NEW CRYSTALLINE N-(COUMARIN-4-YL)-L-PYROGLUTAMIC ACID:
THE FIRST SYNTHESIS AND APPLICATION TO 'H NMR OPTICAL
PURITY DETERMINATION OF ALCOHOLS AND AMINES1,2

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Abstract: Condensation of 3-phenylsulfonyl-4-chlorocoumarin with tert-
butyl L-pyroglutamate potassium salt followed by desulfonylation and
ester-cleavage yielded the novel crystalline N-(coumarin-4-yl)-L-pyro-
glutamic acid(CPYRO-OH), which being evidenced to be a versatile and
reliable 'H nmr optical purity determination agent for chiral alcohols
and amines.

With the recent explosive progress in the diverse protocols for asymmetric synthesis, the
design and development of new chiral derivatizing agents(CDAs) for an accurate, reliable,
and convenient 'H NMR enantiomeric excess(e.e.) determination remain a constant need de-
spite a number of methods, e.g., polarimeter, GLC, and HPLC.3 During our studies on the
coumarin chemistry,4 we frequently experienced that, in addition to remarkable solidity
enhancement by coumarin nuclei, a sharp singlet proton signal of coumarin C-3 always ap-
ppears at quite lower fields, 6.0-7.0 ppm,5 than OMe protons(a quartet) in Mosher's acid,6
the most well-known CDA, which makes attractive in the 'H NMR e.e. determination due to
the lesser overlap disturbance by other protons present in the substrate. Thus, it appears
to us that the coumarin-containing amino acid might prove to be a promising candidate as a
chiral derivatizing agent for 'H NMR e.e. determination for chiral alcohols and amines.
Our envisagement was realized and we report here our preliminary results.

In contrast to the preparation of 4-piperidinocoumarin from piperidine and 4-chlorocoum-
arin by Zagorevskii7 and of 4-pyrrolidinocoumarin from pyrrolidine and 4-hydroxycoumarin
by Badran,8 attempts to condense pyroglutamic acid and its esters with both coumarins
above have all failed to produce any desired coumarino-amino acid. However, according to
the literature9 and our own results,9b an electron-withdrawing group at the C-3 position
of 4-chlorocoumarin makes the condensation proceed extremely easily and considering 'H NMR
e.e. determination of coumarino-amino acids, a selection of sulfonyl group replaceable
by hydrogen is essential. As seen in Scheme 1, following the preparation of 3-phenylsulfonyl-4-hydroxycoumarin from aspirin chloride and methyl phenylsulfonylacetate via a modification of the Anschütz method, condensation of 3-phenylsulfonyl-4-chlorocoumarin with tert-butyl L-pyroglutamate potassium salt gave an 85% yield of the desired tert-butyl N-(3-phenylsulfonylcoumarin-4-yl)-L-pyroglutamate. Removal of phenylsulfonyl group by Zinc dust and saturated aq. ammonium chloride followed by ester-cleavage with CPY3COOH furnished the new optically pure N-(coumarin-4-yl)-L-pyroglutamic acid[CPYRO-OH] in high yield.

Results of the observed diastereotopic nonequivalence (Δ δ ppm) of the typical sharp singlet proton (≈6.3 ppm) at coumarin C-3 of CPYRO-OH are shown in Table 1, wherein appearance of other proton signals in many organic compounds except for the active methylenic and the non-substituted vinylic compounds etc. is rarely scarce. Either racemization or kinetic discrimination was not induced throughout derivatization, as depicted in Table 2, by comparing the known enantiomeric ratios(%e.e.) of the weighed compositions of the two representative enantiopure methyl mandelates and methyl leucinates with diastereomeric ratios(%d.e.) from the ¹H NMR integration of their resultant ester and amide derived by CPYRO-OH.¹¹

