Enantiomeric Separation of Chiral [α-(1-Naphthyl)
Ethyl]Ammonium Perchlorate by Silica Gel-bound
Chiral Pyridino-18-Crown-6 Ligands

P. Huszthy, J.S. Bradshaw, A.V. Bordunov and R.M. Izatt

Department of Chemistry
Brigham Young University
Provo, UT 84602-4670

Dr. R. Guard
Office of Naval Research
800 North Quincy Street
Arlington, VA 22217-5000

The separation of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (R) and
(S) forms using silica gel-bound dimethylpyridino-18-crown-6 ligand [(S,S)-1] with methanol as
an eluent is reported. We also report the synthesis of a new silica gel-bound diphenyl-substituted
pyridino-18-crown-6 ligand [(R,R)-2] by the following reactions. Dimethyl chelidamate (7) was
first alkylated with 11-iodoundec-1-ene (6) on the phenolic oxygen and the resulting ether diester
was reduced to form 4-undecenyloxy-2,6-pyridinedimethanol (8). Tosylation of 8 gave ditosylate
9 which was cyclized with (RR)-diphenyl-substituted tetraethylene glycol [(R,R)-10] to form
crown (RR)-11. Ligand (RR)-11 was treated with triethoxysilane using a platinum catalyst. The
resulting chiral crown-substituted triethoxysilane, (RR)-12, was reacted with silica gel in toluene
at 90° to attach the ligand to silica gel. The results of the separation of (R)- and (S)-NapEt using
new silica gel-bound crown (RR)-2 with methanol as the eluent are also presented.

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by

P. Huszthy, J.S. Bradshaw, A.V. Bordunov and R.M. Izatt

Department of Chemistry
Brigham Young University
Provo, UT 84602-4670

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ENANTIOMERIC SEPARATION OF CHIRAL [α-(1-NAPHTHYL)ETHYL]AMMONIUM PERCHLORATE BY SILICA GEL-BOUND CHIRAL PYRIDINO-18-CROWN-6 LIGANDS

P. Huszthy, J.S. Bradshaw, A.V. Bordunov and R.M. Izatt

Abstract

The separation of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (R) and (S) forms using silica gel-bound dimethylpyridino-18-crown-6 ligand [(S,S)-1] with methanol as an eluent is reported. We also report the synthesis of a new silica gel-bound diphenyl-substituted pyridino-18-crown-6 ligand [(R,R)-2] by the following reactions. Dimethyl chelidaminate (7) was first alkylated with 11-iodoundec-1-ene (6) on the phenolic oxygen and the resulting ether diester was reduced to form 4-undecenyloxy-2,6-pyridinedimethanol (8). Tosylation of 8 gave ditosylate 9 which was cyclized with (R,R)-diphenyl-substituted tetraethylene glycol [(R,R)-10] to form crown (R,R)-11. Ligand (R,R)-11 was treated with triethoxysilane using a platinum catalyst. The resulting chiral crown-substituted triethoxysilane, (R,R)-12, was reacted with silica gel in toluene at 90° to attach the ligand to silica gel. The results of the separation of (R)- and (S)-NapEt using new silica gel-bound crown (R,R)-2 with methanol as the eluent are also presented.
Introduction

In continuation of our studies on enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands [1-7], we have studied the enantiomeric separation of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands covalently bonded to silica gel [8]. One and a half decades ago, Cram and coworkers published their pioneering paper [9] on the separation of the enantiomers of several racemic organic ammonium salts using a silica gel-bound chiral bis(binaphthyl)-22-crown-6 ligand. After covalently attaching the chiral ligand to silica gel they treated the adsorbent with an excess of chlorotrimethylsilane to form a less polar material. This treatment reduced tailing and gave better separations on their solid stationary phase. They used a mobile phase consisting of chloroform or dichlomethane solutions of the racemic ammonium salts and 18-crown-6, ethanol, or 2-propanol as carriers [9]. Our preliminary results of the separation of [α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) into its (R) and (S) forms using silica gel-bound chiral crown (SS)-1 (see Figure 1) with acetone/methanol (7/3, v/v) as the eluent were not completely satisfactory [8].

