Table I. Hyperfine Coupling Constants for PBN Adducts (in gauss)

<table>
<thead>
<tr>
<th></th>
<th>(A_N)</th>
<th>(A_H)</th>
<th>(A_D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H_2) or (D_2) on ZnO</td>
<td>14.8</td>
<td>7.41</td>
<td>1.08</td>
</tr>
<tr>
<td>CO/(H_2) irradiation(^a)</td>
<td>15.0</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>irradiation of liquid alkanes(^b)</td>
<td>14.8</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reference 3. \(^b\) Reference 2.

tained with the desorbed material permits the radical species to be identified (Figure 2). The spectrum obtained with adsorbed \(H_2\) (trace a) is attributed to the addition of \(H^+\) to \(I\); the hyperfine pattern consists of a 1:1:1 triplet due to \(^{14}\)N, further split into 1:2:1 triplets due to two equivalent \(\beta\) protons. With \(D_2\) (trace b), the addition product of \(D^+\) to \(I\) gives a triplet–doublet–triplet splitting pattern, with the smaller triplet due to the \(\beta\) deuterium.

Figure 2 (b) also shows small amounts of the hydrogen addition product and another unidentified radical which was not present if a non-hydrogen-containing solvent such as carbon tetrachloride was used. A sample of ZnO was exchanged with \(D_2\) and then outgassed in the usual way. Adsorption of hydrogen on this sample gave a spectrum showing the hydrogen addition product with a very small contribution from the deuteration addition product.

Figure 2. EPR solution spectra of PBN adducts desorbed from ZnO containing (a) adsorbed \(H_2\) and (b) adsorbed \(D_2\).

Asymmetric Reductions with a Chiral 1,4-Dihydropyridine Crown Ether\(^1\)

Sir:

We are interested in the catalytic cycle shown in eq 1. A 1,4-dihydropyridine (DHP) is contained in a segment (for example a crown ether) capable of complexing a metal ion, \(M^+\). The encapsulated \(M^+\) then complexes with a carboxyl

\[
\text{1,4-DHP crown + } M^+ \rightleftharpoons 1,4\text{-DHP } M^+ \text{ crown}
\]

\[
\begin{array}{cccc}
\text{O} & \text{Na}_2\text{S}_2\text{O}_4 & \text{Pyr}^+\text{crown} & \text{RCHR}^+ + M^+ \\
\text{RCR} & \downarrow & \text{H}^+ & \text{OH}
\end{array}
\]

\[\text{(1)}\]

compound, forming a ternary complex in which the carboxyl group is activated toward hydride acceptance through its complexation to \(M^+\).\(^2,3\) The pyridinium salt (Pyr\(^+\)) formed on reduction of the carboxyl group is reduced back to 1,4-DHP with \(\text{Na}_2\text{S}_2\text{O}_4\).\(^4\) Such a cycle has attractive synthetic and biomimetic aspects,\(^5\) especially if the 1,4-DHP–crown combination is chiral and is capable of carrying out reductions with a significant degree of asymmetric induction.\(^6\) We report here the preliminary results of work intended toward the achievement of the above goals.\(^7\)

The synthetic route to the desired 1,4-DHP–crown compounds is shown in Scheme I. Chiral starting materials were the tert-butyl esters of optically pure \(L\)-alanine (2a) and \(L\)-

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References and Notes

Table I

<table>
<thead>
<tr>
<th>Substrate/product</th>
<th>Conditions (reaction time, h)</th>
<th>Work-up procedure</th>
<th>NMR yield, %</th>
<th>Alcohol isolated yield, %</th>
<th>[α]D (obs) lit. deg (concn)</th>
<th>Absolute config of excess enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5COClC6H5 (9)</td>
<td>a. b (72)</td>
<td>d</td>
<td>65 (100)</td>
<td>58</td>
<td>[α]D + 9.7 (0.19)</td>
<td>+12.8, j p. n 88 S</td>
</tr>
<tr>
<td>C6H5COO2C6H5 (11)</td>
<td>c. e (72)</td>
<td>f</td>
<td>80 (100)</td>
<td>61</td>
<td>[α]D + 89.9 (0.76) k</td>
<td>+104 k m.o 86 S</td>
</tr>
<tr>
<td>C6H5CONH2 (13)</td>
<td>c. e (72)</td>
<td>f</td>
<td>67 (100)</td>
<td>69</td>
<td>[α]D + 47.8 (0.55) l</td>
<td>+ 74.7 l p. o 64 S</td>
</tr>
<tr>
<td>C6H5CONHCH2C6H5 (15)</td>
<td>c. e (75)</td>
<td>i</td>
<td>65 (100)</td>
<td>37</td>
<td>[α]D + 26.5 (0.58) k</td>
<td>+34.4 k m.r 78 S</td>
</tr>
</tbody>
</table>

