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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 (*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.

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

by

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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 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 (*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 (*S*,*S*)-**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 (*S*,*S*)-**1** with methanol as the eluent. We also report the use of (*R*,*R*)-**2** for the separation of the enantiomers of NapEt. Silica gel-bound chiral crown (*R*.*R*)-**2** differs from silica gel-bound chiral crown (*S*,*S*)-**1** in two features: a) (*R*,*R*)-**2** has a longer connecting arm to silica gel by seven carbon atoms; and b) instead of two methyl substituents, (*R*,*R*)-**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 (*S*,*S*)-**1** by two phenyl groups to form (*R*,*R*)-**2** should improve chiral recognition and subsequently chiral separation.

Results and Discussion

The separation of (*R*)- and (*S*)-NapEt using silica gel-bound (*S*,*S*)-**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 (*S*,*S*)-**1**. The eluent was methanol. 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 [illegible] better separation by [illegible]-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

[1] Davidson, R.B., Bradshaw, J.S., Jones, B.A. Dalley, N.K., Christensen, J.J., Izatt, R.M., Morin, F.G., Grant, D.M.: *J. Org. Chem.*, **49**, 353 (1984)

[2] Bradshaw, J.S., Huszthy, P., McDaniel, C.W., Zhu, C.-Y., Dalley, N.K., Izatt, R.M., Lifson, S.: *J. Org. Chem.*, **55**, 3129 (1990)

[3] Huszthy, P., Bradshaw, J.S., Zhu, C.-Y., Izatt, R.M., Lifson, S.: *J. Org. Chem.*, **56**, 3330 (1991)

[4] Bradshaw, J.S., Huszthy, P., McDaniel, C.W., Oue, M., Zhu, C.-Y., Izatt, R.M., Lifson, S.: *J. Coordination Chem.*, **B 27**, 105 (1992)

[5] Huszthy, P., Oue, M., Bradshaw, J.S., Zhu, C.-Y., Wang, T.-M., Dalley, N.K., Curtis, J.C., Izatt, R.M.: *J. Org. Chem.*, **57**, 5383 (1992)

[6] Izatt, R.M., Zhu, C.-Y., Huszthy, P., Bradshaw, J.S.: "Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems," in *Crown Ethers: Toward Future Applications*, ed. by S. R. Cooper, VCH Press, New York, pp. 207-233, 1993

[7] Chu, I.-H., Dearden, D.V., Bradshaw, J.S., Huszthy, P., Izatt, R.M.: *J. Am. Chem. Soc.*, **115**, 4318 (1993)

[8] Bradshaw, J.S., Huszthy, P., Wang, T.-M., Zhu, C.-Y., Nazarenko, A.Y., Izatt, R.M.: *Supramolecular Chemistry*, **1**, 267 (1993)

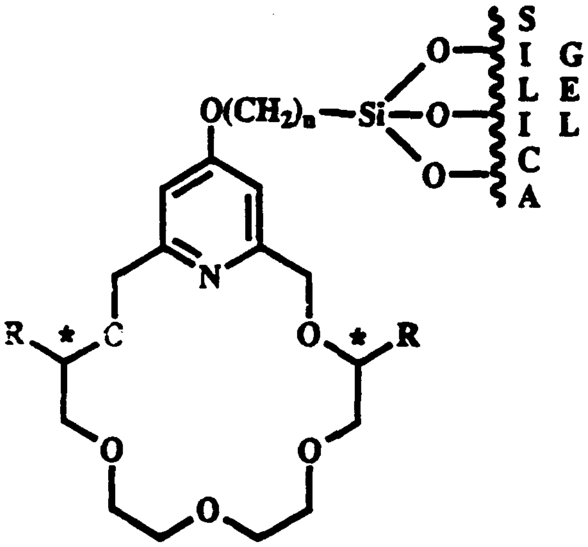
[9] Sousa, L.R., Sogah, G.D.Y., Hoffman, D.H., Cram, D.J.: *J. Am. Chem. Soc.*, **100**, 4569 (1978)

[10] Pirkle, W.H., Sowin, T.J.: *J. Chromatogr.*: **396**, 83 (1987)

[11] Dobashi, A., Dobashi, Y., Kinoshita, K., Hara, S.: *Anal. Chem.*, **60**, 1985 (1988)

