



Separations by Shape: Molecular Shape Recognition in Liquid Chromatography

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Abstract

Molecular shape can provide a basis for chromatographic separations that is distinct from other interaction mechanisms often considered in liquid chromatography. Molecular shape recognition, or shape selectivity, is most evident for the separation of isomeric compounds that have constrained molecular structures, such as polycyclic aromatic hydrocarbons. A central feature of shape-selective columns is conformational order within the stationary phase; this aspect of stationary phase morphology is revealed through spectroscopic studies and molecular dynamics simulations, and is correlated with chromatographic performance.

Keywords Shape selectivity · Conformational order · Retention mechanism · Isomers · Stationary phase

Background and Historical Perspective

Separations in liquid chromatography result from a myriad of interactions between solutes, the mobile phase, and the stationary phase [1]. These interactions are broadly referred to as retention mechanisms, and historically, they have included such designations as adsorptive, partitioning, dispersive, induced-dipole, polar–polar, ionic, chiral, and size–exclusion interactions, depending on the assumed processes. With few exceptions, solute retention results from a combination of enthalpic and entropic interactions, and the complexity of these processes limits the ability of the analyst to predict column selectivity and develop separation methods for arbitrary mixtures. Solute retention can be described in thermodynamic terms by Eq. (1)

$$\ln(k) = -\Delta H^\circ / RT + \Delta S^\circ / R + \ln(\phi), \quad (1)$$

where k is the capacity factor, ΔH° and ΔS° refer to the change in standard enthalpy and entropy for solute retention, and ϕ denotes the phase ratio, which is defined as the volume of the stationary phase divided by the volume of the mobile phase (note that $k = K\phi$, where K is the equilibrium coefficient). Given the form of Eq. (1), it can be expected that plots of $\ln(k)$ vs $1/T$ (i.e., Van't Hoff plots) will be linear, and this is in fact often observed in reversed-phase liquid chromatography over limited temperature intervals. Nonlinear Van't Hoff plots provide clues to the origin of solute retention, since nonlinearity must result from changes in ΔH° , ΔS° , and/or ϕ that occur with temperature. Nonlinear Van't Hoff plots thus suggest the existence of one or more retention mechanisms that change with temperature. As we will see (vide infra), temperature plays a key role in molecular shape recognition in LC.

The concept of shape selectivity in liquid chromatography is rooted in the early 1980s in a series of publications by Sander and Wise that described selectivity differences observed among different types of C18 columns, used for the separation of polycyclic aromatic hydrocarbons (PAHs) [2, 3]. The authors recognized that the separations of PAHs differed markedly among C18 columns prepared by different synthetic approaches. The most common approach used in the synthesis of chromatographic sorbents is based on reactive silane reagents (Fig. 1).

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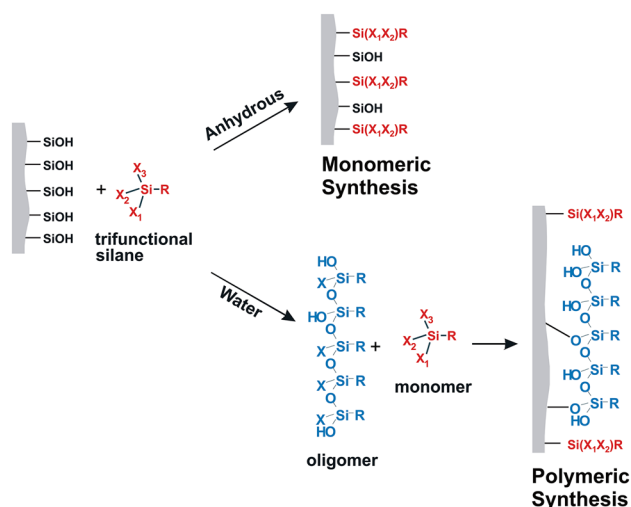


Fig. 1 Synthetic approaches used in the preparation of monomeric and polymeric alkyl stationary phases

In the absence of water, trifunctional silanes react with silica to form a monomeric layer; this reaction is sterically limited to about 50% coverage of the existing surface silanols and the corresponding columns are referred to as monomeric columns. If water is introduced into the reaction, a mixture of silane oligomers and monomers is produced at least temporarily in solution. Some evidence exists to suggest that the oligomers are relatively small—perhaps consisting of 5 units and less [4]. These species can go on to react with silica to produce a polymeric phase. This reaction is sterically limited, and it is likely that the resulting surface consists of oligomer and monomer units. Even with a large excess of water, the resulting surface coverage of polymeric columns rarely exceeds about $5\text{--}6\ \mu\text{mol}/\text{m}^2$.

