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Foreword

HILIC at 21: Reflections and perspective

Without being named as such, HILIC began in 1975 with the analysis of sugars by amino-silica columns [1,2]. Its extension to polar solutes in general can be connected in part to Ronald Reagan and Mikhail Gorbachev. In 1987, as a result of their policy of *glasnost*, Pine Bluff Arsenal in Arkansas was tasked with incinerating the American stocks of 3-quinuclidinyl benzilate, a chemical warfare agent also called Agent BZ. The technical staff discovered that all of the products of partial pyrolysis coeluted in reversed-phase chromatography (RPC), leaving them unable to follow the course of the chemical's destruction. One of them discussed the problem with an acquaintance who ran an analytical lab down the hall from my recently founded company. He in turn asked if I had any ideas. Since the compound was an alkaloid with a potential positive charge on the nitrogen atom and our company manufactured a weak cation-exchange column, I decided to try running it by ion-exchange chromatography. The retention was inadequate to resolve the compounds. I systematically varied the salt; the salt concentration; the pH. Nothing helped. Finally I tried varying the % methanol in the mobile phase. This didn't have much effect either until the level reached 80%. At that point retention increased dramatically with resolution adequate for the analysis. Pine Bluff Arsenal proceeded to order ten PolyCAT A® columns, a decent order in those days, and Agent BZ was successfully incinerated. Months later I was assessing the variables involved in retention of peptides on our prototype strong cation-exchange material. Retention was stronger at pH 3 than at pH 4, but when the level of methanol in the mobile phase exceeded 60%, retention again increased dramatically no matter what the pH [3]. Some force independent of electrostatic effects seemed to be present. Shortly thereafter, I noticed the same effect in a paper on analysis of peptides on a neutral size exclusion column [4]. By now this behavior seemed more than coincidence. These observations started the set of experiments that resulted in the paper that promoted the new mode of "Hydrophilic Interaction Chromatography", for separation of polar compounds in general [5].

HILIC moved into labs at a slow but steady pace, with about 80 papers published by 2002. The pace picked up with alacrity in 2003, when Waters Corp. began to promote its Atlantis® silica columns for HILIC and SeQuant AB introduced its ZIC-HILIC® material [6]. Their manifest success encouraged other companies to introduce their own silica, diol, and other columns for the purpose. By 2009, usage of HILIC had surpassed that of every mode of chromatography except RPC. HILIC is now well-established for some applications such as analysis of pharmaceuticals. It seems unlikely that HILIC will surpass RPC. Both are convenient general-purpose methods that complement each others' selectivity. Much of the content of this issue involves papers that examine the mechanisms involved in HILIC, generally by constructing models and then testing them with various standards. The paper by Dinh et al. is a particularly noteworthy example. HILIC sees occasional use for peptides in proteomics. Looking ahead, it can potentially solve a problem in proteomics that RPC seems unable to handle: the separation of intact proteins in volatile solvents for top-down analysis via mass spectrometry. The paper in this issue by T. Tetaz et al. provides an early demonstration of this.

As a result of recent advances in mass spectrometry and computation, developed for proteomics and metabolomics, it is now possible to characterize and identify thousands of compounds upon elution in chromatography. This makes it feasible to study the mechanisms in HILIC through an inductive approach, using the chromatographic behavior of numerous analytes to identify trends in retention. The progress in proteomics made possible by HILIC may be reciprocal. To quote Mikhail Tswett: "Every scientific advance is an advance in method [7]."

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