



# Metolachlor stereoisomers: Enantioseparation, identification and chiral stability



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## ABSTRACT

Metolachlor is a chiral herbicide consisting of four stereoisomers, which is typically used as a racemic mixture or is enriched with the herbicidally active 1'S-isomers. Because studies on the enantioselective behavior of phyto-biochemical processes and the environmental fate of metolachlor have become significant, a practical method for analyzing and separating metolachlor stereoisomers must be developed. In the present study, the enantiomeric separation of metolachlor was achieved using OD-H, AS-H, OJ-H and AY-H chiral columns. The effects of different organic modifiers in an *n*-hexane-based mobile phase were investigated, and various temperatures and flow rates, which may influence metolachlor separation, were also explored. The optimal resolution was obtained using an AY-H column with *n*-hexane/EtOH (96/4) as the mobile phase at a rate and temperature of 0.6 mL min<sup>-1</sup> and 25 °C, respectively. The absolute configuration of the four stereoisomers was identified as  $\alpha SS$ ,  $\alpha RS$ ,  $\alpha SR$ ,  $\alpha RR$  using computed and experimentally measured ECD and VCD spectra. Thermal interconversion and solvent stability experiments were also performed. Pure metolachlor stereoisomers in different organic solvents and water at 4 °C or 30 °C were stable. These results were used to establish a sound method for analyzing, preparing, characterizing, and preserving individual metolachlor stereoisomers in most natural environments.

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## 1. Introduction

Metolachlor (2-chloro-*N*-[2-ethyl-6-methylphenyl]-*N*-[2-methoxy-1-methylethyl] acetamide) is a pre-emergent selective herbicide for the control of a variety of annual grass and broad leaf weeds in corn and other crops [1]. An asymmetric carbon atom in the alkyl moiety of metolachlor, as well as hindered rotation about the Ar–N bond, yields two sets of enantiomers:  $\alpha SS/\alpha RR$  and  $\alpha RS/\alpha SR$ . Metolachlor was initially placed on the market as a racemic product. However, Moser et al. [2] found that C\*S-metolachlor (with respect to the C chiral center,  $\alpha RS$  and  $\alpha SS$ ) showed the highest herbicidal activity, while C\*R-metolachlor ( $\alpha RR$  and  $\alpha SR$ ) possessed superior antifungal properties. Although racemic metolachlor was replaced by C\*S-metolachlor-enriched products in many places to reduce herbicide usage and eschew the side effects of unnecessary enantiomers, C\*R-metolachlor has been identified in water [3,4] and other media.

Enantiomers possess identical physico-chemical properties, making them difficult to separate and analyze. Nevertheless, a vari-

ety of biological metabolic pathways have shown stereoselectivity. Although reports on the successful separation of metolachlor enantiomers have been limited, GC-CSP (gas chromatography-chiral phase separation) [5] and  $\gamma$ -CD-MEKC (cyclodextrin-modified micellar electrokinetic chromatography) [6] have provided partial resolution of the four isomers of metolachlor. Muller et al. [7] reported on the application of the achiral Hypercarb HPLC column and the chiral Chiralcel OD-H HPLC column for the separation and isolation of two metolachlor isomers in high enantiomeric purity. The absolute configurations of the four stereoisomers were assigned through polarimetric measurements in reference to previous data, and the kinetics of thermal interconversion was also studied. Polcaro et al. developed a method using a mixture of diethyl ether (DEE) and *n*-hexane as the mobile phase on an OD-H column, allowing the full separation of all four stereoisomers, which have not been previously resolved on any other chiral stationary phases [8]. However, DEE must be freshly prepared prior to HPLC analysis. And conformation transformations may occur under certain circumstances, such as exposure to heat and polar solvents, promoting isomer inversion and racemization. Jayasundera et al. identified the labile sites of metolachlor, as well as conformational and configurational changes in different chemical environments [9].

