

## Separation of Enantiomers as Differently Sized Pseudoenantiomeric Salts

David E. Bergbreiter\* and Li Zhang

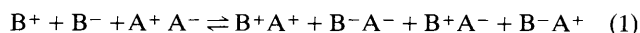
Department of Chemistry, Texas A&M University, College Station, Texas 77843, USA

Ethylene oligomers terminally functionalized so as to contain a chiral amine are used either alone or in the presence of a structurally and chemically similar low molecular mass antipode to separate a racemic sulfonic acid.

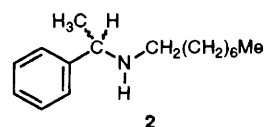
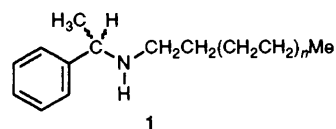
Techniques for separation and purification of enantiomers have long interested chemists.<sup>1</sup> Recently, a range of polymeric chiral stationary phases for gas and liquid chromatography have been developed, which are generally useful for analytical and preparative separations.<sup>2</sup> More recently, significant success in chiral molecular recognition using solid chiral layered metal phosphonates and phosphonates has been reported.<sup>3</sup> Solid phases such as hollow-fibre membranes containing bound enzymes used in kinetic resolutions are yet another example of practical heterogeneous chiral recognition.<sup>4</sup> These newer separation/resolution techniques continue to be of interest despite the continuing major strides in stoichiometric and catalytic asymmetric synthesis. Here, we describe another method for separating enantiomers. Our approach uses a pair of compounds that act as pseudoenantiomers—compounds that chemically behave as enantiomers but, which differ because one has a larger chain attached.

An underlying premise of this work was that pairs of enantiomerically similar chiral amine bases ( $B_{PE}^+$  and  $B_{C8}^+$  or  $B_{PE}^-$  and  $B_{C8}^-$ ) could be prepared with chemically similar reactivity. Our prior work has shown that catalysts with an alkyl or a polyethylene chain are equivalent in reactivity when in solution.<sup>5</sup> The poly(ethylene) chain usually has little or no steric or electronic effect on the end group. However, a polyethylene chain alters substantially the solubility of an attached group, making it insoluble at room temperature.

Normally, treatment of 1 equiv. each of a mixture of a basic resolving agent ( $B^+$  and  $B^-$ ) with 2 equiv. of a strong acid ( $A^+$  and  $A^-$ ) would yield an optically inactive mixture containing four diastereoisomers  $B^+A^+$ ,  $B^-A^-$ ,  $B^+A^-$  and  $B^-A^+$  [eqn. (1)]. While each diastereoisomer of a pair ( $B^+A^+/B^-A^-$  or  $B^-A^+/B^-A^-$ ) could be present in unequal amounts and be



potentially separable, the enantiomeric pairs ( $B^+A^+/B^-A^-$  and  $B^+A^-/B^-A^+$ ) would be present in equal amounts and would not be separable from one another. However, a different situation would arise if a polymeric resolving agent such as **1** derived from poly(ethylene) ( $B_{PE}^+$  or  $B_{PE}^-$ ) and a low molecular mass amine like **2** ( $B_{C8}^+$  or  $B_{C8}^-$ ) were used.



