Tetrahedron 74 (2018) 4846–4856

Contents lists available at ScienceDirect

Tetrahedron

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

Comparison of chiral NMR solvating agents for the enantiodifferentiation of amines

Brooke Benedict, Christopher E. Lietz, Thomas J. Wenzel*

Department of Chemistry, Bates College, Lewiston, ME, 04102, USA

ARTICLE INFO

Article history:
Received 29 May 2018
Received in revised form
26 July 2018
Accepted 27 July 2018
Available online 3 August 2018

Keywords:
Chiral solvating agents
Amines
Enantiodifferentiation
Enantiomeric purity
NMR spectroscopy

ABSTRACT

Chiral, enantiomerically pure organic-soluble acids are often used as NMR chiral solvating agents (CSAs) for analyzing the enantiopurity of amines. However, the reports that describe CSAs for amines provide limited comparisons to other previously reported reagents. As such, it is difficult to know which among the many CSAs to pick when studying a new amine. We report a comparison of thirteen commercially available CSAs for the analysis of primary, secondary and tertiary amines in chloroform-*d*. (*R*)-α-methoxyphenylacetic acid, (*R*)-(-)-*O*-acetylmandelic acid, (*R*)-2-methoxy-2-(1-naphthyl)propionic acid and (*R*)-(-)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate are identified as the best four to use as a starting point for the analysis of a new amine.

1. Introduction

NMR spectroscopy is often used for analyzing the enantiopurity of compounds. In an achiral environment, enantiotopic nuclei on the two enantiomers are isochronous and have identical chemical shifts. In an enantiopure chiral environment, enantiotopic nuclei become anisochronous and may exhibit different chemical shifts in the NMR spectrum. Enantiopure chiral derivatizing agents (CDAs), chiral solvating agents (CSAs), metal complexes and liquid crystals are commonly used for determining enantiopurity of analytes by NMR spectroscopy [1–14].

CDAs form a covalently bonded derivative with the analyte. The products of reacting the two enantiomers with the CDA are diastereomers and may have different chemical shifts in the NMR spectrum. In addition to requiring a derivatization reaction, CDAs are subject to the possibility of kinetic resolution in which one enantiomer of the analyte reacts faster than the other. Also, it is possible that some loss of configuration of either the CDA or analyte can occur in the derivatization reaction. Kinetic resolution and any loss of configuration will compromise the analysis of enantiopurity.

CSAs associate with the analyte through non-covalent interactions. Under conditions of fast exchange, the NMR spectrum of the analyte is a time average of its unbound and CSA-bound form. The complexes of the two enantiomers of the analyte with the CSA are diastereomeric and may have different chemical shifts. Alternatively, the association constants of the two enantiomers with the CSA may be different, which will result in different time-averaged solvation environments and may cause differences in the chemical shifts. CSAs are not subject to the possibility of kinetic resolution and loss of configuration of the CSA or analyte is seldom a consideration. Another advantage of using CSAs is that they only need to be mixed with the analyte in an appropriate solvent prior to recording the NMR spectrum.

Numerous CDAs and CSAs have been developed for use in NMR spectroscopy [1–14]. A limitation is that the effectiveness of most new chiral NMR reagents reported in the literature is not adequately compared to already-existing reagents. Many CDAs and CSAs are evaluated with only a limited range of analytes that differ from report to report. Also, spectra of analytes with CSAs present are often recorded with different concentrations, thereby compromising a direct comparison of their relative effectiveness.

The analysis of amines is an example where comparisons of the effectiveness of different CSAs are inadequate. A common strategy for the analysis of chiral amines is to use an enantiomerically pure chiral carboxylic acid in a solvent such as chloroform. An acid-base neutralization reaction occurs and an ion pair between the

* Corresponding author.
E-mail address: twenzel@bates.edu (T.J. Wenzel).

https://doi.org/10.1016/j.tet.2018.07.053
0040-4020/

ammonium salt and carboxylate ion occurs. However, an investigator with a new analyte will have considerable uncertainty as to which CSA to choose unless it has a structure that closely corresponds to the structure of an analyte in a prior report.

We report herein a comprehensive evaluation of the effectiveness of thirteen commercially available CSAs for the NMR enantiodifferentiation of chiral primary, secondary and tertiary amines. We identify four CSAs that are most effective and collectively cause enantiodifferentiation in the NMR spectra of all of the analytes that are examined. These four CSAs are recommended as the starting point for an investigator wishing to determine the enantiopurity of a new amine analyte.

