Chemistry Research Journal, 2019, 4(4):106-109

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

A Simple and Fast Resolution of Racemic Diaminocyclohexane using Tartaric acid

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Abstract A racemic mixture of diaminocyclohexane has been successfully resolved using L- and D- isomers of tartaric acid to afford the corresponding enantiomers in excellent yield and enantiomeric excess. The method provided an alternative approach to the commonly reported procedures which utilise the use of synthetically difficult and economically expensive polymers.

Keywords Chiral compounds, Racemic mixture, Resolution, Tartaric acid

Introduction

The majority of the over-the-counter drugs are characterized by the presence of chiral center(s) and most often the desired effect rest on one isomer but the other isomer may be undesirable or even harmful [1]. For instance, L-propranolol has more β-blocking activity than its D-isomer by a factor of 100% [2], and (S)-verapamil is effective calcium channel blocker while (R)-verapamil produces cardiac side effects [3]. Thus, considering the importance of chirality vis-á-vis drug activity, the United States Food and Drug Administration (USFDA) has mandated the pharmaceutical companies to test each enantiomer of a chiral drug separately for therapeutic efficacy and safety [4]. Practically, the resolution of the racemic mixture is an option of obtaining pure isomers provided that it is simple and economical. Currently, most of the reported methods utilized liquid and polymer membranes [5-9]. Although this approach demonstrated good permeability and enantioselectivity, unfortunately it suffers setbacks of durability and stability [10, 11]. Hence, it is essential to develop new methods that employ cheap materials with low-energy consumption, large processing capacity, and continuous mode of operation. In this work, an attempt has been made to employ a commercially available tartaric acid as a resolving agent for the racemic mixture of diaminocyclohexane.

Materials and Methods

All chemicals used were purchased from sigma-Aldrich and used without further purification. NMR spectra were recorded on Bruker Avance III HD spectrometer (400 MHz). All signals were expressed as ppm down field from TMS, referenced to the deuterated carbon signals in ^{13}C NMR (77.36 ppm). Measurements of optical rotations were performed using a Perkin Elmer 141 polarimeter. Elemental analyses were conducted using an Elementar Vario micro cube.

Resolution of (±)-trans-diaminocyclohexane

A 100 ml round bottom flask was charged with either L-(+)- or D-(–)-tartaric acid (1.48 g, 9.86 mmol), and distilled water (5 mL). The mixture was stirred at room temperature until complete dissolution occurred, at which point a mixture of (±)-*trans*-diaminocyclohexane (2.36 g, 19.7 mmol) was added at such a rate that the reaction temperature just reached 70^{o}C. To the resulting solution was added glacial acetic acid (0.96 mL, 17 mmol) at a rate such that the reaction temperature did not exceed 90^{o}C. A white precipitate formed immediately upon addition of the acid, and the slurry was vigorously stirred as it cooled to room temperature. The mixture was then cooled to <5^{o}C in an ice bath and the precipitate was collected by vacuum filtration. The wet cake was washed with 5^{o}C water (3 mL) and rinsed with methanol (5×3 mL). The *R*,*R*-1,2-diammoniumcyclohexane mono-(+)-tartarate (2.28g, 90%) and *S*,*S*-1,2-diammoniumcyclohexane mono-(–)-tartarate salts were both obtained as white solid (2.34g, 90%). The analytical data given below are for the respective salts. But in order to obtain the enantiomers as free bases, each of the salts was dissolved in CH_2Cl_2 (5 mL) and treated with 3 mL of 4M NaOH to afford the respective enantiomers as colourless liquid.

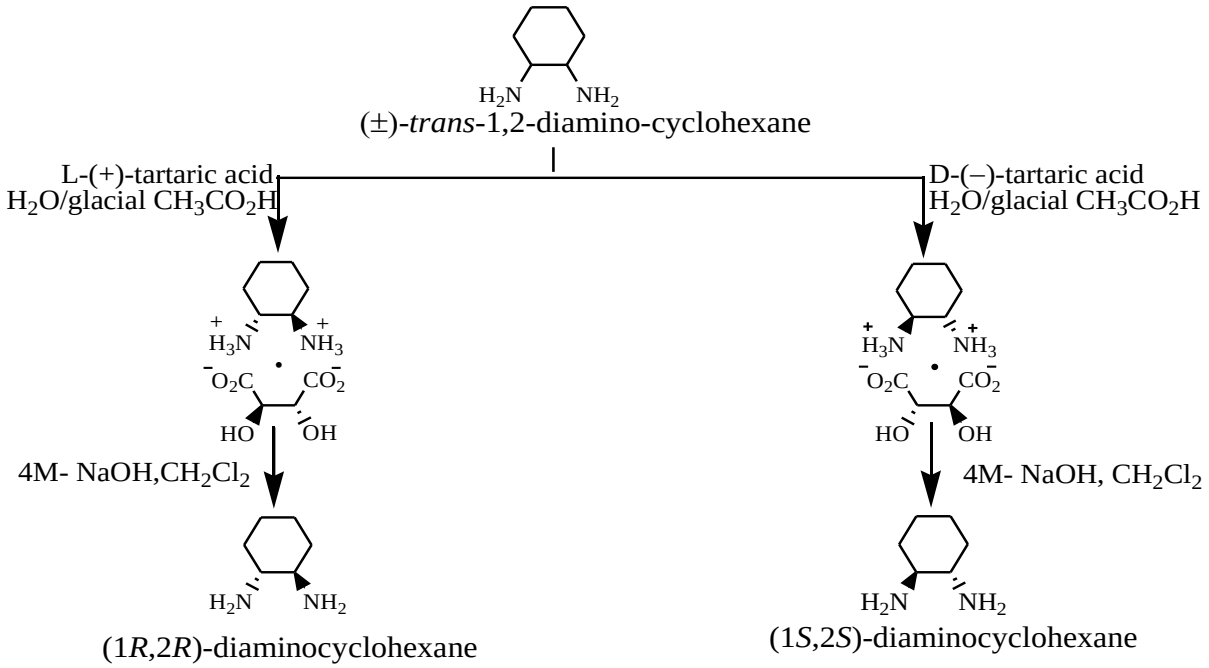
R,*R*-1,2-diammoniumcyclohexane mono-(+)-tartarate