Origins of Shape Selectivity

To understand how monomeric and polymeric stationary phases may provide different chromatographic properties, it is useful to consider how covalently modified surfaces differ from bulk liquids and solids. With bulk liquid alkanes, the alkyl chains have translational freedom of motion, and the molecules can assume random orientations and conformations. With bulk solid alkanes, the alkyl chains are largely ordered in an all-*trans* conformational state in a crystalline lattice. Alkyl modified surfaces constitute an intermediate state, since the proximal end of the tethered alkane is restricted from movement by the covalent bond and the distal ends of the chains have additional degrees of freedom. The extent of this freedom, and the average conformation of the chains, influence chromatographic performance.

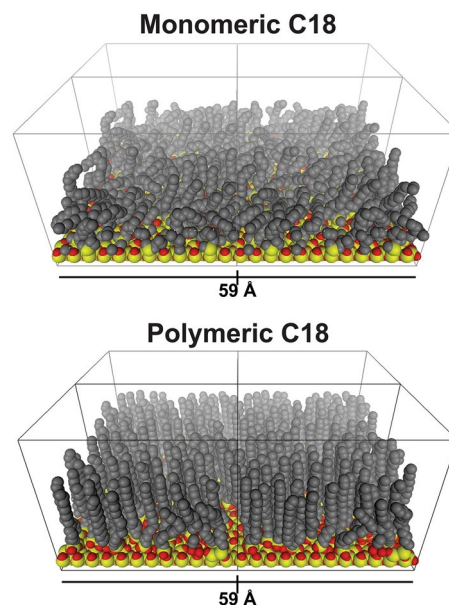


Fig. 2 Perspective views of monomeric C18 and polymeric C18 stationary phases obtained from molecular dynamics simulations. (Adapted from reference [5])

Molecular dynamics simulations of monomeric and polymeric C18 surfaces are shown in Fig. 2.

Differences in conformational order result from the different surface coverages that are characteristic of monomeric and polymeric surface modification chemistries. It seems reasonable to assume that the different morphologies of the monomeric and polymeric stationary phases influence the retention process, even though both models represent immobilized octadecane.

One of the first comprehensive approaches to the description of reversed-phase retention was advanced by Karger et al. [6] and Horvath and Melander [7]. Termed “the hydrophobic effect” and “the solvophobic effect”, respectively, these theories treated the stationary phase as a passive acceptor of the solute species. The driving force for retention is viewed as the reduction in area of the nonpolar surfaces exposed to the polar mobile phase environment that results from contact of solute molecules with the bonded phase ligands. This process differs from adsorption, because attractive forces between solute and bonded phase molecules are thought to be small. On the other hand, hydrophobic forces are opposed by attractive association of solute molecules with the mobile phase. The balance of these forces results in retention that is dependent on the polarity of the solute, the mobile phase and the stationary phase. Several problems exist with the hydrophobic retention model. Because the stationary phase plays a passive role, differences in selectivity between different columns are not fully explained. For example, shape selectivity variations among monomeric and polymeric

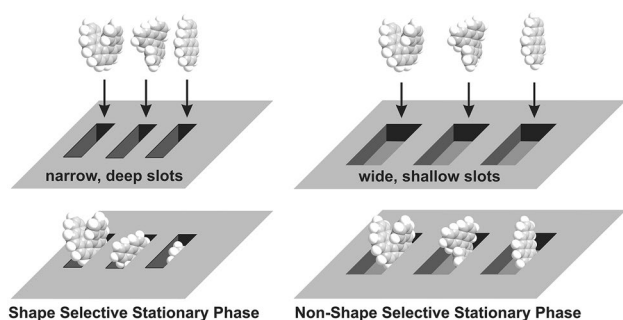


Fig. 3 Representation of the "Slot Model" for planar and nonplanar PAHs. Ordered, higher density stationary phases exhibit narrow, well-defined slots that provide shape discrimination. Disordered, lower density stationary phases exhibit less well-defined slots that do not discriminate based on molecular shape

C18 columns are not directly accounted for by this model, because both columns provide similar "hydrophobic" stationary phase environments.