* NMR experiment. +55 °C. +0.14 M in 6 substrate, and MgCl2·H2O in C6H5CN (CD3CN). Reaction was carried out under N2. + The reaction mixture was concentrated, ether was added, and the precipitated 6 ClO4 was filtered off. This procedure was repeated twice with the residue. The amount of the combined ether extracts was concentrated, filtered, and subjected to preparative TLC (silica gel, C6H5). After Kugelrohr distillation the 1H NMR spectrum of the alcohol 10 still showed some minor impurities. A sample was subjected to LC (silica gel, 82:16 CH2Cl2:hexane) and distilled against heating. No impurities were detectable by either 1H NMR spectroscopy or LC. + Room temperature. + Water was added to the reaction mixture. After 30 min the solvent was evaporated, and the residue was dissolved in dry CH2Cl2. + The alcohol was isolated by column chromatography (silica gel, 9:1 CH2Cl2:CH3COCH3) and was pure by both 1H NMR and LC. + The alcohol was isolated by column chromatography (silica gel, 8:2 CH2Cl2:CH3COCH3), and further purified by LC (silica gel, 8:2 CH2Cl2:CH3COCH3) and was pure by both 1H NMR and LC. + 9:1 CH2Cl2:CH3COCH3. + For optically pure material (R). + Reference 15. + For optically pure material (S). + Reference 17. + Corrected for recovered substrate.

Scheme I

Scheme 1

Valine (2b). Reactions of these amino acid esters with 1 gave, respectively, 3a (80% yield, mp 137.3–138.6 °C, [α]D + 26.8° (c 1.00, C2H5O2CH3)) and 3b (88% yield, mp 170.1–170.4 °C, [α]D + 27.9° (c 1.00, C2H5O2CH3)). For the crucial ring-closure reaction 3a and 3b were first deblocked with trifluoroacetic acid (TFA) and were then converted to their dicesium salts and allowed to react with 1,5-dibromo-compounds are good and spectral data are in accord with the proposed structures. We believe that all pyridine compounds reported here are optically pure (note that inversion at one asymmetric center produces a meso diastereomer). As far as we are aware this is the first report of the synthesis of amino acid containing "crown ethers".

The results of several reductions with 6 are given in Table I. Reactions were carried out under nitrogen in acetonitrile with equimolar amounts of 6, substrate, and MgCl2·H2O. 12 In the presence of oxygen, 6 was completely oxidized to the perchlorate salt of 5 with detectable reduction of substrate. We observed a direct correlation between the sensitivity of 6 to oxidation and the ease of reduction of the substrate. In the absence of MgCl2·H2O 5 is a popular substrate for reductions with or without oxygen no significant oxidation of 6 or reduction of substrate occurred.

Reduction by 6 of 2-benzoylpyridine (7) to alcohol 8 proceeded only slowly (72 h) even at the relatively high temperature of 55 °C. Data for the maximum rotation of 8 as well as its absolute configuration have not been reported and therefore this reaction was not examined further. Optical data are, however, available for the alcohol 10 derived from trifluoroacetophenone (9), which is a popular substrate for reductions by 1,4-dihydropyridines. We found the reaction to be very sluggish, taking 5 days at 55 °C to go to completion. The degree of asymmetric induction in 10, 68%, is, however, quite satisfying. The reductions of the ethyl ester (11) and amide (13) of phenylglyoxylate proceeded exceptionally smoothly. The optical reductions in 12 and 14 of, respectively, 86 and 64% are also very good indeed considering that the chiral centers in 6 are five bonds removed from the site of hydride donation. 13 The reduction of the N-ethylamide 15 to alcohol 16 has been attended thus far by experimental difficulties: the isolated chemical yield is poor but the optical induction is high with the same stereochemical result (S configuration; see below) as observed in other reductions.

In all cases care was taken to avoid optical fractionation of the alcohol during workup. 14 The recovered perchlorate of pyridinium salt 5 could be reduced by dithionite back to 6 with undiminished rotation. This complete, albeit in two separate reactions, the catalytic cycle of eq 1.

These results represent some of the highest asymmetric in-
ductions ever achieved with optically active 1,4-dihydropyridines. The consistent formation of an excess of the $S$ enantiomer (the relative priorities of the groups are the same for all the optically active alcohols allowing direct comparison) strongly suggests structurally related transition states for reduction. $^{14}$ NMR shielding effects in the presence of Mg$^{2+}$ indicate complexation of Mg$^{2+}$ close to the diethylene glycol bridge of 6. Assuming that the oxygen of carbonyl group complexes to Mg$^{2+}$ with the carbonyl carbon oriented toward the 4 position of the 1,4-dihydropyridine, that the phenyl substituent is the largest group, and that complexed $\alpha$-dicarbonyl compounds assume a cis conformation for the carbonyl groups, the observed $S$ configurations can be predicted. It is important to note that 6 is rather rigid owing to the two amide linkages.

Further experiments are in progress.$^{19}$

References and Notes

1. Dedicated to Professor E. Hovinga, University of Leiden, on the occasion of his 70th birthday.


13. An optical induction of 100 % has been reported for a case in which the hydrate is donated from the optically active source. The term "hydrate donation" as used here is a formalism having no mechanistic implications.

14. Ohnishi$^{19}$ has demonstrated that no optical fractionation occurs during workup of alcohol 12.
