J. Am. Chem. Soc. **1998,** *120,* 6617−6618 6617

Direct Observation of Stereotopic Group Recognition in Solution and Solid State

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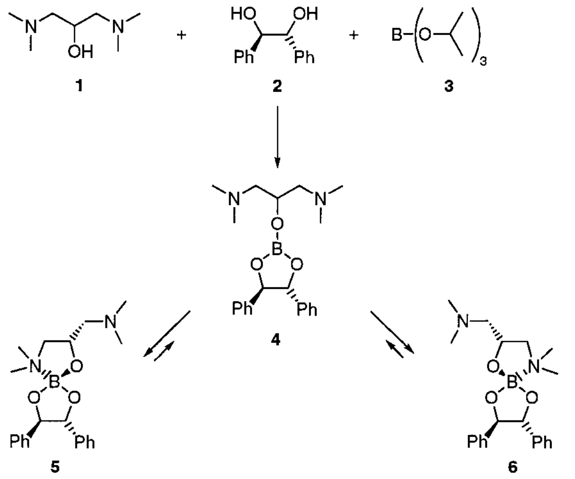
Received January 20, 1998

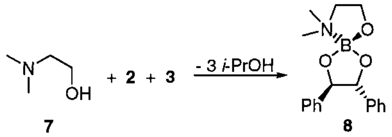
Desymmetrization of prochiral or *meso* compounds using enzymes,[1] chiral chemical reagents or catalysts[2] is an important methodology for asymmetric synthesis. The actual (bio)chemical conversion has been postulated to be preceded by selective recognition of one of two enantiotopic groups of the prochiral or *meso* compound by the enzyme[1] or by the chiral reagent or catalyst,[2i] but this has never been proven spectroscopically. The first direct evidence for enantiotopic group recognition in solution was described recently.[3] In this study, one of two enantiotopic groups of a *meso*-bisammonium guest molecule was found to be complexed selectively by a chiral crown ether host, as shown by NMR spectroscopy. However, visualization of this phenomenon by X-ray crystallography was not achieved. Furthermore, due to the low stability constant of the complex, it was not possible to utilize the host/guest complex in a synthetic reaction to convert the *meso* compound into a chiral product. In this communication, we describe the selective complexation of one of two enantiotopic amino groups of a prochiral diamine by a chiral boron compound, characterization of the relevant complexes in solution and in the solid state, as well as stereoselective conversion into a chiral product.

Compound **1** was chosen as the prochiral substrate, the goal being to bind one of the two enantiotopic amino groups selectively. To achieve this, we envisioned a one-pot reaction[4] of the substrate **1**, the chiral diol **2**, and triisopropyl borate **3**. Ligand exchange at boron with concomitant removal of 2-propanol was expected to provide the intermediate **4**, which should spontaneously form the two possible products **5** and **6** in a thermodynamically controlled process involving the complexation of the pro-*S* and pro-*R* amino groups, respectively (Scheme 1).

Scheme 1



Scheme 2



Indeed, upon performing the reaction, compounds **5** and **6** were obtained as the sole products as shown by ^{11}B, ^{1}H, and ^{13}C NMR spectroscopy (CD$_2$Cl$_2$ as solvent). The ^{11}B NMR spectrum displays a broad signal at 10.6 ppm, expected for tetracoordinated boron, and leads to the conclusion that in each complex, one of the amino groups is coordinated to boron, while the other remains noncoordinated (cf. **5** and **6**). The ^{1}H and ^{13}C NMR spectra are fully in accordance with this conclusion. At −78 °C, the exchange between the two complexes is slow on the NMR (300 MHz) time scale, the ratio of diastereomers being roughly 3:1.[5] Although at this stage it was not possible to make unambiguous configurational assignments, we suspected on the basis of molecular models that the major diastereomer is **5**, formed by the coordination of the pro-*S* amino group.

At room temperature, a rapid exchange process occurs. Two equally intense signals for the dimethylamino groups were observed by both ^{1}H and ^{13}C NMR spectroscopy. Since the coordination and decoordination of the dimethylamino groups is rapid on the NMR time scale, as is the N-inversion of the noncoordinated group, it can be concluded that each signal corresponds to the two methyl groups of a single dimethylamino group. To shed light on the process, the NMR spectra of an analogous complex **8** and its achiral amino alcohol precursor **7** (Scheme 2)[6] were recorded and compared with those of **5** and **6**. The sum of the changes of the ^{1}H chemical shifts (0.30 and 0.18 ppm, respectively) of the dimethylamino groups in the diastereomeric mixture of **5** and **6** relative to noncomplexed **1** turned out to be equal to the analogous chemical shift change (0.48 ppm) of **8** relative to **7**. As a consequence, the observed ^{1}H chemical shift changes of **5**/**6** can be correlated with the relative amounts of coordination of each of the two dimethylamino groups to the boron center. This direct measure of the enantiotopic group recognition in solution under fast exchange conditions at ambient temperature amounts to 62:38.