We originally explained the retention differences observed for planar and nonplanar solutes with an empirical representation we called the "Slot Model" [8] (Fig. 3).

Spaces between the alkyl chains are viewed as slots into which solute molecules penetrate. Bulky molecules are hindered from penetration into narrow slots and have reduced interaction with the stationary phase (i.e., reduced retention). More compact molecules with planar geometries penetrate the spaces between the chains more completely and exhibit increased retention. Similarly, molecules with large length-to-breadth ratio (L/B) [9] geometries fit into existing slots more easily than square-shaped molecules ($L/B \approx 1$). The effect of phase length and bonding density on shape selectivity can be discussed in terms of this model.

Densely loaded phases are characterized as ordered systems and can be visualized as having narrow, deep slots. Such phases exhibit increased shape recognition compared with disordered systems with more widely spaced chains (wider, shallower slots). In terms of this model, both planar and nonplanar solutes are thought to equally penetrate wide slots and little discrimination is possible. Only narrow planar molecules can penetrate the spaces between the chains in ordered phases, and enhanced shape discrimination results. Phase thickness corresponds to slot depth, and greater shape recognition results with increasing chain length.

Molecular dynamics simulations provide a tantalizing representation of the stationary phase that can be viewed in terms of the Slot Model [5, 10]. Space-filling models can be simplified by representing the surface defined by the contact of a spherical probe of defined radius with the space-filling model. The so-defined Connolly surface [11] makes cavity features apparent that are less evident with a space-filling model representation (see Fig. 4) [12].

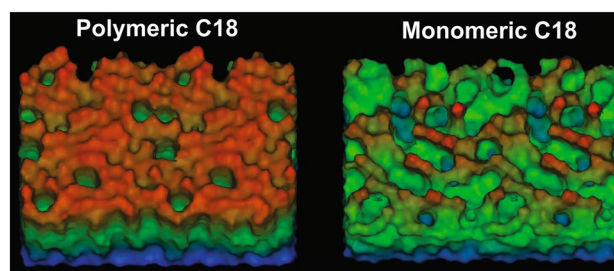


Fig. 4 Connolly molecular surface representations of polymeric C18 and monomeric C18 stationary phases using a 0.2 nm probe. Blue represents the alkyl chains adjacent to the silica surface, green represents alkyl chain midsection, and red represents chain ends. (Adapted from reference [12])

For high-density stationary phase models, cavities are apparent; these features are less well defined for lower density models. The cavities result from stable alkyl chain associations that are persistent over the life of the simulation. An analogy can be made to the Slot Model representations for high-density shape-selective stationary phases (with narrow, deep slots), and for low-density non-shape-selective stationary phases (with wide, shallow slots).

A differing view of stationary phase morphology was described by Siepmann et al. based on configurational-bias Monte Carlo simulations [13]. As with the Slot Model, persistent sites of preferential solute interaction exist within the stationary phase; however, these sites are not characterized as pre-existing cavities, since alkyl chains occupy this space in the absence of solutes. Solute molecules are retained within the stationary phase, and elongated solutes align with the long axis perpendicular to the silica surface. Bulky solutes are preferentially retained in regions with less-crowded chain spacing, and extended solutes are preferentially retained in regions with closer spaced chains.

Spectroscopic Characterization of Chromatographic Stationary Phases

Over the past 30 years, advances in the theory and practice of spectroscopy and improvements in instrumentation have significantly facilitated the study of covalently modified surfaces. A diverse array of spectroscopic methods have been used to characterize the structure and chemical properties of stationary phases that have included solid-state nuclear magnetic resonance spectroscopy (NMR) [14–16], Fourier transform infrared spectroscopy (FTIR) [17], Raman spectroscopy [18], and small-angle neutron scattering (SANS) [19, 20].

NMR is an extremely powerful technology that can be used to reveal a variety of details about the chromatographic surface [16]. Different types of information are

disclosed by probing different nuclei. For example, ^{29}Si cross polarization magic angle spinning solid-state NMR unambiguously reveals the nature of silane bonds, i.e., whether monofunctional, difunctional, or trifunctional silanes were used in the surface modification reaction, and additionally, if endcapping was performed (i.e., endcapping is a secondary silanization with reactive methyl silanes to bond residual silanols). ^{13}C NMR offers a way of studying alkyl conformational order. Two signals have been attributed to specific alkyl chain conformations. A signal at 32.6 ppm is attributed to *trans*-alkyl chain conformations, and the signal at 30 ppm is attributed to *gauche* chain conformations. The ratio of these signals reflects the degree of conformational order. Trends in ^{13}C NMR spectra are shown in Fig. 5 for changes in bonding density, alkyl chain length, and temperature [14].

