Journal of Pharmaceutical and Biomedical Analysis 98 (2014) 130–139

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Structural and temperature effects on enantiomer separations of bicyclo[2.2.2]octane-based 3-amino-2-carboxylic acids on *cinchona* alkaloid-based zwitterionic chiral stationary phases

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ARTICLE INFO

Article history:
Received 7 April 2014
Received in revised form 8 May 2014
Accepted 10 May 2014
Available online 17 May 2014

Keywords:
Enantiomer separation
HPLC
Zwitterionic chiral stationary phases
Bicyclo[2.2.2]octane-based
3-amino-2-carboxylic acids
Temperature effect

ABSTRACT

Procedures for the direct high-performance liquid chromatographic enantiomer separation of four bicyclo[2.2.2]octane-based 3-amino-2-carboxylic acids were developed in polar-ionic mode on zwitterionic chiral stationary phases (CSPs) based on cinchonane alkaloide quinine, quinidine and chiral sulfonic acid motifs. The effects of the mobile phase composition including the type of acid and base additives, the structures of the analytes and temperature were investigated.

Experiments were performed at constant mobile phase compositions in the temperature range 10–50 °C in order to study the effects of temperature, and thermodynamic parameters were calculated from plots of ln k or ln α *vs.* $1/T$. Some mechanistic aspects of the chiral recognition process are discussed with respect to the structures of the analytes. It was found that the enantiomeric separations were in most cases enthalpically driven, but entropically driven separation was also observed. The sequence of elution of the enantiomers on the pseudo-enantiomerically behaving CSPs was determined in all cases.
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1. Introduction

In consequence of their biological effects, conformationally constrained alicyclic β-amino acids have generated great interest among synthetic and medicinal chemists in the past decade, and they have become a hot topic in organic and bioorganic chemistry [1]. These compounds are found in natural products and antibiotics. They are also considered important precursors for pharmacologically interesting β-lactams and other bioactive compounds [2–7]. Moreover, these compounds may be applied as building blocks in peptide synthesis: the incorporation of novel β-peptides, and especially foldamers, with unique properties, has recently been attracting attention because of the feasibility of derivatization with various side-chains in the α and β positions [8–11].

Conformationally constrained bicyclo[2.2.2]octane β-amino acids are of great interest, in view of their roles in both synthetic and medicinal chemistry [12–14]. These compounds (Fig. 1) simultaneously combine the particular structural properties of constrained cyclic amino acids and those of β-amino acids, which are more resistant than α-amino acids to enzymatic degradation. The interest in these bicyclic amino acids is highlighted by publications on several investigations in recent years [15–17].

Since the biological and physicochemical properties of amino acids are strongly related to their stereochemistry, enantioselective high-performance liquid chromatography (HPLC) is routinely used for the discrimination of enantiomers. For HPLC enantioseparations of β-amino acids, chiral derivatizing agents [18], chiral stationary phases (CSPs) based on macrocyclic glycopeptides [19–25], *Cinchona* alkaloids [26,27], (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acids [28–34], cyclodextrins [35,36], cyclofructans [37] and polysaccharides [38] have been used.

The effects of temperature in enantioselective separations have been studied extensively and a number of papers have been published on this issue [39–46].

The dependence of the retention of an analyte on temperature can be expressed by the van't Hoff equation, which may be interpreted in terms of mechanistic aspects of chiral recognition:

$$\ln k = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} + \ln \phi \quad (1)$$

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http://dx.doi.org/10.1016/j.jpba.2014.05.012
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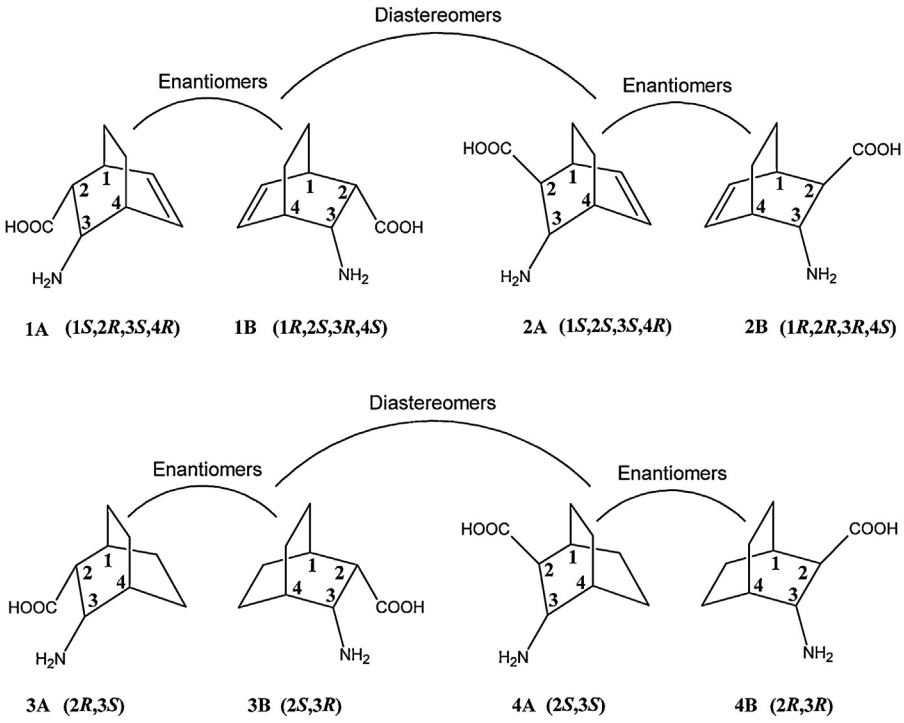

