Introduction

Packed-column (pc) supercritical fluid chromatography (SFC) [1] instruments with gradient elution capability can perform not just SFC but a wide variety of chromatographic techniques [2]. These include enhanced-fluidity liquid chromatography [3], near- or subcritical fluid chromatography, and conventional liquid chromatography (LC). In fact, it is most accurate not to think of these as SFC instruments, but as instruments approaching the requirements of unified chromatography, working within the entire range of temperature, pressure, and mobile phase composition afforded by the phase behavior of the mobile phase fluid [2]. The additional features appearing on SFC instruments, and not included on conventional LC instruments, are simply the ability to pump a primary fluid as volatile as CO_2 without cavitation, control of the mobile phase pressure at the column outlet (beyond 40 MPa), and the control of the column temperature over a wide range (often −50–300°C or higher).

Packed-column SFC instruments, whether used for SFC or another of the related chromatographic techniques, are usually operated with downstream pressure control and upstream flow control (with respect to the column location). The mobile phase flow-rate, its composition, the column outlet pres-

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sure, and the column temperature are all independently programmable with this approach. Pressure regulation at the outlet allows control of the mobile-phase boiling temperature for all liquid mobile phases, and mobile-phase strength for compressible fluids. At the same time this combination of features also allows volumetric mixing of mobile-phase components at the inlet in a fashion identical with gradient elution in LC. The column-outlet pressure is controlled downstream from the column using a programmable back-pressure regulator, valve, or nozzle, in combination with a pressure transducer and electronic control. (We will use 'regulator' to represent back-pressure regulator, valve, and nozzle.) Peak retention times are highly reproducible because flow restrictors are not required for adjusting mobile phase velocities.

Detection in pcSFC and related techniques is frequently accomplished with UV–visible absorption. The detector is simply inserted in the flow path between the column outlet and the pressure regulator as in Fig. 1. The only significant modification required of a UV–visible LC detector for pcSFC use is the replacement of the cell with one capable of operating without damage at the column-outlet pressure.

A problem exists, however, when it is desired to interface a pcSFC instrument executing any of the pressurized-outlet chromatographic techniques with a low-pressure detector like a mass spectrometer (MS), an evaporative light scattering detector (ELSD), or nearly all of the commonly used gas chromatography detectors. Several reports have appeared in which

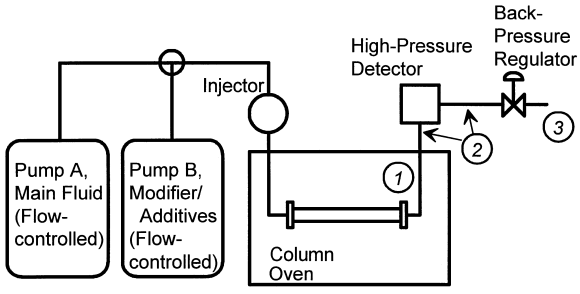

Fig. 1. Schematic diagram of the packed-column SFC configuration most often used when the detector can be operated at column-outlet pressure. The numbered locations have corresponding points on Fig. 4.

workers have simply connected the outlet of a pressure regulator to the inlet of a low-pressure detector, as in Fig. 2a [4–12]. This regulator-detector arrangement can lead to several problems. First, peak broadening may occur in the hardware between the column outlet and the detector inlet. Although mixing is not a problem in a well-designed system [10], the pressure in the transfer tube between the regulator and the detector is not controlled. The solvent strength of near-critical and especially supercritical fluids is highly pressure-dependent. Because the pressure in the transfer tube is reduced below the column-outlet value by the regulator, and because the temperature is also changed from the value at the column outlet, the mobile phase strength in the transfer tube is unknown, uncontrolled, and may be diminished for some solutes. There is no guarantee that solutes completely soluble in the mobile phase at the column outlet will still be soluble in the transfer tube with this approach.

