RSC Chromatography Monographs

Quantitative *In Silico* Chromatography

Computational Modelling of Molecular Interactions

Toshihiko Hanai

ROYAL SOCIETY OF CHEMISTRY

Quantitative In Silico Chromatography

Computational Modelling of Molecular Interactions

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Preface

Modern chromatography began when Martin and Synge developed "partition chromatography" in 1941. In 1958, Kovats proposed an index to predict gas chromatography retention times, leading to discussion of the mechanism of retention and studies to validate retention time prediction. With the separation of saccharides using a combination of ion-exchange resin and aqueous ethanol without ion-exchange by Samuelson *et al.* in 1965, a variety of combination systems were investigated for liquid chromatographic separation. In particular, the relationship between the structure and the chromatographic behavior of a variety of mono- and di-substituted benzenes on an anion-exchange resin was studied with anhydrous ethanol as the eluent. It was found that retention depends on the type and position of the substituents, with the degree of adsorption being, at least partially, related to electron-withdrawing ability. The results suggested that molecular adsorption on the solid phase occurred by the formation of either charge-transfer or hydrogen-bonding interactions between the analyte and the anionic groups on the resin. These findings were confirmed in studies using a variety of packing materials, ion exchangers, bonded-phase silica gels, and organic polymers for the chromatographic separation of organic acids and saccharides in organic solvent mixtures. These results also supported the importance of hydrogen bonding for analyte retention on the solid phase. Similar experiments were carried out to analyze the chromatographic behavior of phthalate esters in aqueous solvent systems, and showed that elution order was related to solubility (hydrophobicity), leading, in 1974, to a liquid chromatography classification scheme based on solubility factors, as proposed by Hanai. Furthermore, in 1979, Hanai *et al.* demonstrated an optimized method for reversed-phase liquid chromatography using the octanol–water partition coefficient. The quantitative analysis of retention mechanisms proved to be difficult, however, in the absence of fast personal

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computers and computational software designed for general use by non-specialists.

In recent years, analytical chemists have increasingly turned their attention to drug discovery and drug analysis and to solve fundamental biologically significant questions in physiology and genetics. New technologies have been developed, and a variety of instruments have been redesigned for biomedical applications. For example, the development of capillary column gas chromatography, in which separation power is based on a very high theoretical plate number, answered questions about sample purity, and the development of high-performance liquid chromatography opened a new era in bio-related fields by allowing faster separations of unstable macromolecules. The improved thin layer liquid chromatography technique, high-performance planar liquid chromatography, is capable of the simultaneous analysis of many samples, providing an overview of the components present in complex mixtures, and permitting two-dimensional separation under different conditions with the possibility of multiplexed detection.

Capillary column gas chromatography (GC)/mass spectrometry (MS) has also been used to achieve more difficult separations and to perform the structural analysis of molecules, and laboratory automation technologies, including robotics, have become a powerful trend in both analytical chemistry and small molecule synthesis. On the other hand, liquid chromatography (LC)/MS is more suitable for biomedical applications than GC/MS because of the heat sensitivity exhibited by almost all biomolecules. More recent advances in protein studies have resulted from combining various mass spectrometers with a variety of LC methods, and improvements in the sensitivity of nuclear magnetic resonance spectroscopy (NMR) now allow direct connection of this powerful methodology with LC. Finally, the online purification of biomolecules by LC has been achieved with the development of chip electrophoresis (microfluidics).

As a complementary approach to these technological advances, computational chemical analysis is a promising technique with the potential to analyze the mechanisms of molecular interaction between analytes and solid phases, especially given the feasibility of modeling the three-dimensional structures of biological macromolecules, such as proteins. Importantly, this technology can be easily used to study the retention mechanisms in chromatography for a variety of model phases. Furthermore, theoretical calculations can provide significant insight into organic reaction mechanisms, which can be applied to study highly sensitive detection in chromatography, such as bromate and chemiluminescence detection. As a consequence, combining chromatography and computational chemistry offers new possibilities in developing a quantitative description of molecule interactions relevant to analytical separations. Furthermore, a combination of quantitative molecular recognition analysis and electron transfer, can permit the study of enzyme reaction mechanisms.

In this book, I propose and describe one approach to combining these methods, and illustrate the power of this strategy in biological applications.

For example, this method reveals a high correlation coefficient between measured capacity ratios and the sum of theoretically calculated molecular interaction energy and molecular property values, opening the possibility for quantitative analysis of chromatographic retention mechanisms.