$[\alpha]_D^{20}$ = +12.3 (*c*, 2 in H_2O); Anal. Calcd for $C_{10}H_{20}N_2O_6$ % : C, 45.45; H, 7.63; N, 10.60. Found: C, 45.41; H, 7.50; N, 10.59.

S,*S*-1,2-diammoniumcyclohexane mono-(–)-tartarate

$[\alpha]_D^{20}$ = –12.3 (*c*, 2 in H_2O); Anal. Calcd for $C_{10}H_{20}N_2O_6$ % : C, 45.45; H, 7.63; N, 10.60. Found: C, 45.44; H, 7.61; N, 10.62.

Results and Discussion



Scheme 1: Resolution of racemic diaminocyclohexanediamine

Scheme 1 shows the use of L- and D-tartaric acids to form the diastereomeric salts and thus resolve (±)-*trans*-1,2-diaminocyclohexane. The appropriate tartaric acid was dissolved in distilled water and stirred to obtain a homogenous solution. This was followed by the addition of the racemic mixture, followed by heating to ensure the temperature reached 70^{o}C.

Glacial acetic acid serves as a catalyst facilitating proton transfer and results in immediate formation of the respective salts as white precipitates. After thorough washing with water and methanol, both (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartarate and (*S*,*S*)-1,2-diammoniumcyclohexane mono-(–)-tartarate salts were obtained in excellent yields of 90%. Characterisation was performed using polarimetry to ascertain the optical purity of each salt, and the results showed that at 2M concentration in water and 20^{o}C in the presence of sodium light, the salts possessed equal and opposite specific rotations of +12.3° and –12.3°, which agreed with the literature value of 12.4° corresponding to 99% ee [12] Elemental analysis was also conducted to confirm the presence of nitrogen in the salts. In both case 10.59% nitrogen was found close to the calculated value of 10.62%. Furthermore, each salt was suspended in dichloromethane and then treated with 4M-NaOH (Scheme 1) to liberate the free amines. Stirring and extraction with ether afforded the *R*,*R*- and *S*,*S*-diaminocyclohexanes as colourless oils. The ^{13}C NMR spectrum of both of the enantiomers are of course identical (Figure 1).

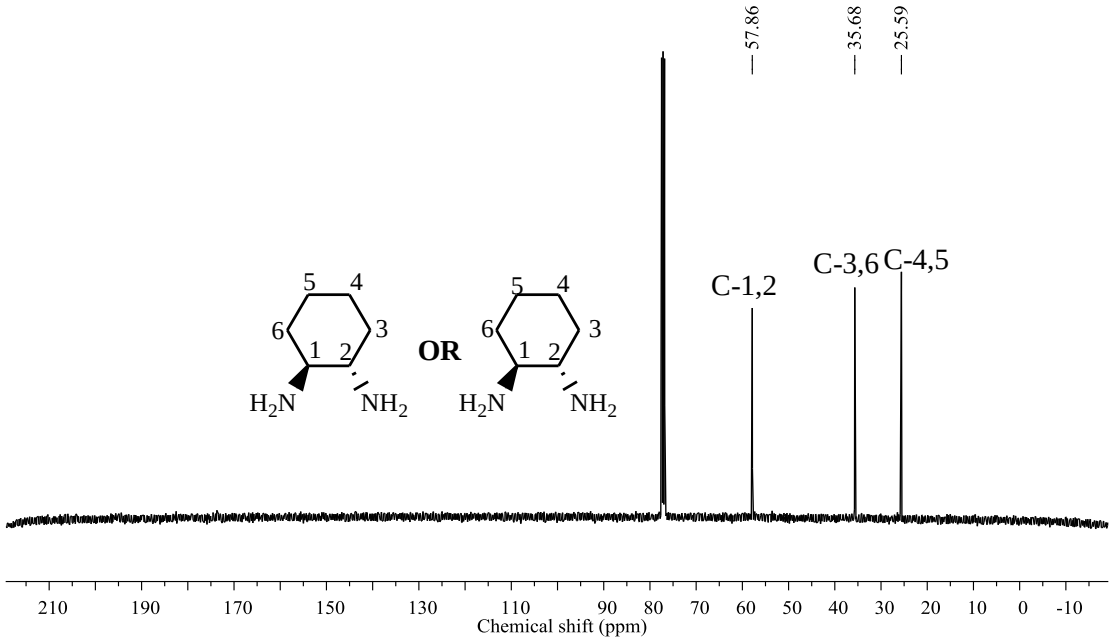


Figure 1:100 MHz ^{13}C NMR spectrum of either R,R- or S,S-diaminocyclohexane in $CDCl_3$

Conclusion

The resolution of a racemic mixture of diaminocyclohexane has been achieved using commercially cheap L- and D-isomers of tartaric acid to afford the corresponding diaminocyclohexane enantiomers in excellent yields and enantiomeric excess. This methodology is so efficient that the resolution was successfully performed at a gram scale. More importantly, the method has been developed without the incorporation of synthetically expensive and difficult materials that currently dominate this area of research.

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