Phase separation may also occur in the transfer tube. Even though the temperature is (usually) lower outside the oven, the decreased pressure beyond the regulator may cause highly volatile mobile-phase mixtures to separate into liquid and vapor phases, or boil off completely in the transfer tube. When separate liquid and vapor phases are both present, solutes will tend to partition into and travel with the liquid phase. A liquid film may form on the transfer-tube walls, or drops of liquid may coalesce or break apart as they travel. There may be a range of drop sizes and velocities which would depend on conditions, and which would lead to irregular mass transfer and peak broadening. These events can contribute to noisy or missing peaks, poor peak shapes, loss of resolution, and poor quantitation.

These problems have been somewhat managed by splitting a portion of the column outlet flow (before pressure reduction) to the low-pressure detector through a restrictor, as shown in Fig. 2b [1,10,13–15]. This approach allows control of the pressure in the transfer tube, but the splitting requirement worsens the detection limit (in terms of solute concentration in the original sample) by the value of the split ratio. Furthermore, the split ratio may not stay fixed throughout the chromatogram, particularly if conditions are programmed in any way. Thus, quantitation of solutes by peak-area ratio measure-

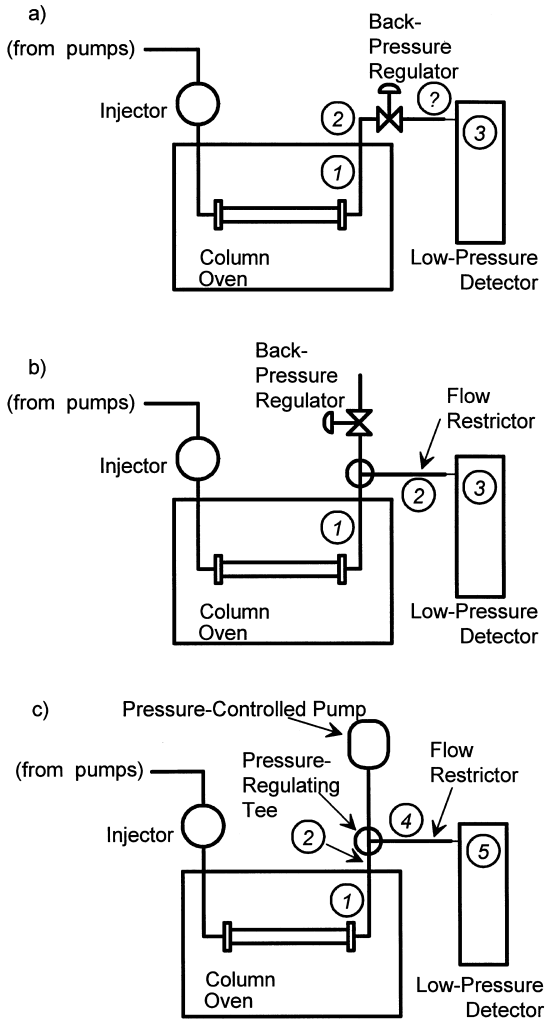

Fig. 2. (a) This configuration is often used with low-pressure detectors. The pressure in the regulator-detector transfer tube is uncontrolled and may lead to poor solute mass transfer and distorted peaks if liquid–vapor phase separation occurs. The numbered points correspond with points in Fig. 4. (b) If the transfer tube to the detector is a restrictor, it can be connected to a splitter at a point between the column outlet and the pressure regulator. This arrangement provides pressure control to the detector inlet but introduces the quantitation problems associated with splitters. The numbered points correspond with points in Fig. 4. (c) Replacing the regulator in (b) with a pump and delivering a fluid under pressure control into the tee provides both pressure control and quantitative transfer of solutes from the column outlet to the detector inlet. Liquid–vapor separation can be avoided if parameters are chosen knowing the phase diagram of the resulting mixture. The numbered points correspond with points in Fig. 7.

ments, such as with internal standards, may be both untrustworthy and difficult to check.