2. Results and discussion

The criteria used in selecting CSAs to test for the analysis of amines involved commercial availability, acceptable cost, and prior reports that demonstrated their effectiveness or indicated their likelihood at being effective for the analysis of amines. We selected thirteen different CSAs for comparison (Fig. 1). Ten are carboxylic acids: (*R*)-α-methoxyphenylacetic acid (≧99% ee) (**C1**) [15,16], (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (≧99% ee) (**C2**) [17–23], *N*-Boc-L-phenylglycine (95% ee) (**C3**) [8], *N*-(3,5-dinitrobenzoyl)-(*R*)-(-)-α-phenylglycine (99% ee) (**C4**) [8], (*S*)-mandelic acid (≧99% ee) (**C5**) [21,22,24–28], (*R*)-(-)-*O*-acetylmandelic acid (99% ee) (**C6**) [15,26,29,30], dibenzoyl-L-tartaric

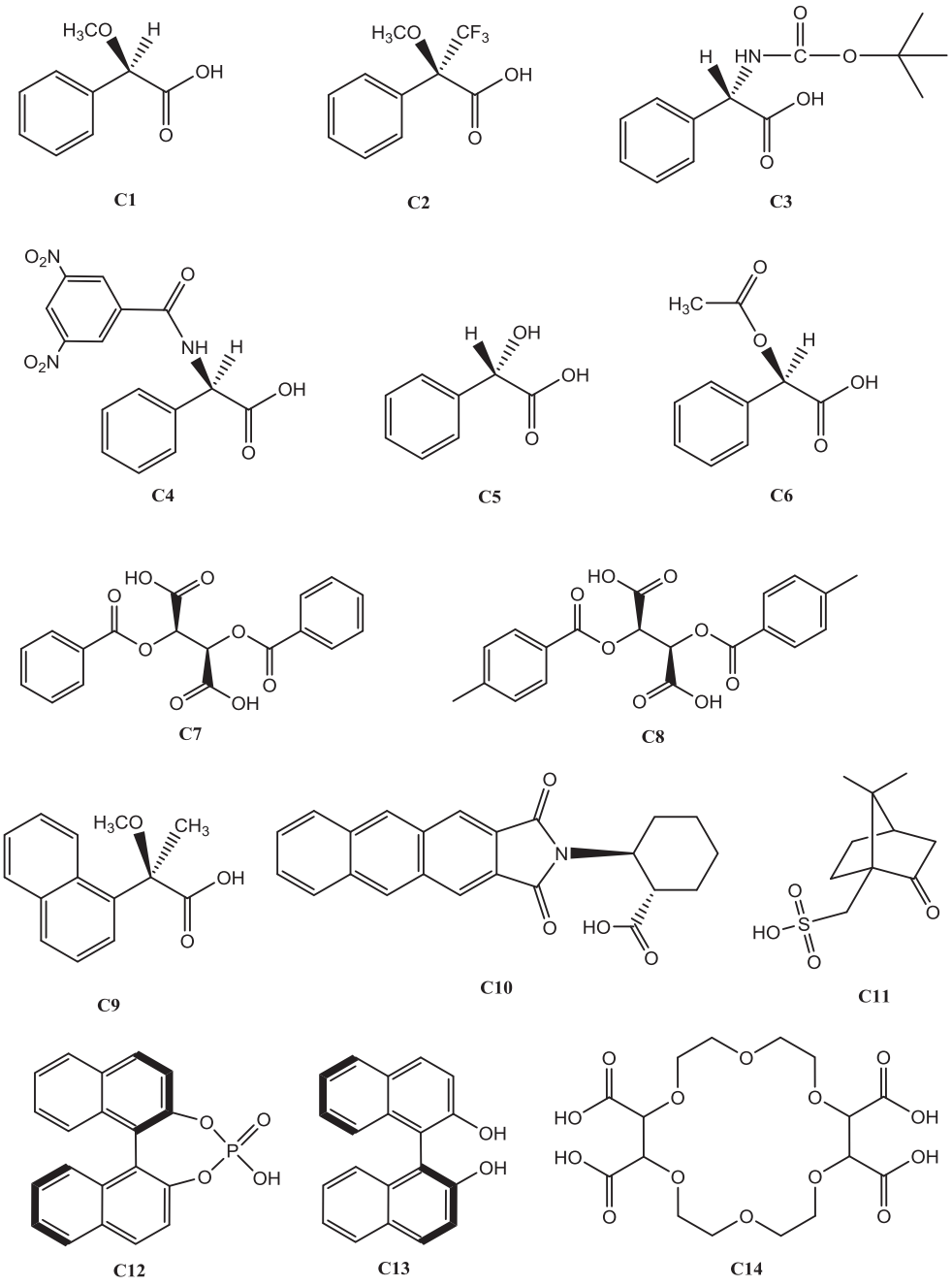

Fig. 1. Chiral solvating agents.