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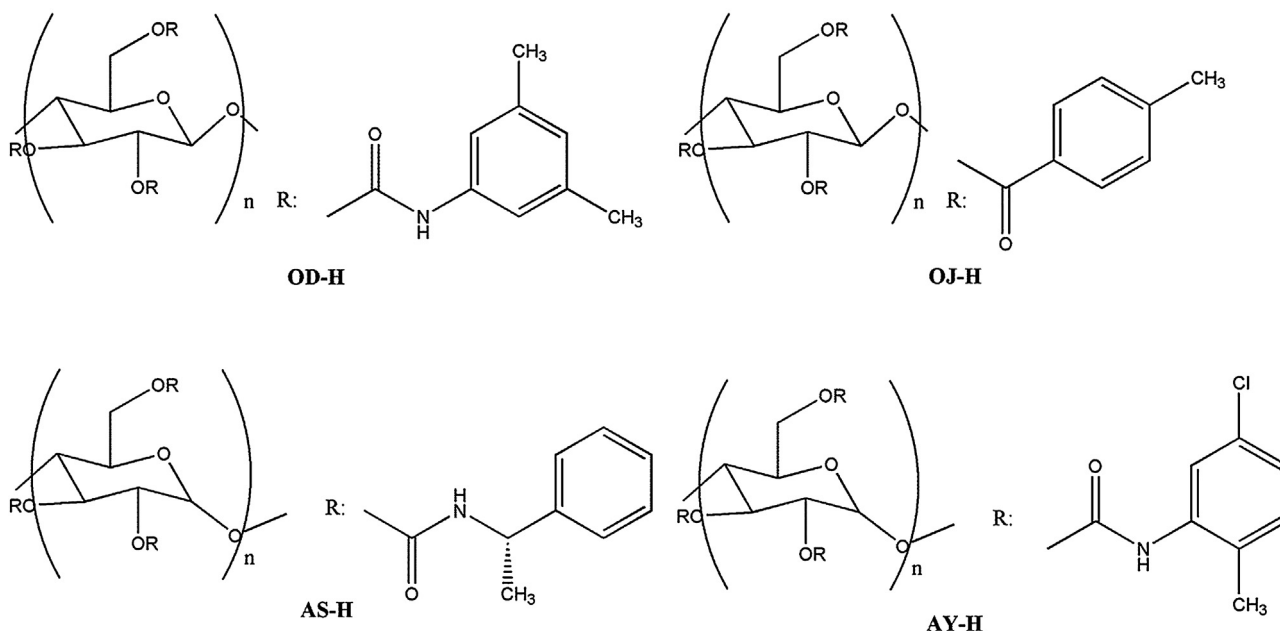


Fig. 1. The structures of the four CSPs on the chiral columns.

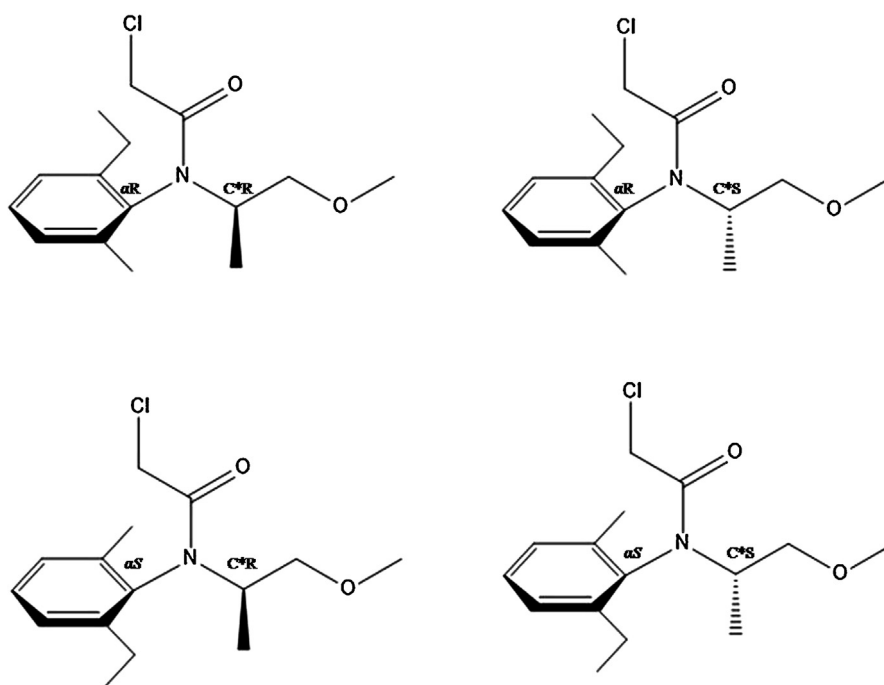


Fig. 2. Chemical structure of the four isomers of metolachlor.

Herein, we focused on developing a simple method for the separation of all four stereoisomers of metolachlor. The resolution of Chiralcel OD-H, Chiralcel AS-H, Chiralcel OJ-H and Chiralcel AY-H was compared, and the effects of the mobile phase composition, column temperature, and flow rates on the resolution were also investigated. The absolute configurations were assigned based on their optical rotation in ECD and VCD spectra, using both experimental and calculated data. The chiral stability of the four stereoisomers at 4 °C and 30 °C in different organic solvents and water was also determined. The current study provided an optimal approach for the acquisition of pure stereoisomers and the characterization of the absolute configurations of metolachlor. The results also offered

further clarification on the thermal interconversion and solvent stability of the stereoisomers.

## 2. Materials and methods

### 2.1. Chemicals and reagents

Racemic metolachlor (>97%) and C<sup>\*</sup>S-metolachlor were provided by Shandong Qiaochang Chemical (QCC). All HPLC grade solvents were obtained from Sigma. Stock solutions were prepared at a concentration of 1 mg mL<sup>-1</sup> in *n*-hexane and were stored at 4 °C.

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