**Table 1** Separation of enantiomeric sulfonic acids using a macromolecular chiral amine.<sup>a</sup>

Base	Calculated isomer ratio	Optical rotation (calc.) <sup>b</sup>	Optical rotation (obs.) <sup>c</sup>
B <sub>PE</sub> <sup>+</sup> and B <sub>C8</sub> <sup>-</sup>	82:18 (B <sub>C8</sub> <sup>-</sup> A <sup>+</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>-</sup> )	-48.1 <sup>d</sup>	-46.2
B <sub>PE</sub> <sup>+</sup> and B <sub>C8</sub> <sup>+</sup>	82:18 (B <sub>C8</sub> <sup>+</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>+</sup> A <sup>+</sup> )	+48.1 <sup>d</sup>	+35.8
B <sub>PE</sub> <sup>-</sup> and (B <sub>C8</sub> <sup>+</sup> /B <sub>C8</sub> <sup>-</sup> )	47:3:18:32 (B <sub>C8</sub> <sup>+</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>+</sup> A <sup>+</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>+</sup> )	+10.0	+6.6
B <sub>PE</sub> <sup>+</sup> and (B <sub>C8</sub> <sup>+</sup> /B <sub>C8</sub> <sup>-</sup> )	3:47:32:18 (B <sub>C8</sub> <sup>+</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>+</sup> A <sup>+</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>+</sup> )	-10.0	-7.2
B <sub>PE</sub> <sup>+e</sup>	82:18 (A <sup>+</sup> :A <sup>-</sup> )	-8.8	-8.8
B <sub>PE</sub> <sup>+e</sup>	82:18 (A <sup>-</sup> :A <sup>+</sup> )	+8.8	+10.1
B <sub>PE</sub> <sup>-</sup> and B <sub>C8</sub> <sup>-</sup>	50:50 (B <sub>C8</sub> <sup>-</sup> A <sup>+</sup> :B <sub>C8</sub> <sup>-</sup> A <sup>-</sup> )	-27.0	-27.9
B <sub>PE</sub> <sup>+</sup> and B <sub>C8</sub> <sup>+</sup>	50:50 (B <sub>C8</sub> <sup>+</sup> A <sup>-</sup> :B <sub>C8</sub> <sup>+</sup> A <sup>+</sup> )	+27.0	+25.9

<sup>a</sup> The reactions used 1 equiv. each of the amines B<sub>PE</sub> and B<sub>C8</sub> listed in toluene with the racemic sulfonic acid (2 equiv.) at 110 °C for 20 min. The solutions were analysed polarimetrically at 25 °C after separation of the polymeric ammonium sulfonate salt by cooling, precipitation and either filtration or centrifugation. <sup>b</sup> The calculated optical rotations are based on [α]<sub>D</sub> (25 °C) values of +60.3 (B<sub>C8</sub><sup>+</sup>A<sup>+</sup>), -60.3 (B<sub>C8</sub><sup>-</sup>A<sup>-</sup>), +6.4 (B<sub>C8</sub><sup>-</sup>A<sup>+</sup>), -6.4 (B<sub>C8</sub><sup>+</sup>A<sup>-</sup>), +45.7 (B<sub>C8</sub><sup>+</sup>), -45.7 (B<sub>C8</sub><sup>-</sup>), +13.8 (A<sup>+</sup>) and -13.8 (A<sup>-</sup>) measured at concentrations comparable with those that would obtain in solutions after precipitation of any polymeric salts. <sup>c</sup> Measured optical rotations were obtained with solutions that were ca. 0.01 mol dm<sup>-3</sup> in ammonium salt (or acid if B<sub>C8</sub> were absent). <sup>d</sup> Only 1.8 equiv. of A<sup>+</sup>/A<sup>-</sup> were used. <sup>e</sup> Only 1 equiv. of the B<sub>PE</sub> listed was used.

Here, the enantiomers of **1** and **2** could react with a racemic acid (A<sup>+</sup> and A<sup>-</sup>) to form two pairs of pseudoenantiomeric ammonium salts (B<sub>PE</sub><sup>+</sup>A<sup>+</sup>/B<sub>C8</sub><sup>-</sup>A<sup>-</sup> or B<sub>PE</sub><sup>+</sup>A<sup>-</sup>/B<sub>C8</sub><sup>-</sup>A<sup>+</sup>). While these salts are expected to be soluble in hot toluene, the pseudoenantiomers B<sub>PE</sub><sup>+</sup>A<sup>+</sup> and B<sub>C8</sub><sup>-</sup>A<sup>-</sup> (or B<sub>PE</sub><sup>+</sup>A<sup>-</sup> and B<sub>C8</sub><sup>-</sup>A<sup>+</sup>) should have very different solubilities at 25 °C owing to the known insolubility of polyethylene derivatives [*i.e.* the salt(s) of B<sub>PE</sub><sup>+</sup> or B<sub>PE</sub><sup>-</sup>]. Thus, these salts could be separated merely by cooling a hot toluene solution.