In this paper, we report a good, almost base-line separation of NapEt into its (R) and (S) forms using silica gel-bound chiral crown (SS)-1 with methanol as the eluent. We also report the use of (RR)-2 for the separation of the enantiomers of NapEt. Silica gel-bound chiral crown (RR)-2 differs from silica gel-bound chiral crown (SS)-1 in two features: a) (RR)-2 has a longer connecting arm to silica gel by seven carbon atoms; and b) instead of two methyl substituents, (RR)-2 contains two phenyl moieties at the chiral centers. These changes were made because silica gel-bound chiral stationary phases eleven carbon atoms removed from the support were very effective for chiral solute separations [10-13], and second, the substitution of two methyl groups in (SS)-1 by two phenyl groups to form (RR)-2 should improve chiral recognition and subsequently chiral separation.

Results and Discussion

The separation of (R)- and (S)-NapEt using silica gel-bound (SS)-1 is shown in Figure 2. This separation study was carried out in a manner similar to that reported [8]. Very concentrated methanol solution of racemic NapEt was placed on a column containing (SS)-1. The
Methanol was used because it allows for a good separation of enantiomers, reduces greatly the time for a separation, and reduces tailing to a great extent. The amounts of (R)- and (S)-NapEt in each fraction were determined by HPLC using the N-acetyl derivatives of (R)- and (S)-NapEt [8]. Because (S,S)-1 interacts more strongly with (R)-NapEt, (S)-NapEt passes through the column first and (R)-NapEt last as observed in Figure 2.

The separation of (R)- and (S)-NapEt using silica gel-bound (R,R)-2 is shown in Figure 3. This separation was performed as described above using (S,S)-1. Since the parent chiral diphenyl-substituted crown [(R,R)-4] exhibits less recognition for the enantiomers of NapEt as mentioned above, the separation using (R,R-2) was not as good as that using (S,S)-1. As shown in Figure 3, (R)-NapEt elutes first from the column because (R,R)-2 interacts with (S)-NapEt more strongly. Although a clean separation of enantiomers by (R,R)-2 was not achieved in this one experiment, it is clear that recognition did take place. Another solvent system could be found and might lead to better separation by (R,R)-2.

**Experimental**

*Separation of R-(+) and S-(-) Isomers of NapEt on (S,S)-1 with Methanol as Eluent*

This separation was carried out in the same manner using the same column filled with 4.2 g of (S,S)-1 as reported [8] with the following exemptions: a) prior to separation, 50 ml of 1/4 (v/v) triethylamine/methanol and then 100 ml of pure methanol were passed through the column and b) instead of a 3/7 (v/v) methanol/acetone mixture, pure methanol was used as an eluent. The flow rate was 0.048 ml/min. The calculated [8] concentrations of (R)- and (S)-NapEt were plotted versus the ml of eluent as shown in Figure 2.

*Separation of R-(+) and S-(-) Isomers of NapEt on (R,R)-2 with Methanol as Eluent*

This separation was carried out in the same manner as described above for (S,S)-1 using (R,R)-2 silica gel-bound chiral diphenylpiridino-18-crown-6 with pure methanol as an eluent. The flow rate in this case was 0.017 ml/min. The calculated [8] concentrations of (R)- and (S)-NapEt were plotted versus the ml of eluent as shown in Figure 3.
References


Fig. 1. Silica gel-bound chiral pyridino-18-crown-6 ligands

(S,S)-1, R = CH$_3$, n = 3
(R,R)-2, R = C$_6$H$_5$, n = 11
Figure 2. A smooth curve showing the separation of (R) and (S)-NapEt on (S, S)-1 using methanol as eluant.
Figure 3. A smooth curve showing the separation of $(R)$- and $(S)$-NapEt on $(S, S)$-2 using methanol as eluant.