Quantitation can be improved by eliminating the tee and the pressure regulator and transferring the entire effluent flow to the detector through a restrictor [16]. This technique has been used extensively in open-tubular-column SFC with flame-ionization and MS detectors. However, this approach requires upstream pressure control in the SFC system (since pressure must be controlled somewhere in the chromatograph when a compressible, solvating mobile phase is in use). Flow control is not easily adjustable with upstream pressure control, and retention times are hard to reproduce between different restrictors. Volumetric mixing from two pumps and (composition) gradient elution are also much more difficult with upstream pressure control.

The regulator-detector and the splitting approaches have been used successfully by others in their specific applications. However, we experienced mass-transfer problems for some solutes using the regulator-detector arrangement, and were not satisfied that it could be trusted in every application. Furthermore, we were not willing to make the detection-limit and reproducibility sacrifices required in the splitting and the upstream-pressure-control approaches. This prompted us to develop an interface approach based on phase behavior and on the mass-transfer requirements of low-pressure detectors. Understanding this approach requires a short digression into phase diagrams.

Fig. 3a is a representation of a Type I binary phase diagram, occurring when the two mixture components are miscible as liquids. Here we represent mixtures of CO_2 and methanol [2,17–19]. The figure is bounded by the boiling lines of pure CO_2 and pure methanol in the pressure–temperature planes at 0 and 100% methanol on the composition axis. Only a short section of the CO_2 boiling line, terminating at the critical point of pure CO_2, is visible in the figure. The interior of the shaded portion is the two-phase region where liquid and vapor phases coexist. We have truncated the two-phase region at 25°C in this figure to illustrate the isotherm at that temperature. It is important to remember that the two-phase region continues to lower temperatures. When overall conditions are at any point within the two-phase liquid–vapor (l–v)

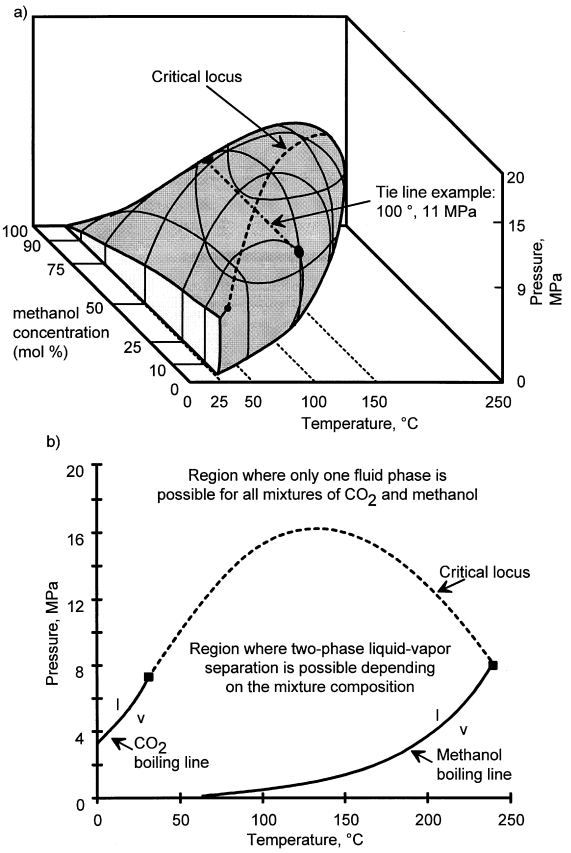

Fig. 3. (a) Representation of the three-dimensional (pressure–temperature–composition) phase diagram for binary mixtures of CO_2 and methanol. The shaded interior is the two-phase liquid–vapor region. Homogeneous fluid exists in the unshaded region. The figure is truncated at 25°C but the two-phase region actually continues to lower temperatures. (b) Representation of the pressure–temperature projection of the three-dimensional phase diagram.

region, the compositions of the resulting two phases are given by a tie line parallel to the composition axis and through the point in question. The compositions of the resulting liquid and vapor phases are given at the places where the tie line intersects the surface of the shaded figure. The vapor is the phase enriched with CO_2. The remaining unshaded volume of the figure (above and around the two-phase region) is a continuous, one-phase region available for chromatography. (Note: phase diagrams are conventionally displayed using mole fraction or mole percent to express composition. Packed-column SFC systems typically set compositions using volumetric ratios measured at the pumps. So, some care is necessary in making comparisons.)