This book is a pebble thrown in a pond. I hope the 'ripples' created will stimulate new research into questions about the basic phenomena of chromatographic separation and, perhaps, improve our understanding of enzyme reaction mechanisms.

Toshihiko Hanai
Yokohama

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CHAPTER 1

Introduction

1.1 Fundamental Phenomena in Chromatography

The quantitative analysis of molecular interactions is of fundamental interest, and the development of computer software has made it easy to calculate the theoretical properties of molecules. Feasibility can be demonstrated using simple, small molecules. Alkanes have demonstrated van der Waals energy contribution, and alkanols demonstrated the additional hydrogen-bonding energy contribution. Ion–ion interactions were related to the electrostatic energy contribution, and amino acids demonstrated the contribution of steric hindrance.

Chromatography is one technique that is used to measure molecular interaction strengths using model compounds, and an excellent technique for measuring the relative physico-chemical values of molecules in a short amount of time. Molecular recognition, the retention time difference, in chromatography can be quantitatively studied. Typical molecular interaction forces are clearly observed in different types of chromatography as the retention time differences of analytes. The individual molecular interaction forces are solubility factors. Chromatographic retention is based on the combination of solubility factors. Consistent with the concept of "like dissolves like" proposed by Henry Freiser, the retention mechanisms of chromatography are the same. Different types of chromatography demonstrate the typical molecular interaction forces, as summarized in Figure 1.1.[1] If we can reconstruct quantitatively obtained solubility factors, we can quantitatively analyze the chromatographic retention time.

Computational chemical analysis methods provide the molecular interaction energy as the sum of mainly van der Waals, hydrogen bonding, and electrostatic energy values. The van der Waals energy is related to molecular size, hence, the contact surface area between an analyte and an adsorbent contributes to the molecular interaction energy. When hydrogen bonding

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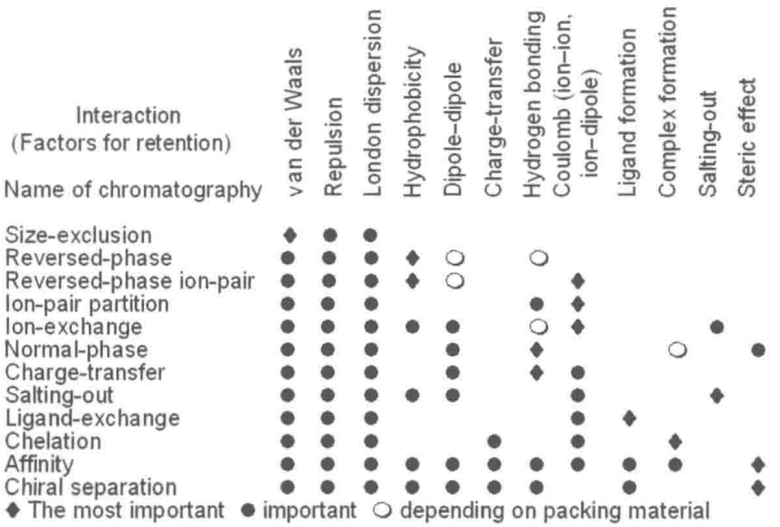

Figure 1.1 Classification in liquid chromatographic methods. Reproduced from ref. 1.

exists between an analyte and an adsorbent, hydrogen-bonding energy contributes to the molecular interaction energy. When ion–ion interactions exist, electrostatic energy contributes to the molecular interaction energy.

The measurement of direct interactions reveals the different strengths of molecular interactions between an analyte and the packing material surface or liquid phase. In gas chromatography, the retained compounds are vaporized and moved toward the column outlet. The analyte's volatility in the carrier gas affects the retention time.

In special cases, polar gases such as ammonia, formic acid and water are doped into the carrier gas to improve the analyte's solubility in the carrier gas. In both supercritical fluid and liquid chromatography, the analyte solubility in the carrier liquid affects the retention time. The carrier liquid is called the *eluent* and/or the *mobile phase*. The prediction of retention times in liquid chromatography is very difficult due to the lack of a solubility prediction method. However, the retention can be predicted by computational chemical methods using model phases.[2]

General computational chemical analysis of liquid chromatographic retention is performed without solvents in the calculation. Generally, mixed solvents with and without pH-controlled ions are present as the eluent components in liquid chromatography. At present, these solvent systems cannot be handled by computational chemical calculations. The measurement of direct interactions, however, reveals the different strengths of molecular interactions between an analyte and the packing material surface. The difference in molecular interaction energy values can be used as a relative retention time.

A typical example of a van der Waals energy contribution was observed in the analysis of chromatographic retention using a graphitized carbon

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