Fig. 1. Structure of analytes.

in which k is the retention factor, ΔH° is the standard enthalpy of transfer of the solute from the mobile phase to the stationary phase, ΔS° is the standard entropy of transfer of the solute from the mobile phase to the stationary phase, R is the gas constant, T is the absolute temperature and ϕ is the phase ratio of the column: $\phi = V_S/V_M$.

This equation reveals that a plot of ln k *vs.* $1/T$ is linear, with slope $-\Delta H^\circ/R$ and intercept $\Delta S^\circ/R + \ln \phi$, if ΔH° is invariant with temperature. Since the value of ϕ is often not known, the $\Delta S^{\circ *}$ values [$\Delta S^{\circ *} = \Delta S^\circ + R \ln \phi$] calculated from the intercepts of the plots *via* Eq. (1) are generally used. Any uncertainty in the phase ratio affects the $\Delta S^{\circ *}$ values virtually equally.

Chromatographic selectivity is determined by the difference in free energy $\Delta(\Delta G^\circ)$ of adsorption of the enantiomers:

$$\Delta(\Delta G^\circ) = -RT \ln \alpha = \Delta(\Delta H^\circ) - T\Delta(\Delta S^\circ) \quad (2)$$

where α is the selectivity factor ($\alpha = k_2/k_1$). If $\Delta(\Delta H^\circ)$ is constant within the given temperature range, in a plot of ln α *vs.* $1/T$ the slope is $-\Delta(\Delta H^\circ)/R$ and the intercept is $\Delta(\Delta S^\circ)/R$.

Newly developed *Cinchona* alkaloid-based zwitterionic CSPs were recently applied for the enantiomeric separation of acids, amines, amino acids and small peptides [47–51]. Selector-selectand (SO–SA) interactions and the enantioselective retention of the analytes are mainly governed by ion-exchange processes. Besides the coulombic interactions, other types of secondary interactions, such as H-bonding, π–π, dipole–dipole and/or van der Waals interactions, may be involved in the chiral discrimination process [27,47–49,52].

The present paper describes the enantioseparation of four bicyclo[2.2.2]octane-based 3-amino-2-carboxylic acids (Fig. 1) on *Cinchona* alkaloid quinine(QN)- and quinidine(QD)-based zwitterionic chiral selectors (SOs) (Fig. 2) containing a weak tertiary-amine group, which upon protonation becomes an anion-exchanger site, and a strong sulfonic acid group, which becomes a cation-exchanger site. In the polar-ionic mode (PIM) of elution (mobile phase: MeOH/MeCN containing acidic and basic additives), the effects of the mobile phase composition, including the type of acidic and basic additives were investigated, methanol/acetonitrile (MeOH/MeCN) being applied as bulk solvent in the mobile phase. The effects of the structural features of SAs and SOs on the retention, enantioselectivity and thermodynamic parameters are discussed.

2. Experimental

2.1. Synthesis

The analytes in this study (Fig. 1) possess unsaturated or saturated bicyclic skeletons with carboxy and primary amino groups in an *endo-exo* or *diendo* position. The starting *diendo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (**1**) and racemic ethyl *diendo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate were prepared by a literature method [53]. *Diendo*-amino acid **1** was transformed into *cis*-amino acid **3** with H_2 in the presence of Pd/C [53]. Isomerization of ethyl *diendo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate with NaOEt in EtOH resulted in ethyl *2-exo-3-endo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate. *Diendo*- and *endo-exo*-amino ester derivatives were transformed into *cis*- and *trans*-amino ester derivatives of **3** and **4** with H_2 in the presence of Pd/C. When subjected to microwave irradiation in H_2O at 150 °C for 1 h, the *cis* and *trans* esters gave amino acids **2** and **4**. Ethyl *diendo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate was resolved with *O,O′*-dibenzoyltartaric acid *via* diastereomeric salt formation. The syntheses of the enantiomers of *diendo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (**1A** and **1B**), 2-*exo*-3-*endo*-3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (**2A** and **2B**), and *cis*- and *trans*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid (**3A**, **3B**, **4A** and **4B**) were achieved *via* isomerization, hydrogenation and hydrolysis of the corresponding ester enantiomers [54]. The stereochemistry and absolute configurations of the synthetized compounds were determined by NMR spectroscopy and X-ray crystallography [53,54].

The difference between analytes **A** and **B** is due to the difference in the steric orientation at positions 1, 2, 3 and 4 (Fig. 1); they are enantiomers. Hence, the configurations of the enantiomers

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