[12] Yamashita, J., Satoh, H., Oi, S., Suzuki, T., Miyano, S., Takai, N.: *J. Chromatogr.*, **464**, 411 (1989)

[13] Uray, G., Linder, W.: *Chromatographia*, **30**, 323 (1990)



(*S*,*S*)-1, R = CH_3, n = 3
(*R*,*R*)-2, R = C_6H_5, n = 11

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

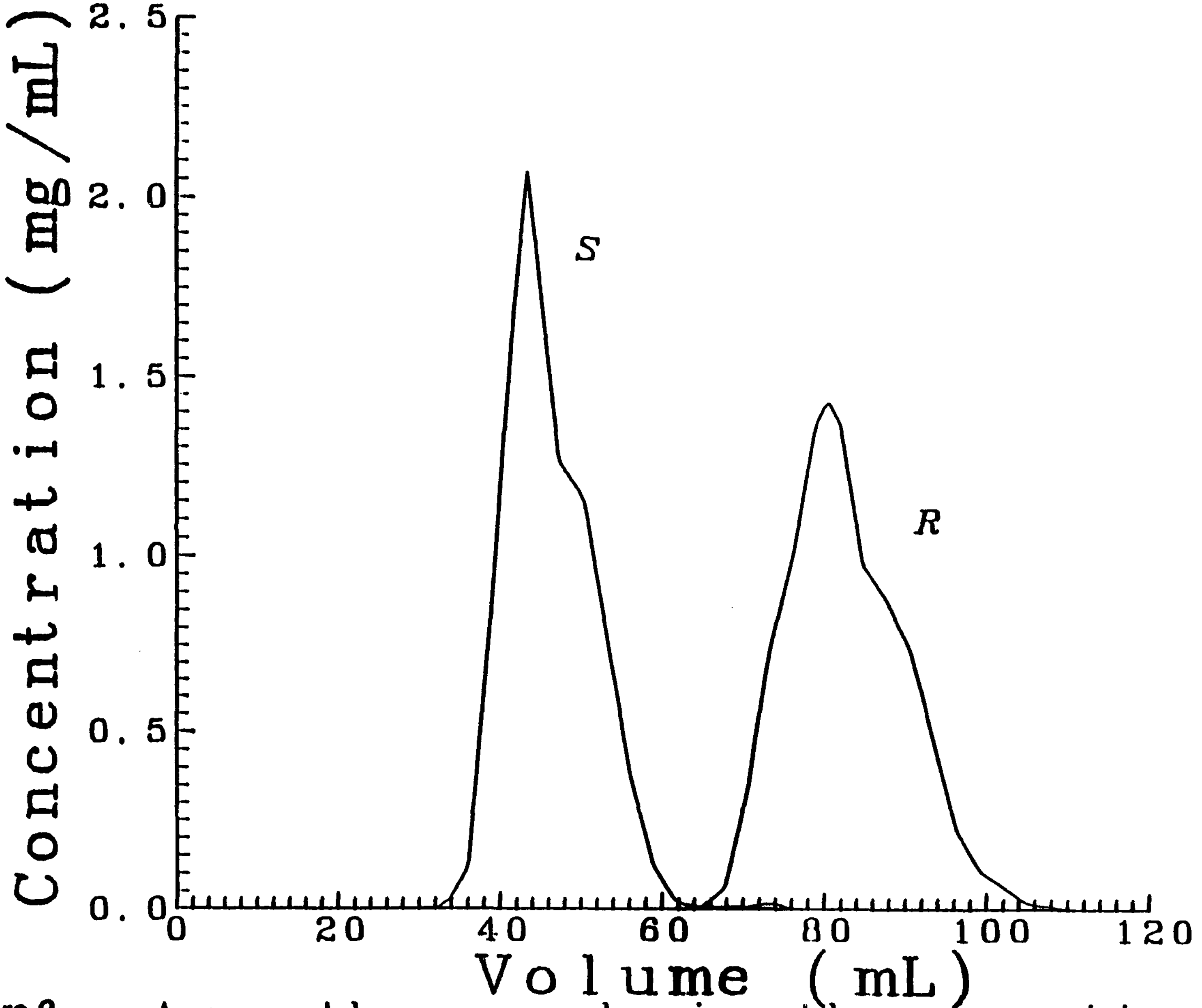


Figure 2. A smooth curve showing the separation of (*R*)- and (*S*)-NapEt on (*S*, *S*)-1 using methanol as eluant.