Complete three-dimensional phase diagrams of binary mixtures containing CO_2 are only available for a few cosolvents, and are difficult to work with in printed media. Two-dimensional projections of the locus of mixture critical points (taken along the composition axis) are a convenient alternative. We have reported these curves for 21 mixtures of CO_2 and common cosolvents, as well as a simple flow-injection procedure for quickly generating these projections using open-tubular-column SFC instrumentation [20–24]. Fig. 3b is the P–T projection for CO_2–methanol. The interior of this figure is a region where l–v phase separation may occur, depending on the mixture composition. The exterior is a region where only a single fluid phase exists for all composition ratios of CO_2 and methanol.

Let us assume we are performing chromatography with the column maintained at 75°C, its outlet at 15 MPa, and the mobile-phase composition set at 10% methanol. Using the arrangement in Fig. 1, and assuming the transfer tube outside the oven and the detector are operated at 25°C (with instantaneous temperature change when the mobile phase leaves the oven, to simplify explanations), the column outlet would be operated at point 1 in Fig. 4a. The detector is operated at the same pressure, but at 25°C at point 2 in the phase diagram. The figure clearly shows that no l–v separation will occur for the constant-pressure, constant-composition, temperature change from point 1 to 2. This will be so regardless of the location of point 1 as long as the pressure is set higher than the peak pressure of the corresponding isopleth (that is, a slice of the figure at constant composition). Note, the peak pressure of the isopleth may be higher than the mixture critical pressure for that composition. In addition, it is clear from phase diagram data (but difficult to see in the pseudo-three-dimensional Fig. 4a) that if the column-outlet pressure were maintained above about 16.5 MPa we would never experience a mobile-phase l–v separation upon the isobaric transition from any elevated oven temperature to 25°C for all possible mixtures of CO_2 and methanol. When phase separation is avoided we would expect no mass-transfer artifacts in reaching point 2 as long as the solutes stay complete-

ly dissolved in the mobile phase at 25°C. Pressure is reduced to ambient (0.1 MPa) at the outlet of the back-pressure regulator by venting to atmosphere, represented by point 3.

In Fig. 4b we indicate the same points, 1, 2, and 3, as in Fig. 4a, and corresponding to the locations similarly indicated in Fig. 1. As with the complete phase diagram, the P–T projection clearly shows that no l–v separation will occur for the constant-pressure temperature change from point 1 to 2. It is also completely clear from Fig. 4b that setting the column-outlet pressure above 16.5 MPa will ensure there is no possibility of l–v separation occurring between the column outlet and a column-pressure detector.

