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On the enantioselectivity of the mass transfer kinetics and the adsorption equilibrium of Naproxen on the chiral stationary phase (*R*, *R*)-Whelk-O1 under reversed-phase conditions

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ABSTRACT

The adsorption of the Naproxen enantiomers on a Pirkle-type chiral stationary phase (CSP) (*R*, *R*)-Whelk-O1 from 0.01 M acetic acid solution in a methanol–water (85/15, v/v) mixture was studied using techniques of frontal analysis and elution chromatography. Adsorption was found to follow a model that assumes retention of a solute on two types of surface sites, enantioselective and nonselective. Some minor deviations from the classical bi-Langmuir model were found, but they were well accounted for by assuming the coexistence of two groups of enantioselective sites: sparse sites of strong affinity toward (*R*)-Naproxen and a more numerous type of low-energy sites exhibiting a somewhat different affinity toward the two enantiomers. Special consideration is paid to the adsorption of the methanol–water mixture on the surface of the CSP. The bonded organic layer exhibits hydrophobic properties, so the adsorbed layer is enriched in methanol throughout the whole range of mobile phase compositions. The study of the mass transfer kinetics was carried out by analyzing the dependence of the HETP on the flow velocity. It revealed the enantioselective character of the intraparticle transport processes. Other aspects of the column dynamics, such as axial dispersion, the external and internal mass transfer were also discussed.

1. Introduction

The resolution of the Naproxen enantiomers (Fig. 1) on a Whelk-O1 chiral stationary phase (CSP) (Fig. 2) [1,2] is the most prominent example of direct chromatographic enantioseparation. Since its publication in 1992 [1], it has been abundantly cited in numerous reviews and has become an obligatory part of chapters and treatises on chiral separations. It illustrates the potential of chiral chromatography to solve complicated separation problems, like the direct resolution of the racemates of underivatized acids. It is also one of the most successful demonstrations of a rational approach for the design of chiral selectors that has since then become an important tool in the development of CSPs [2]. The nature of the enantiodiscrimination between the Naproxen enantiomers by the Whelk-O1 chiral selector was comprehensively studied [3–9]. However, the macroscopic mechanisms of adsorption of Naproxen on this CSP remain unclear. Apparently, only a recent publication [10] discusses the adsorption isotherms of the Naproxen enantiomers on this CSP while there are no data on their mass transfer kinetics.

The main goal of this work is to fill in the gaps in our knowledge of the equilibrium and the dynamics of adsorption on this important Pirkle-type phase. The work was carried out under reversed-phase conditions (with a methanol–water mobile phase). This choice was dictated by a requirement of a high solubility of the analyte in the mobile phase, which is necessary for the measurement of adsorption isotherms over a wide concentration range. Besides, the application of Whelk-O1 in the reversed-phase mode has been poorly covered. A few examples of the use of this CSP with water-containing mobile phases have been previously reported [11–13]. The retention of several chiral analytes in reversed-phase liquid chromatography and in the so-called polar organic mode were studied using a linear chromatography method [14,15]. Therefore the extension of investigations involving aqueous solutions is of separate interest.

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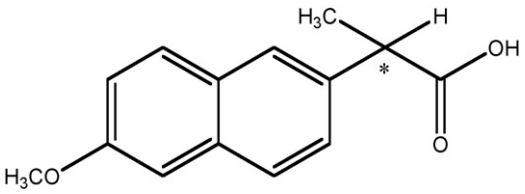

Fig. 1. Structure of Naproxen. Symbol "star" shows the location of the chiral center.

2. Theory

2.1. The concepts of excess and total adsorption

The two definitions of the adsorbed amount, excess and total amounts adsorbed, are used in this work. A detailed description of those concepts can be found in Refs. [16,17]. Only a brief summary useful for the subsequent discussion is given. The excess amount adsorbed is defined as the excess of solute contained in the adsorption system compared to what would be contained in a hypothetical system in which the solute concentration is uniform throughout the whole volume of mobile phase and equal to the equilibrium concentration in the bulk phase of the real system [17]. This value is directly measured in an adsorption experiment. The measurement does not require any prior knowledge of the size, structure, and properties of the actual adsorbed phase, in contrast to the value of the total adsorbed amount, which is defined as the amount of solute contained in an adsorbed layer of finite thickness [18].