Increased order is observed with increases in bonding density, increases in alkyl chain length, and decreased temperature. For each of these trends, the ratio of *trans*/*gauche* alkyl conformations increases, which indicates a more ordered stationary phase morphology. Corresponding increases in shape discrimination for PAH isomers, and other similar families of compounds, are observed with increased stationary phase order.

Related information on conformational order has been obtained from FTIR [17, 21] and Raman spectroscopy [18]. Spectral assignments within the fingerprint region for paraffins were applied to the spectra of alkyl modified silica. Changes in the FTIR spectra at 1354 cm^{-1} (bend conformation) and 1367 cm^{-1} (kink conformation) were observed as a function of temperature, with more ordered states indicated by a reduction in conformational defects at lower temperatures. Complementary information is obtained from Raman spectroscopy. Similar trends were observed that indicated

increased conformational order with decreased temperature and increased bonding density.

Finally, information about the dimensions of stationary phases has been obtained from small-angle neutron scattering [19, 20]. Using a contrast matching experiment, scattering from the stationary phase was isolated from pore scattering to measure the thickness of the stationary phase for monomeric and polymeric alkyl modified silica (Fig. 6).

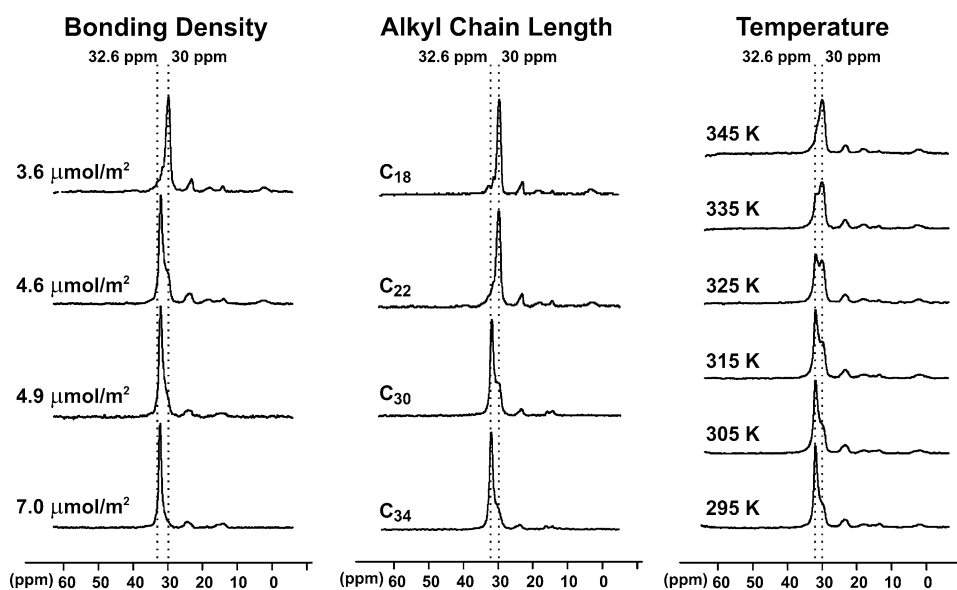
For the monomeric alkyl surfaces, a linear relation was observed between the thickness and the number of carbon atoms in the bound ligands that ranged from 1 nm (C8 phase) to 1.7 nm (C18 phase) to 2.5 nm (C30 phase). The thickness of a C18 phase prepared by polymeric surface modification chemistry was slightly thicker than the corresponding monomeric C18 phase (2.1 vs 1.7 nm, respectively). The dimensions of the stationary phases are consistent with the molecular dynamics simulations and the empirical Slot Model.

Chromatographic Performance

Large differences in selectivity are often observed among monomeric and polymeric columns for separations of isomers with constrained molecular shape [3, 8, 22, 23]. These differences are particularly evident for PAHs and carotenoids [24, 25], due in part to the large number of isomers present in complex mixtures (Fig. 7).