The phase diagram reveals some of the problems

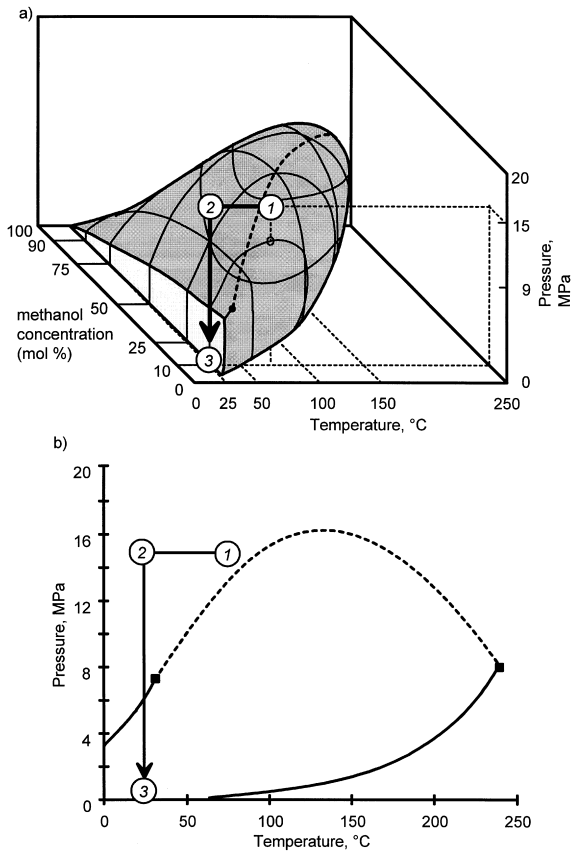

Fig. 4. (a) Path through the phase diagram for the interface configurations in Figs. 1 and 2a and b. (b) Corresponding path through the pressure–temperature projection of the three-dimensional phase diagram.

using the regulator–detector arrangement in Fig. 2a. Again, we will assume that the temperatures change is instantaneous when the mobile phase leaves the oven. The column outlet is at point 1 in Fig. 2a and 4a. Temperature is reduced outside the oven, and the inlet of the back-pressure regulator is at point 2. In the case of an ELSD or an atmospheric-pressure-ionization (API) interface for MS, the detector spray chamber or API source is operated at point 3. The pressure in the regulator-detector transfer tube is not under control and may be anywhere on the path between points 2 and 3. If the pressure in this tube should be too low, l–v separation becomes possible before solutes reach the detector.

In this paper we present an alternate pressure-control and detector-interfacing approach not requiring a pressure regulator or nozzle. A separate pump is used to introduce a pressure-regulating fluid into a tee between the column outlet and detector, in conjunction with a flow restrictor at the detector inlet, as in Fig. 2c. By operating this pump under pressure control rather than flow control, all the advantages of independent and simultaneous downstream pressure control and upstream flow control are maintained. Unlike restrictor interfaces used with upstream pressure control, in our arrangement the flow-rate on the column is determined by the upstream pumps, just as with the conventional downstream pressure-control arrangement of Fig. 1. Our restrictor affects only the flow-rate of the pressure-regulating fluid. The rate of solute mass transfer to the detector is unchanged by the pressure-regulating fluid, so we expect no signal loss and no compromise of quantitation for true mass-sensitive detectors. With knowledge of the phase behavior of the resulting mixture we can select parameters that avoid phase separation.

This arrangement is somewhat similar to that described by Takeuchi et al. where a relatively low-pressure syringe pump was used to prevent boiling of the column effluent in high-temperature liquid chromatography [25]. Raynie et al. used high-pressure argon as a ‘make-up gas’ to control linear velocity in open-tubular-column SFC [26]. The gas was introduced at the column outlet ahead of a pinhole restriction.

Sanders et al. [27] and Jedrzejewski and Taylor [28] added a ‘particle-forming solvent’ to pcSFC

effluent in their particle-beam interfaces for pcSFC–MS. At first glance, these approaches to pcSFC–MS interfacing are similar to our postcolumn addition of a pressure-regulating fluid. However, the purpose of the postcolumn addition of fluid by Sanders et al. and by Jedrzejewski and Taylor was the formation of particles that would efficiently traverse the particle-beam interface and provide good mass spectrometric signals. These solvents in these reports were added under flow control with other means for controlling pressure. In our work the additional fluid controls the outlet pressure while providing similar detection benefits.

2. Experimental

2.1. Instrumentation

We used a Model G1205A pcSFC instrument equipped with a series 1050 multiple wavelength UV–visible detector (Hewlett-Packard, Little Falls, DE, USA). This instrument is normally equipped with a computer-controlled nozzle working in concert with a downstream pressure transducer to control the column-outlet pressure. Modifications for use of the pressure-regulating fluid involved: (1) adding a pressure-regulating fluid pump, (2) connecting the outlet of the UV detector to a tee (i.e., the pressure-regulating tee) to introduce the pressure-regulating fluid, (3) connecting the downstream pressure transducer to the pressure-regulating fluid pump via union number 6 in the pump manifold to provide instrument-control feedback, and (4) blocking the outlet of the instrument's original pressure-regulating nozzle by inserting a plug in the outlet of union number 7. For all work, the UV–vis detector was left in line outside the oven and ahead of the pressure regulator or pressure-regulating tee.