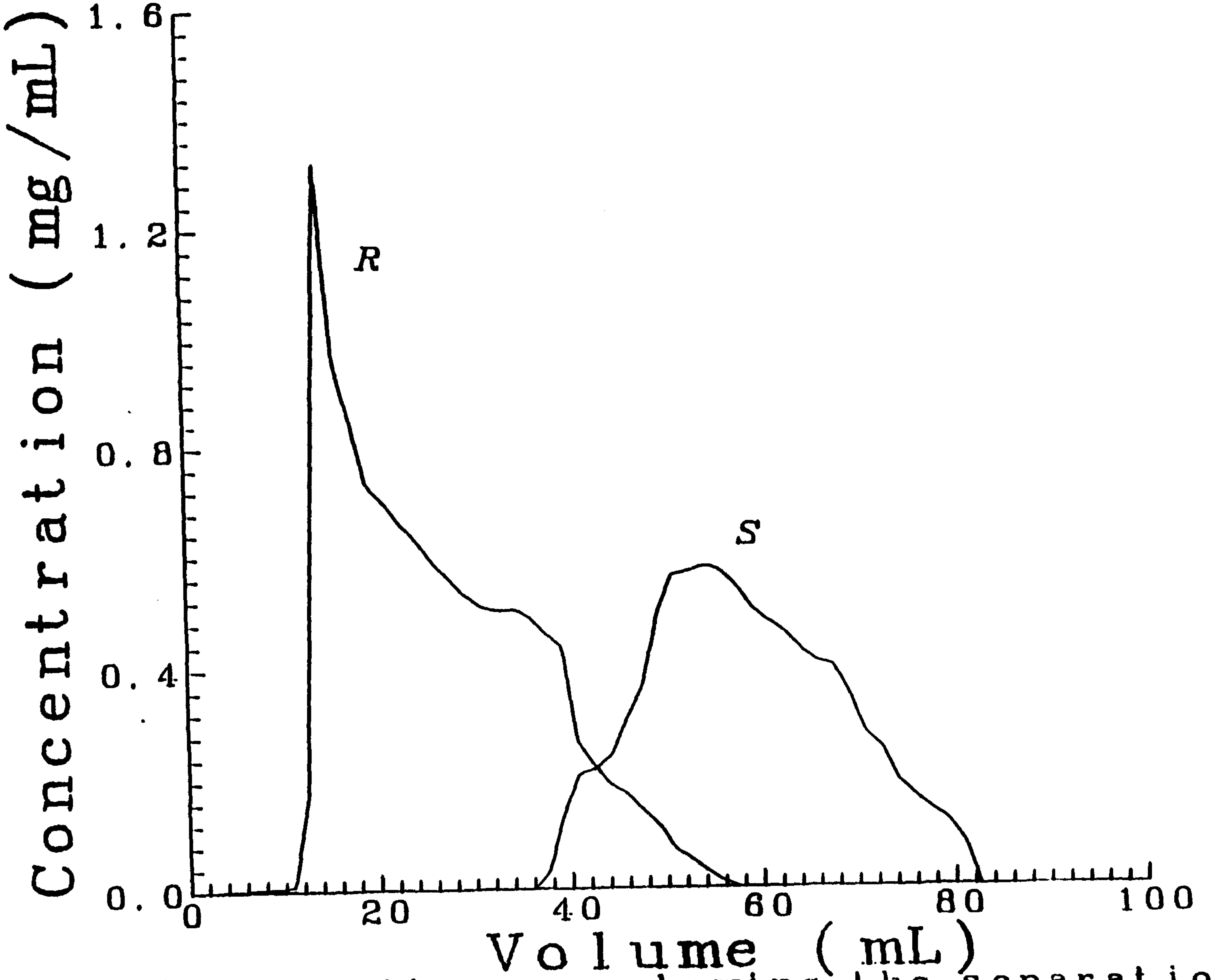


Figure 3. A smooth curve showing the separation of (*R*)- and (*S*)-NapEt on (*S*, *S*)-2 using methanol as eluant.