In this example, poor resolution of the PAH and carotenoid isomers was achieved with monomeric C18 columns, whereas improved separations were possible with polymeric C18 and polymeric C30 columns. For PAHs, retention is strongly correlated with *L/B* ratio, as indicated by the *L/B* values below the structures. Solutes with *L/B* ratios near

Fig. 5 ^{13}C solid-state NMR spectra of covalently modified silica substrates. Signals at 32.6 ppm correspond to *trans*-alkyl chain conformations (ordered state) and signals at 30.0 ppm correspond to *gauche* chain conformations (disordered state). Left: C18 modified silica with different bonding densities; center: silica modified with alkyl chains ranging from C18 to C34; right: C18 modified silica at temperatures ranging from 295 to 345 K. (Adapted from reference [14]; used with permission)



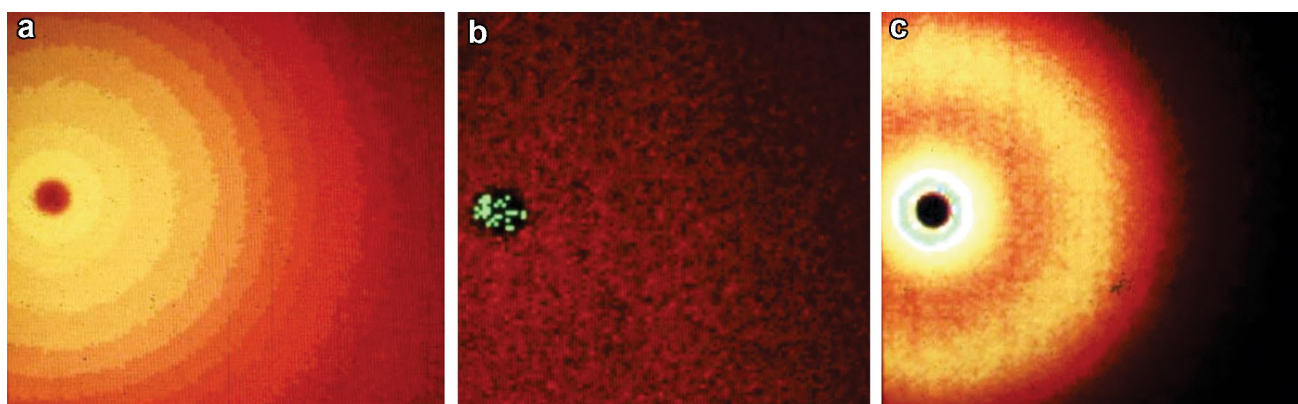


Fig. 6 Small-angle neutron scattering patterns of chromatographic sorbents. **A** Porous silica, **B** porous silica with maskant fluid, and **C** bonded silica with maskant fluid

1 elute early in the chromatogram, and solutes with larger L/B ratios elute later. For carotenoids, polar xanthophylls elute prior to nonpolar hydrocarbon carotenoids, but for each group, *cis* isomers usually elute prior to *trans* isomers.

A shape selectivity factor has been developed based on the retention of two nonplanar and planar PAHs, namely tetrabenzonaphthalene (TBN) and benzo[*a*]pyrene (BaP) [26]. Values for $\alpha_{\text{TBN/BaP}} < 1$ are representative of polymeric stationary phases with enhanced selectivity toward shape constrained isomers. Values > 1.7 are more characteristic of monomeric stationary phases with reduced shape selectivity. The three parameters described above in the context of conformational order (i.e., alkyl chain length, bonding density, and temperature) also affect changes in shape selectivity. Thus, increased chain length, increased bonding density, and decreased temperature each result in increased selectivity for mixtures of shape constrained isomers. These relationships are central to the development of specialized stationary phases by column manufacturers, and to the development of chromatographic methods by analysts.

Concluding Remarks and Future Prospects

Complementary research efforts on alkyl stationary phases offer a consistent and compelling model of the structure and function of these chromatographic surfaces. Ordered systems that contain a higher fraction of *trans*-alkyl conformations and higher chain rigidity provide enhanced shape recognition. Such ordered systems result from stationary phases prepared with polymeric syntheses, higher bonding densities, longer alkyl chain lengths, and operation at reduced temperature. Disordered systems that contain a higher fraction of *gauche* bonds have higher alkyl chain mobility and provide reduced shape recognition.