The pressure-regulating fluid pump was a Model 260D high-pressure syringe pump (Isco, Lincoln, NE, USA). This pump was operated under pressure control and its controller, separate from the chromatograph, was used to set the column-outlet pressure when the pressure-regulating fluid interface was used. The outlet of the pressure-regulating pump was also connected to the postcolumn pressure transducer of the SFC instrument, as described earlier, via another tee near the 260D pump outlet. In this arrangement the flow-rate of the pressure-regulating pump generally ranged from 0.2 to 1.5 ml/min and depended on the pressure set point, the mobile-phase flow-rate at the column outlet, the restriction at the detector inlet, and the viscosity of the fluid mixture flowing into the restrictor.

We used a Model 55 ELSD equipped with an SFC nebulizer tube (Sedex, Richards Scientific, Novato, CA, USA). The union normally coupling the effluent transfer line to the ELSD nebulizer was replaced by a low-dead-volume tee (ZT1C, Valco Instruments, Houston, TX, USA) which serves as the pressure-regulating tee, as shown in Fig. 2c. A PEEK sleeve, 1.59 mm (1/16-in.) O.D., 0.375 mm I.D., and a PEEK ferrule (Upchurch Scientific, Oak Harbor, WA, USA) were used to couple the outlet of the tee to a fused-silica tube, 5 cm×0.375 mm O.D., 0.050 mm I.D. (Polymicro Technologies, Phoenix, AZ, USA), used here as a linear flow restrictor. This fused-silica restrictor replaced the restrictor supplied with the ELSD. The nebulizing gas pressure was 0.06 MPa. The nebulizer and scattering chamber temperatures were set at 40°C with a Model 110A circulating bath (Neslab Instruments, Portsmouth, NH, USA).

A mass spectrometer, a Model API III$^+$ tandem quadrupole mass spectrometer (PE-Sciex, Concord, Ontario, Canada), when used, was interfaced in place of the ELSD in the same manner. The MS operation and modifications to the ionspray interface are described in detail in [29].

2.2. Chromatographic conditions

The column was a Deltabond Cyano, 250 mm long×4.6 mm I.D., packed with 5-μm particles with 300-Å pores (Keystone Scientific, Bellefonte, PA, USA). The primary mobile phase component was CO_2 (SFC/SFE grade, Air Products, Plumsteadville, PA, USA). The modifier component of the mobile phase and the pressure-regulating fluid was methanol (HPLC Grade, J.T. Baker, Phillipsburg, NJ, USA). The total mobile-phase flow was 2 ml/min (measured at the upstream pumps). The column oven temperature was 60°C and the postcolumn pressure was 20 MPa.

2.3. Sample preparation

Solutions of anthracene (Chem Service, West Chester, PA, USA) were prepared in dichloromethane (HPLC grade, J.T. Baker). Solutions of octanoylphenolpentaoxyethylene (C_8-phenyl-EO_5, The Procter and Gamble Company, Cincinnati, OH, USA) were prepared in hexane (HPLC grade, J.T. Baker).

3. Results and discussion

3.1. Retention times and peak asymmetry

Solute retention times were not significantly different using either the G1205A pressure-regulating nozzle or the pressure-regulating fluid interface as long as the pressure settings were the same. When we used the nozzle to interface the pcSFC instrument with both the ELSD and MS detectors as in Fig. 2a, we sometimes observed peak asymmetry and tailing. With the ELSD the severity of these problems tended to increase with the polarity of the solutes. Fig. 5a illustrates this problem using pcSFC–MS to analyze the C_8-phenyl-EO_5 surfactant standard. With the pressure-regulating fluid interface, the peak shapes and the signal-to-noise ratio were greatly improved. This allowed both a reduction in the methanol content of the mobile phase and an increase in the mobile phase flow-rate. (A reduction in methanol concentration increases mass transfer problems in the regulator-detector arrangement.) Fig. 5b illustrates these improvements for a peak one-tenth the mass on column as in Fig. 5a [29].