To demonstrate the potential of this approach to enantiomer separation, we have examined a simple thermodynamic separation of 10-camphorsulfonic acid (as A<sup>+</sup> or A<sup>-</sup>) using various enantiomeric forms of **1** and **2** (**1** as B<sub>PE</sub><sup>+</sup> or B<sub>PE</sub><sup>-</sup>, **2** as B<sub>C8</sub><sup>+</sup> or B<sub>C8</sub><sup>-</sup>). While our results show that recycling experiments using the polymeric amine **1** and racemic sulfonic acid do serve as a way to resolve a chiral sulfonic acid (91% e.e. after three cycles), our experiments were designed mainly to show that the pseudoenantiomeric amines **1** and **2** had comparable reactivity and that they and their salts were readily separable from one another. Experiments carried out with varying amounts of the enantiomers of the amines **1** and **2** with a chiral sulfonic acid confirmed this expectation (Table 1).

The desired enantiomers of **1** and **2** were prepared from the 1-phenylethylamine using a terminally carboxylated ethylene oligomer PE<sub>Olig</sub>-CO<sub>2</sub>H<sup>6</sup> or octanoic acid by forming an amide and reducing it (LiAlH<sub>4</sub>). Both the chiral polymeric amines PE<sub>Olig</sub>-CH<sub>2</sub>NCH(Me)C<sub>6</sub>H<sub>5</sub> and their sulfonate salts were completely insoluble at room temperature but did dissolve in refluxing toluene.

Experiments using either B<sub>PE</sub><sup>+</sup> or B<sub>PE</sub><sup>-</sup> with a racemic mixture of (1*S*)-(+)- or (1*R*)-(-)-10-camphorsulfonic acid (A<sup>+</sup> or A<sup>-</sup>, respectively) formed preferentially the B<sub>PE</sub><sup>+</sup>A<sup>+</sup> and B<sub>PE</sub><sup>-</sup>A<sup>-</sup> sulfonate salts with a stereoselectivity of ca. 64%. Using this stereoselectivity and assuming equivalent stereoselectivity for reactions of the enantiomers of **2** (B<sub>C8</sub><sup>+</sup> or B<sub>C8</sub><sup>-</sup>) with the racemic sulfonic acid, the composition of mixtures formed using various mixtures of enantiomers of **1**, **2** and 10-camphorsulfonic acid were calculated. Measured values for the specific rotations of the salts of **2** and the pure enantiomers of **2** were used to calculate the expected [α]<sub>D</sub> value of the mixtures. A linear relationship between [α]<sub>D</sub> and concentration was assumed. Reasonably good agreement with experiment was found, suggesting that the pseudoenantiomers **1** and **2** behave similarly.

As expected from the stereoselectivity in reactions of **1** with 10-camphorsulfonic acid, **1** can be used to resolve this acid. When 1 equiv. of **1** was allowed to equilibrate with 2 equiv. of

the racemic sulfonic acid, the remaining acid in solution had a measured e.e. of 64%. Two repetitions of this equilibration process using fresh B<sub>PE</sub><sup>+</sup> with the partially resolved sulfonic acid led to a solution of the sulfonic acid having 82% (2nd cycle) and 91% e.e. (3rd cycle). As expected, equivalent amounts of **1** and the sulfonic acid led to complete consumption of the amine.

The sulfonic acid from the salts of **1** was also recovered by treatment of the salt with a hot toluene solution of methanesulfonic acid followed by filtration and evaporation of the solvent. The sulfonic acid solution so formed consisted predominantly of the sulfonic acid that was enantiomeric to the sulfonate that was part of the sulfonate salt formed with **2**.

This pseudoenantiomer concept might also be useful in enantioselective reactions where the pseudoenantiomeric polymeric and low molecular mass resolving agents would be kinetically equivalent toward their respective favoured enantiomeric substrates. In such instances, it should be possible to achieve high substrate conversions to product and still separate the products if the products were covalently attached to the polymeric and low molecular mass pseudoenantiomer. This approach and related chromatographic applications are presently being studied.

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