Disordered systems result from monomeric synthesis, low bonding densities, short alkyl chain lengths, and operation at elevated temperature. An appreciation of these aspects of shape selectivity can facilitate development and optimization of chromatographic methods.

The potential exists for the development of other types of highly ordered stationary phases. Because silane chemistry is simple and well established, the development of novel chromatographic stationary phases is dominated by this approach, and progress is at least partially limited by the availability of relevant silanes. Other synthetic pathways offer additional flexibility in the preparation of novel stationary phases. For example, aldehydes can be linked to aminopropylsilica through the formation of Schiff bases. Using this approach, ordered molecular species that contain an aldehyde functional group can be covalently bonded to silica without preparation of a reactive silane.

Anecdotal studies of other novel shape-selective stationary phases include immobilized perfluorinated alkanes [27], aromatic compounds (fused ring PAHs and phenyl compounds) [28], liquid crystalline phases [29, 30], and immobilized bulk polymers [31]. The latter class of stationary phases remains largely unexplored. We obtained promising results for a highly shape-selective phase based on immobilized poly(ethylene-*co*-acrylic acid) [31]. In principle, any species that exhibits a well-defined rigid molecular shape has the potential to offer shape discrimination as a stationary phase. Thus, the same solutes that are the subject of shape-selective separations could themselves provide the basis for shape recognition as stationary phases. The challenge lies in developing appropriate linking chemistry and in fine tuning column properties to produce practical and efficient chromatographic performance.

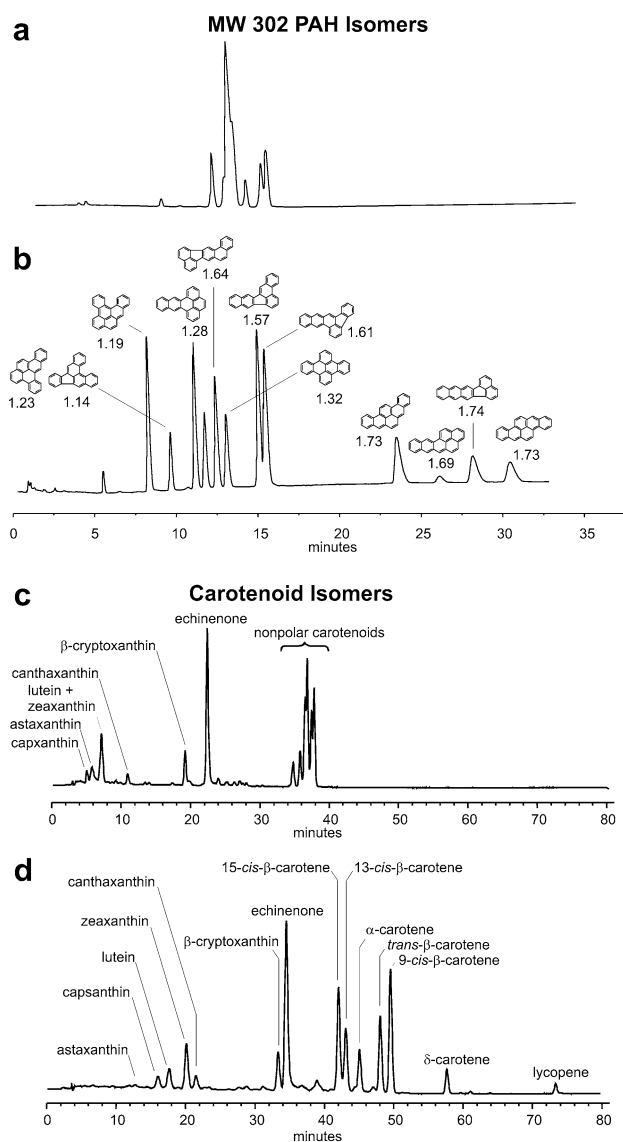


Fig. 7 Upper figure: separation of MW 302 PAH isomers on **A** monomeric C18 and **B** polymeric C18 columns. (Adapted from reference [23]). The elution order of the solutes is correlated with L/B (values provided below structures). Lower figure: separation of carotenoid isomers on **C** monomeric C18 and **D** polymeric C30 columns. (Adapted from reference [24])

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Declarations

Conflict of interest There is no conflict of interest to report.

Ethical approval This article does not contain any studies with animals or human participants.

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