Insights into chromatographic enantiomeric separation of allenes on cellulose carbamate stationary phase

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ABSTRACT

Allenes are cumulenes with three contiguous carbons linked together through double bonds. 1,3-disubstituted allenes are not superimposable on their mirror image; as a consequence they are chiral. Chiral allenes are increasingly important in organic synthesis due to their interesting reactivity. Because of their applications in the field of asymmetric catalysis and in the pharmaceutical industry their optical purity is always a parameter which needs to be determined. In this article, we report the enantiomeric separation of hexa-3,4-diene-3-ylbenzene, an aromatic allene, on a cellulose carbamate (Chiralcel OD-3) stationary phase, using heptane as the mobile phase. Spectroscopic studies using infrared (IR) and vibrational circular dichroism revealed that, in the presence of heptane, the stationary phase undergoes a conformational change due to intermolecular H-bonding between the C=O and N—H of the neighboring polymer chains. Van't Hoff plots for the retention factor, k, showed that the retention of the two enantiomers is dominated by the enthalpy, while the plot for the selectivity, α, is entropy driven. This suggests that the enantioselectivity is a result of inclusion of the enantiomers in the cavities of the chrial stationary phase. VCD spectra, along with density functional theory calculation (DFT) of the interaction between each enantiomer and the chiral stationary phase, supported the chromatographic elution order findings.

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1. Introduction

Allenes are one of the most attractive building blocks for organic synthesis. They have three-carbon functional groups with a 1,2-diene moiety which can be a precursor in the synthesis of complex and strained target molecules. As such, they have a wide range of applications in many fields of chemistry. Their unique reaction behavior, where the reactivity is spread over three contiguous carbon atoms, has been successfully applied to the field of pharmaceuticals, dyes, and polymers [1]. The central carbon has a linear sp hybridization leading to a 90° twist in the middle of the molecule. The terminal carbons of allene are sp^2 hybridized. If the allene unit has two different substituents in position 1,3-, two structures are obtained which are not superimposable on their mirror images; they are therefore chiral. Chiral allenes are classical examples of molecules that contain a stereogenic axis [2]. Due to the two contiguous C=C bonds they show unique physical and chemical properties which make them very useful in organic synthesis – in particular in catalytic asymmetric synthesis and natural product synthesis [1,3,4], with immediate applications in the pharmaceutical industry. As a consequence their optical purity is always a parameter which needs to be determined.

Quantum mechanics computation of allenes showed that the frontier molecular orbital (FMO) for chiral allenes is extended with a helical topology. With extended non-linear π interactions, allenes exhibit extended conjugation. For the chiral allenes, the FMO and molecular modeling of the highest occupied molecular orbital (HOMO) show a left-handed helix for one enantiomer and a right-handed helix for the other [5].

Lately, the advancement in the vibrational spectroscopy made it possible to apply electronic circular dichroism in the vibrational spectroscopy. Vibrational circular dichroism (VCD) is the extension of electronic CD (ECD) into infrared and near-infrared regions of the spectrum where vibrational transitions occur within the ground

electronic state of the molecule. VCD is the differences of vibrational spectra with respect to left (LCP) vs. right circularly polarized (RCP) radiation. VCD measure the difference in the absorbance of LCP and RCP infrared radiation for a vibrational transition [6]. The technique is very sensitive to chirality of compounds, allowing the determination in solution of absolute configuration of organic molecules, conformational changing of biopolymers and interactions of biopolymers with small organic molecules.

Allenes were intensively studied using infrared (IR) and VCD spectroscopy; extensive quantum mechanical calculations were also performed [7,8]. Rode et al. [8] described a VCD theoretical calculation for a series of halogenated allenes and showed the influence of halogen on the VCD and IR spectra. Narayanan et al. [7] used fixed partial charges (FPC) and localized molecular orbital (LMO) models of VCD to generate calculated VCD results, which were compared with the experimental results. When comparing the experimental results, the authors concluded that the FPC model gives better results than the LMO model.

There are several studies on the enantiomeric separation of chiral allenes. Thus, Pietruszka et al. described the synthesis of a homologous series of 1-tert butyl-3-alkyl-allenes as well as 1,2-cyclonadiene and higher homologues. The authors achieved the enantiomeric separation of all the compounds using gas chromatography with functionalized β and γ cyclodextrins as chiral stationary phases [9]. Although the enantiomeric separation was achieved, no mechanistic details on the interactions were provided.

Due to their capabilities of interacting through inclusion complexes, β-cyclodextrin and its hydroxyl derivatives were used for enantiomeric separation of allenic derivatives. Thus, Xu et al. [10] and Wang et al. [11] reported the separation of 2,3-alenoic acids using capillary zone electrophoresis, with β-cyclodextrin, hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin as the chiral selector in the running buffer. Wang et al. [11] added 2-propanol and sodium dodecyl sulfate in order to improve the enantioselectivity. These authors studied the influence of several parameters, such as buffer pH and ionic strength, in order to improve the resolution between enantiomers.