The operational definition of the excess adsorbed amount adopted in this work relies on the assumption of a constant total volume of the liquid phase in the system, V_0 [16]:

$$\Gamma_i = \frac{(c_{0,i} - c_i)V_0}{V_a} \tag{1}$$

where $c_{0,i}$ and c_i are the concentrations of the component i before and after the equilibrium is established, and V_a is the stationary phase volume.

The expression determining the total adsorption reads

$$q_i = \frac{g\,S}{V_a} c_i \delta + \Gamma_i(c_i) \tag{2}$$

where g is the mass of adsorbent, S its specific surface area, and δ the thickness of the adsorbed layer. Since there are no experimental methods able to determine the analyte distribution in the direction normal to the surface, the assignment of δ relies on a conceptual model of the structure of the adsorbed phase, which is generally arbitrary. Note that for solutions of solids, it is almost always safe to assume that the excess adsorption is equal to the total adsorbed amount, because the solute concentration is restricted by the solubility of the solid, which is generally low enough for the term $(gS/V_a)c\delta$ to be negligible compared to Γ.

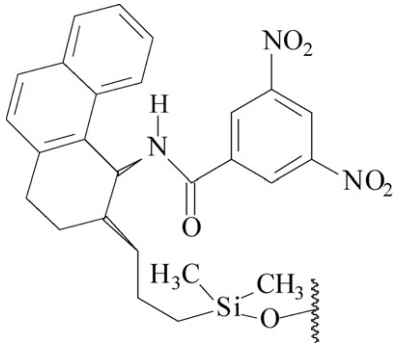

Fig. 2. Structure of the (*R,R*)-Whelk-O1 chiral selector.

2.2. Total adsorption isotherm models

The concept of total adsorption allows the use of an approach based on the law of mass action to studies of liquid/solid equilibria. In the framework of this approach, a number of adsorption isotherm models were developed, including the well-known Langmuir isotherm. This model supposes that there exists on the surface of an adsorbent a finite number of adsorption sites of equal affinity toward a certain compound, the adsorbate. Let $q^\star$ be the concentration of these adsorption sites and b be the adsorption equilibrium constant or adsorption coefficient. Then the isotherm equation reads

$$q = \frac{q^\star bc}{1 + bc} \tag{3}$$

In chiral chromatography, an adsorption model is often considered, in which two types of adsorption sites coexist on the stationary phase, the enantioselective and the nonselective sites. These sites are assumed to interact independently with a chiral analyte [19,20]. The enantioselective sites exhibit different affinities toward the two enantiomers whereas the nonselective sites interact with both antipodes identically. The adsorption isotherm for this model (the so-called bi-Langmuir isotherm) is merely the sum of two Langmuir terms, one for each types of adsorption sites:

$$q = \frac{q^\star_{ns} b_{ns} c}{1 + b_{ns} c} + \frac{q^\star_s b_s c}{1 + b_s c} \tag{4}$$

The indices *ns* and *s* correspond to the nonselective and the selective adsorption sites, respectively. It is obvious that for the enantiomers (*R*) and (*S*), the following conditions are true:

$$b_{ns,R} = b_{ns,S} = b_{ns} \qquad \text{and} \qquad b_{s,S} \neq b_{s,R} \tag{5}$$

The equilibrium adsorption constants at infinite dilution (Henry coefficient, K_H) for this isotherm is given by the expression [19]:

$$K_H = q^\star_{ns} b_{ns} + q^\star_s b_s \tag{6}$$

where b_s is different for both enantiomers while $q^\star_s$, $q^\star_{ns}$, and b_{ns} are identical.

2.3. Mass transfer kinetics

During its migration through a bed of an adsorbent, a solute band broadens due to the influence of two factors: a thermodynamic and a kinetic one. Under linear conditions, only kinetic phenomena cause broadening of chromatographic bands [21]. Therefore the measurements of the peak dispersion of strongly diluted samples provide information on kinetic processes in a chromatographic column. In general, one considers four mechanisms of kinetic band broadening: axial dispersion, the external film mass transfer resistance, intraparticle diffusion, and the rate of adsorption–desorption. The general rate (GR) model of column dynamics takes into account all these mechanisms [21]. The model assumes that (1) the mobile phase percolates through the interstitial volume between stationary phase particles while it is stagnant in the particles; (2) that solute molecules diffuse from the flowing stream to the stagnant mobile phase and across it; and (3) that adsorption–desorption takes place between the stagnant mobile phase within the pores and the adsorbent surface. The set of mass balance and kinetic equations describing the GR model cannot be solved analytically in time domain. However, there exists a solution in the Laplace domain, from which the statistical moments of the band profiles are readily derived [21].