# Preparative Separation of *meso* and racemic Bis(2,3-dihydroxypropyl)amine

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In the industrial production of 3-amino-1,2-propanediol from 3-chloro-1,2-propanediol and ammonia, bis(2,3-dihydroxypropyl)amine (BDA) is found as a bi-product from the reaction between 3-chloro-1,2-propanediol and 3-amino-1,2-propanediol.[1] BDA can be utilized to introduce hydrophilic functions in X-ray contrast media.[2] This paper describes the fractionation of BDA into *meso* and enantiomeric forms.

Initial attempts to separate the *meso* form from the enantiomeric forms directly with liquid chromatography (HPLC) failed. However, after BDA had been completely acylated with trifluoroacetic anhydride (TFAA), two peaks were obtained by gas chromatography as well as by liquid chromatography. In order to establish the identity of each peak, BDA was synthesized from optically active 3-amino-1,2-propanediol and acylated with TFAA. Fractionation and measurement of the optical rotation of the two components showed that the *meso* form eluted first, and that the optically active (+)-pentakis(trifluoroacetyl)BDA eluted as the second peak on silica. Hydrolytic cleavage followed by repeated derivatization with TFAA resulted in complete recovery of (+)-pentakis(trifluoroacetyl)BDA. Thus, optically active BDA could be obtained without isomerization in a three-step procedure consisting of derivatization with TFAA, fractionation on silica and hydrolysis with aqueous ammonia. With BDA synthesized from racemic 3-amino-1,2-propanediol, the *meso* form was separated from racemic BDA. In the fractionation step 0.8 g batches were separated in less than 1 h.

*Experimental. Instruments.* The HPLC equipment consisted of Waters Model 6000A pumps, R-401 differential refractometer, a preparative Perkin-Elmer 10 μm Silica column (250×22 mm) and analytical silica columns (MPLC Spheri 5 Silica from Brownlee Labs. and Supelcosil 3 μm LC–Si from Supelco, Inc.). A Hewlett-Packard HP 5880 A gas chromatograph was equipped with a flame ionization detector and a 2 m×2 mm stainless steel column packed with 3 % 2250 DB on 100/120 mesh Supelcoport, with an oven temperature of 155 °C. Infrared spectra were obtained with a Perkin-Elmer 281B infrared spectrophotometer, and the mass spectra were recorded on a VG 7070 F mass spectrometer with isobutane as chemical ionization gas at an ion source temperature of 140 °C. Higher temperature caused thermal decomposition. Proton NMR spectra were recorded on a JEOL 90 MHz spectrometer in deuterated acetone, and the optical rotations were determined in dichloromethane with a Perkin-Elmer 141 polarimeter.

*Derivatization.* BDA (1 g) was stirred with TFAA (10 ml) in a 100 ml round-bottom flask for 1 h. TFA and unreacted TFAA was removed in a rotary evaporator. The residue was dissolved in dichloromethane, washed with aqueous sodium hydrogencarbonate, dried with magnesium sulfate, filtered and evaporated. In small-scale syntheses (100 mg BDA) TFA and TFAA were removed directly with a stream of nitrogen at 50 °C, without extraction. The yields were 95–97 %. (Found: C 29.68, H 1.67. Calc. for $C_{16}H_{10}O_9NF_{15}$: C 29.78, H 1.56). NMR (acetone-$d_6$): CH 4.2 ppm (2H, m), CH 4.9 ppm (4 H, m), CH 5.9 ppm (2 H, m). MS: $MH^+$ (*m/e* 646, base peak), $MH^+ - TFA$, $MH^+ - 2(CH_2O-COCF_3)$. The infrared spectra confirmed complete *N,O*-acylation by the lack of OH and NH stretching at 3000–3500 $cm^{-1}$.

*Separation procedure.* Pentakis(trifluoroacetyl)BDA (0.8 g), dissolved in 1.5 ml toluene–nitromethane (80:20), was applied on the preparative silica column and eluted with toluene–nitromethane (97:3) at 9.8 ml/min. The *meso* form was collected at 385–440 ml and the enantiomers at 465–535 ml. The total yield of both diastereomers, including synthesis and "heart-cut" fraction collection was 80–87 %. The chromatographic purity of each fraction was determined to 99±1 %. With the gas chromatographic system described above, the enantiomers eluted after 5.50 min and the *meso* form after 6.12 min.

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With optically active starting material (+)-pentakis(trifluoroacetyl)BDA was isolated. The specific rotation, $[\alpha]_D^{20}$, in dichloromethane was determined to $+23.4\pm1°$.

*Hydrolysis and rederivatization.* (+)-Pentakis(trifluoroacetyl)BDA (0.1 g) was added to 5 % aqueous ammonia (10 ml) in a 50 ml round-bottom flask. After 2 h stirring, the solution was evaporated and the residue dried at 110 °C over-night. Chromatography and infrared spectrophotometry showed 100 % conversion to BDA. The hydrolyzed products were rederivatized by the same procedure as the first time. Analysis by HPLC and peak area integration showed that the amounts of the *meso* and the enantiomeric forms had not changed. NMR, IR and mass spectra were equivalent with previous data after the first derivatization.

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