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(2) Reviews: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167. (d) Ward, D. E.; Liu, Y.; How, D. *J. Am. Chem. Soc.* **1996**, *118*, 3025. Recent examples: (e) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395. (f) Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1995**, *36*, 931. (g) Nordström, K.; Moberg, C.; Heumann, A. *J. Organomet. Chem.* **1996**, *525*, 233. (h) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (i) Kinugasa, M.; Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1997**, *119*, 9067. (j) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339.

(3) Reetz, M. T.; Rudolph, J.; Mynott, R. *J. Am. Chem. Soc.* **1996**, *118*, 4494.

(4) Equimolar amounts of the reagents were dissolved in toluene, and the evolving *i*PrOH was coevaporated with toluene to give **5**/**6** in a basically quantitative yield, judged pure by NMR. Crystals of **5** suitable for single-crystal X-ray analysis were prepared by slow evaporation of acetone from a solution of **5**/**6** in acetone under an argon stream. NMR (^{11}B, ^{1}H, and ^{13}C) data of a solution of this solid (reequilibrated to **5**/**6**) were identical to the data for the noncrystallized product. For the crystalline material, satisfactory elemental analysis and mass spectrometric data were obtained.

(5) Obtained by integrating the ^{13}C NMR signals at 43−46 ppm (Me$_2$N, two signals for **5** and **6** each); see Supporting Information.

(6) Prepared from **7**, **2**, and **3** in a procedure analogous to the preparation of **5**/**6**; see ref 4. Note that only one signal is observed by ^{1}H NMR spectroscopy for the dimethylamino group of **8**, although the methyl groups are in principle diastereotopic owing to complete coordination of this group to the boron center with concomitant slowing down of the N-inversion.

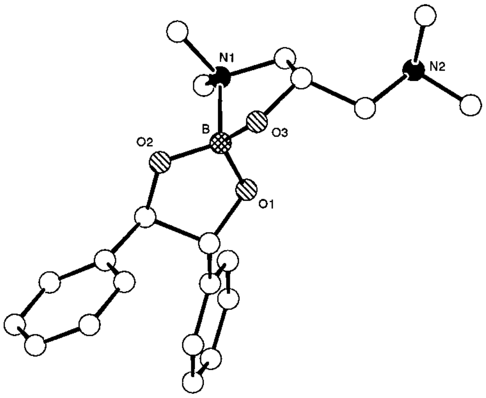


Figure 1. Molecular structure of **5** (no hydrogen atoms shown). Selected bond lengths [Å]: B−O1 1.444(3), B−O2 1.428(3), B−O3 1.441(3), B−N1 1.670(3).

In hope of obtaining information regarding the structure in the solid state, crystals were grown from a solution of **5**/**6** in quantitative yield. The X-ray structural analysis[7] shows the presence of a single diastereomer, namely **5** in which the pro-*S* amino group is coordinated to the boron center (Figure 1). All crystals contained the same diastereomer, as proven by the powder diffraction pattern after mortaring the whole crystalline sample (Figure 2). Thus, an asymmetric transformation of the second kind has occurred.[8] Upon redissolving compound **5** in CD_2Cl_2 at −78 °C, the previously observed equilibrium $\mathbf{5} \rightleftharpoons \mathbf{6}$ was reestablished immediately (<1 min).

Finally, attempts were made to selectively functionalize the noncoordinated amino group in the complexes **5**/**6** and to release the product from the boron moiety. To this end a mixture of **5**/**6** was treated with methyl trifluoromethanesulfonate (MeOTf) and subsequently with water (Scheme 3).[9] Upon addition of 1 equiv of MeOTf, complete chemoselectivity in favor of the monomethylated products **9**/**10** was observed. Only an excess of MeOTf led to the formation of undesired dimethylated products. Therefore, it can be concluded that the noncoordinated dimethylamino group is methylated more rapidly. Indeed, an NMR study of the methylation process shows that the relative positions and integrals of diagnostic signals (e.g., ^{13}C NMR resonances of the C atoms of the N/O chelate) of the major and minor diastereomers remain unchanged upon methylation. It was not possible to obtain a crystal of **9** for an X-ray analysis. Diastereomeric ratios **9**:**10** of 74:26 were observed when the methylation reaction was performed at −78 °C, and 62:38 at 25 °C. Upon hydrolysis, the enantiomeric excess (ee) of compound **11** was measured[10] to be 48% at −78 °C and 26% at 25 °C, which corresponds to the diastereomeric ratios **9**:**10** observed at the respective temperatures. These selectivity values are essentially identical to the observed diastereomeric ratios **5**:**6** under the same conditions. This strongly suggests that the noncoordinated amino groups of the diastereomers of **5**/**6** have identical reactivity toward methylation. Thus, the ee of **11** comes about exclusively as the result of the thermodynamic process of enantiotopic group recognition in the diastereomeric complexes **5**/**6**.[11]