Pirkle et al. [12] reported on separation of allenic acid derivatives using high performance liquid chromatography (HPLC) with a Whelk-O1 column as a chiral stationary phase. The column was initially designed for the separation of naproxen enantiomers, but it has also been shown to be suitable for the enantiomeric separation of many classes of enantiomers. The chiral moiety is bound to a silica gel matrix and it contains a cleft-like binding site which preferentially interacts simultaneously through face-to-face and face-to-edge interactions with the chiral moiety; it does so without departing from a low energy conformation. Based on the presumed interactions, the authors were able to predict the elution order of the allenic compounds studied.

A different class of allenic compounds, 1,3-diphospha-allenes, were separated into enantiomers on a (+)-poly-(triphenylmethyl methacrylate) chiral stationary phase by HPLC; the separation was monitored by both a UV and an optical activity detector [13]. While NMR with a chiral shift reagent failed to discriminate between the two enantiomers, the only technique which gave satisfactory results was HPLC. Even though the separation was not baseline, it was good enough to establish the specific rotation of each enantiomer.

Due to its chirality, cellulose has been used for a long time for the separation of enantiomers. As a matter of fact, its chiral discrimination properties have been recognized since 1950, when Dalgliesh tried to separate aromatic amino acids on paper chromatography and postulated the three points of interaction required for chiral discrimination [14]. Later on, Lederer reported the separation of tryptophan on cellulose layers [15]. The beauty of cellulose consists in the presence of the hydroxyl groups, which can be chemically

modified, thus improving its enantioselectivity. A large class of compounds has been separated on such stationary phases [16].

Enantioseparation of allenes was reported by Krause et al. [17]. The authors separated allenes bearing ester, thioester, keto and hydroxyl groups by HPLC on a column with a stationary phase of cellulose triacetate. They found that the bulk of the substituents linked to the allene moiety have a great influence on their enantioseparation.

In the present paper we report the enantiomeric separation of an aromatic allene, hexa-3,4-dien-3-ylbenzene, using a commercially available cellulose carbamate chiral stationary phase (Chiralcel OD-3) coated on a 3 μm silica support. First, the absolute configuration of each enantiomer was determined using VCD spectroscopy and density functional theory (DFT) calculations. Second, temperature studies were performed to establish the thermodynamic parameters of the interactions between the two enantiomers and the chiral stationary phase. Third, molecular VCD spectroscopy, DFT calculations, and Molecular Mechanics (MM) and Molecular Dynamics (MD) were used in order to simulate the intimate interaction of each enantiomer with the chiral stationary phase.

2. Experimental

2.1. Material

Chiralcel OD polymer was a gift provided by Chiral Technologies, Inc. (PA, USA). All other reagents were purchased from the Sigma–Aldrich (St. Louis, MO, USA). The allene enantiomers were synthetized by the Chemical Development Department and characterized using ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.38 (d, J = 7 Hz, 2H), 7.29 (m, 2H), 7.16 (m, 1H), 5.49 (m, 9 lines, 1H), 2.40 (m, 21 lines, 2H), 1.76 (d, J = 7 Hz, 3H), 1.42 (s, C$_6$H$_{12}$), 1.13 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 204.4 (s), 137.6 (s), 128.2 (d), 126.3 (d), 125.9 (d), 106.9 (s), 89.5 (d), 26.9 (C$_6$H$_{12}$), 22.8 (t), 14.4 (q), 12.6 (q) (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT).

To make the tris(3,5-dimethylphenyl) carbamate polymer film, a stock solution was prepared by dissolving 10 mg of tris(3,5-dimethylphenyl) carbamate polymer in 1 mL tetrahydrofuran (THF). An aliquot of 200 μL of the stock solution was applied on a 32 mm diameter CaF$_2$ window. The window was subsequently dried under vacuum at room temperature for 8 hours. For the spectroscopic measurements of the dry film in the presence of heptane, the film was subsequently covered with another CaF$_2$ window of the same size, with a 50 μm Teflon spacer between the two windows. Approximately 100 μL of heptane was injected between the two CaF$_2$ windows. The solvent and the film were further equilibrated for 30 minutes prior to the VCD measurements. For the measurements of the interaction of the allene with the Chiralcel OD polymer film, about 3 mg of the pure enantiomer was dissolved in 100 μL of heptane and deposited on a CaF$_2$ window. The window was subsequently dried under vacuum at room temperature for 8 h before the VCD measurement.

2.2. Chromatography

The chromatographic experiments were performed on an Agilent 1100 HPLC system equipped with a vacuum degasser, a binary pump, a column oven and a photodiode array detection (DAD) (Agilent Technologies, Santa Clara, CA, USA). The allene's enantiomers were separated using a commercially available 4.6 mm × 150 mm column, Chiralcel OD-3 (Chiral Technologies), packed with cellulose tris(3,5-dimethylphenyl) carbamate adsorbed on a silica support (3 μm particle size). The mobile phase consisted of HPLC grade heptane which was pumped at flow of 1.3 mL/min. The temperature studies were performed in a range interval between 20 °C and 60 °C.