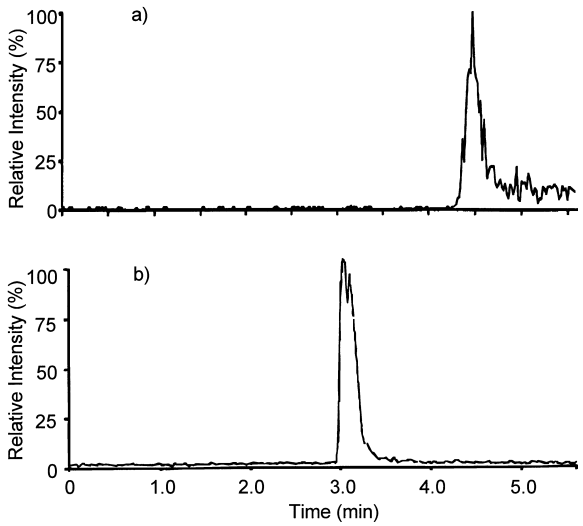

Fig. 5. (a) SFC–ionspray-MS (m/z 425) of octanoylphenolpentaoxyethylene (C_8-phenyl-EO_5) surfactant standard (~500 ng on-column) using the G1205A nozzle to direct effluent to the ionspray interface. Note the peak tailing and noise. Conditions: 1 ml/min of mobile phase (6% methanol in CO_2); 20 MPa postcolumn pressure; 40°C oven temperature; 8 l/min Turbo Ionspray gas at 530°C; 0.34 MPa nebulizer gas pressure; 100 μl/min sheath flow. (b) SFC–ionspray-MS (m/z 425) of 50 ng on-column of C_8-phenyl-EO_5 surfactant standard using the pressure-regulating fluid interface. Conditions: 2 ml/min of mobile phase (3% methanol in CO_2); 20 MPa postcolumn pressure; 60°C oven temperature; 8 l/min TurboIonspray gas at 500°C; 0.32 MPa nebulizer gas pressure; 300 μl/min sheath flow.

3.2. ELSD response vs. mobile phase composition

Fig. 6 compares the relative signals for the regulator-detector and the pressure-regulating fluid interfaces for the detection of anthracene with 0%, 3.5%, 7%, and 15% methanol modifier in the mobile phase. We used the UV detector to verify that well-shaped anthracene peaks containing all the mass injected were exiting the column outlet. With the regulator in use we could not detect a 25-μg anthracene peak with the ELSD when there was no methanol in the mobile phase. We were barely able

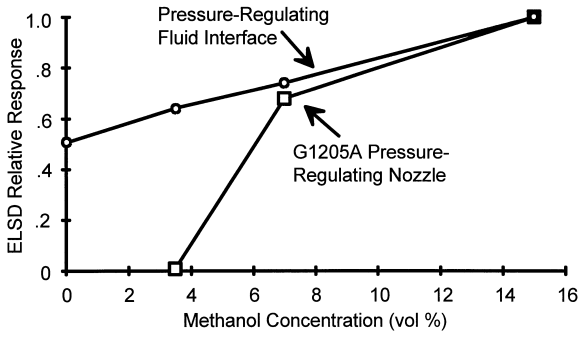

Fig. 6. Relative signal for evaporative light scattering detection of 25 μg of anthracene as a function of mobile phase methanol concentration using the pressure-regulating fluid interface and the direct connection of the pressure-regulating nozzle to the detector inlet.

to detect this mass of anthracene when the mobile phase was 3.5% methanol. Signals continued to improve as we raised the mobile-phase methanol concentration further. However, with the pressure-regulating fluid interface the detector response was much flatter, and a 4-μg anthracene peak was easily detectable with no methanol in the mobile phase. The efficiency of forming particles of the proper size in the ELSD is clearly affected by the methanol concentration in the solution delivered to the detector inlet.