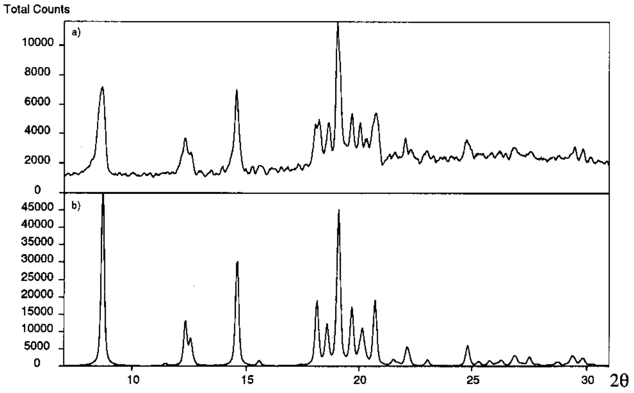
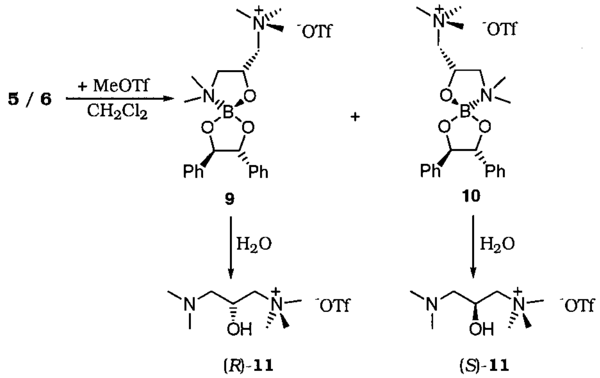


Figure 2. (a) Powder diffraction pattern of mortared crystalline sample grown from **5**/**6** in acetone; (b) powder diffraction pattern calculated by using atomic coordinates and cell parameters obtained from the single-crystal structure of **5**.

Scheme 3



In conclusion, although this system is of no practical synthetic value, it constitutes the first example for which enantiotopic group recognition is observed in both solution and the solid state. In a consecutive methylation step, followed by hydrolysis, a chiral product is obtained for which the enantiomeric purity is equal to the diastereoselectivity in the preceding enantiotopic group recognition event.

Acknowledgment. J.H. gratefully acknowledges a Marie Curie fellowship from the European Commission (contract number ERBFMBICT961429).

Supporting Information Available: Tables of crystallographic data, atomic numbering, schemes, thermal ellipsoid plots, atomic position and displacement parameters, and bond lengths and angles for compound **5** and NMR spectra of **5**/**6** and **9**/**10** together with explanatory comments (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[7] Crystallographic data for **5**: $C_{21}H_{29}BN_2O_3$, M_r 368.3, monoclinic, space group $P2_1$ [No. 4], colorless prism, $a = 10.605(1)$ Å, $b = 9.763(1)$ Å, $c = 10.209(1)$ Å, $\beta = 95.76(1)°$, $Z = 2$, $\rho_{calcd} = 1.16$ g cm^{-3}, μ(Mo Kα) = 0.77 cm^{-1}, Enraf-Nonius CAD-4 diffractometer, 4787 reflections, structure refined (SHELXL97) against F^2 for all data with Chebyshev weights, $R = 0.045$ (observed data), $wR = 0.134$ for 244 parameters, GOF = 1.035, residual electron density 0.151 e Å^{-3}. The powder diffraction pattern was measured on a Stoe STADi 2/PL transmission diffractometer equipped with a position sensitive detector (0.3 mm capillary sample), simulated powder pattern calculated with Visual X^{pow} (pseudo-Voigt profile, 0.5 Gaussian).

[8] Asymmetric transformations of the second kind, also called crystallization-induced asymmetric transformations, are well-known: (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994. (b) Vedejs, E.; Donde, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9293 and references cited therein.

[9] A mixture of **5**/**6** was prepared as described above (ref 4) and dissolved in dichloromethane. The mixture was cooled to −78 °C or kept at room temperature. One equivalent of MeOTf was added and the mixture stirred for 1 h to yield **9**/**10** in basically quantitative yield. This was hydrolyzed at room temperature to **11**, which was isolated as the triflate salt. Satisfactory NMR data were obtained for **9**/**10** and **11**, and mass spectrometric data for **11** (ESI$^+$: *m*/*z* 161).

[10] Obtained by ^1H NMR spectroscopy, using the chiral resolution agent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol; see: Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.

[11] Thermodynamically controlled desymmetrizations are known, e.g.: (a) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391. (b) Ley, S. V.; Downham, R.; Edwards, P. J.; Innes, J. E.; Woods, M. *Contemp. Org. Synth.* **1995**, *2*, 365.