3.3. Navigating through the phase diagram

Fig. 7 illustrates the path through the phase diagrams from the column outlet to the detector inlet using the pressure-regulating fluid interface. In our experimental arrangement the pressure-regulating tee was outside the oven, so the column outlet was again at point 1, and the inlet of the pressure-regulating tee was at point 2. At the outlet of this tee the pressure is still unchanged, but the fluid composition is now enriched with methanol, point 4. At this point the fluid composition is not well controlled since it depends on the flow-rate of the pressure-regulating pump which is pressure-controlled, not flow-controlled. However, the exact composition at this point is not particularly important since we are far away from the two-phase region. The mobile phase is sprayed into the detector, ending in the two-phase region at point 5 and producing the required droplets either at the ELSD nebulizer tube outlet or in the API interface of the MS instrument. If it should ever prove necessary to delay the pressure drop further, integral-type restrictors [30] can be substituted for the linear restrictors used in this work.

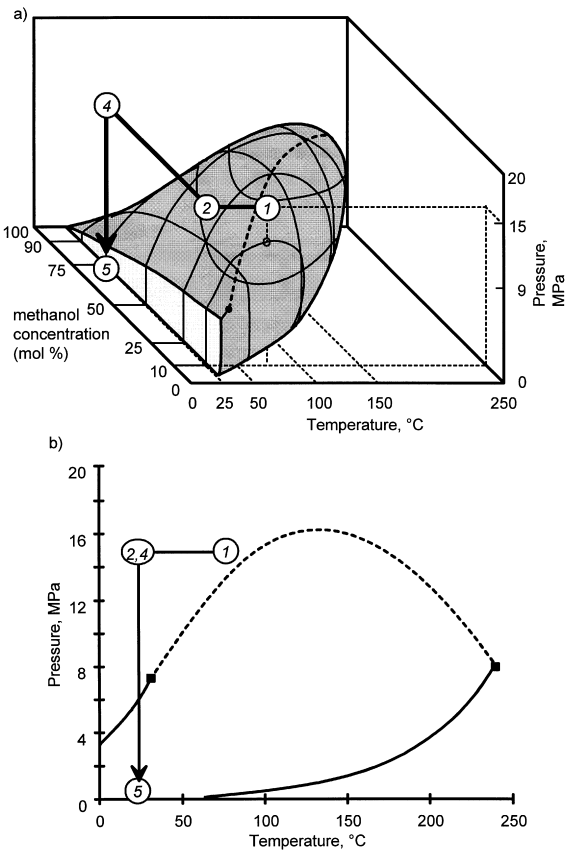

Fig. 7. Path through the phase diagrams for the pressure-regulating fluid interface configuration in Fig. 2c.

This particular path and the corresponding instrumental configuration will work whenever the path segment between points 1 and 2 avoids the two-phase region. However, it is clear that if the column outlet were at a pressure below the peak pressure of the corresponding isopleth and on the high-temperature side of this pressure peak, the isobaric path lowering the temperature to 25°C would intersect the two-phase region. Depending on specific circumstances, it might be preferable to do the mixing in the column oven before lowering the temperature, or to operate the mixing tee at a temperature higher than the column using an additional oven and taking another path through the phase diagram and around the two-phase region.

4. Conclusions

Quick transitions through the two-phase region will not cause problems in every case. However, the pressure-regulating fluid interface can avoid unwanted phase transitions and ensure quantitative solute mass transfer to the detector in every case. It also significantly flattens the response for volatile solutes when the ELSD is used. Other pressure-regulating fluids, such as ethanol or propanol, may further decrease the dependence of ELSD response on mobile-phase composition. However, other fluids

should be used with caution if the mobile phase modifier is methanol since the phase behaviors of the resulting ternary systems are not well known. Until more investigations are reported, we recommend using the same solvent for both the mobile phase modifier and the pressure-regulating fluid.

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