The following remarkable observations are noteworthy. 1) An irksome optical resolution is not absolutely required. 2) A sharp-singlet proton always used for the analysis originated from CPYRO-OH, which being independent of the spectroscopic properties of the substrate. 3) CPYRO-OH is a stable crystalline solid: it showed no change after a two-year storage without any precaution. 4) Generally, base-line resolution was ascertained for racemic substrates in Table 1. 5) In some racemic substrates like entries 1, 4, 15, 19, and 24,
<table>
<thead>
<tr>
<th>Entry</th>
<th>Racemic substrate</th>
<th>$\Delta \delta$</th>
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<th>Entry</th>
<th>Racemic substrate</th>
<th>$\Delta \delta$</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph OH</td>
<td>0.017</td>
<td>9</td>
<td></td>
<td>0.008 b,c)</td>
<td>17</td>
<td>Ph NH$_2$</td>
<td>0.017</td>
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<td>2</td>
<td>Me(CH$_2$)$_5$CHMe OH</td>
<td>0.010</td>
<td>10</td>
<td>Ph COOMe</td>
<td>0.089</td>
<td>18</td>
<td>Me(CH$_2$)$_5$CHMe NH$_2$</td>
<td>0.029</td>
</tr>
<tr>
<td>3</td>
<td>Ph OH</td>
<td>0.020</td>
<td>11</td>
<td>iPr OH</td>
<td>0.069</td>
<td>19</td>
<td>NH$_2$Me</td>
<td>0.019</td>
</tr>
<tr>
<td>4</td>
<td>B$_2$OH</td>
<td>0.006 b,c)</td>
<td>12</td>
<td>iPr COOMe</td>
<td>0.069</td>
<td>20</td>
<td>Ph NH$_2$</td>
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<tr>
<td>5</td>
<td>Ph OH</td>
<td>0.034</td>
<td>13</td>
<td>Ph NH$_2$</td>
<td>0.068</td>
<td>21</td>
<td>NH$_2$COOMe</td>
<td>0.034</td>
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<tr>
<td>6</td>
<td>B$_2$OH</td>
<td>0.040</td>
<td>14</td>
<td>nBu NH$_2$</td>
<td>0.006 b,c)</td>
<td>22</td>
<td>iPr NH$_2$COOMe</td>
<td>0.044</td>
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<tr>
<td>7</td>
<td>OH</td>
<td>0.007 b,c)</td>
<td>15</td>
<td>B$_2$NH$_2$</td>
<td>0.031</td>
<td>23</td>
<td>COOMe</td>
<td>0.049</td>
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<tr>
<td>8</td>
<td>OH</td>
<td>0.024</td>
<td>16</td>
<td>Ph NH$_2$</td>
<td>0.029</td>
<td>24</td>
<td>COOEt</td>
<td>0.128</td>
</tr>
</tbody>
</table>

a) Measured in CDCl$_3$ on a JEOL FX-100 spectrometer unless otherwise specified.
b) By JEOL GX-270(CDCl$_3$).
c) No base-line resolution was observed.

c-0r recognition did perform efficiently wherein the chiral center is 9 atoms distant from the observed nucleus. b) Quite congested secondary alcohol like 2,2-dimethyl-1-phenyl-1-propanol and tertiary alcohols, unfortunately, either do not react with CPYRO-OH or do so in extremely low yield. Further investigations, in order to accomplish the wider applicability, are on going in our laboratory.

REFERENCES AND NOTES

1. Dedicated to the memory of Professor Dr. Shun-ichi Yamada.
2. Thanks are due for a partial financial support of this work through the Japan Research Foundation for Optically Active Compounds.

The multinuclear NMR probes by weight by \textsuperscript{1}H NMR for CDA have been already developed but these are not always accessible or required since appearance of a high-resolution FT-NMR machine. \textsuperscript{18}F; J.A. Dale and H.S. Mosher, J. Am. Chem. Soc., 1973, 95, 512; Y. Takeuchi, N. Itoh, T. Satoh, T. Koizumi, and K. Yamaguchi, J. Org. Chem., 1993, 58, 1812.


11. Besides, derivatization of CPYRO-OH with several other racemic substrates in Table 1 was inspected by NMR integration to yield, at any time, an almost 50:50 mixture of diastereomers. Typical procedure: A solution of 0.42 mmol of CPYRO-OH and 0.46 mmol of 1,1'-carbonyldiimidazole in dry CH\textsubscript{2}Cl\textsubscript{2}(28 mL) and dry DMSO(0.8 mL) was first stirred at rt for 1 h under dry argon and then to this was added a solution of 0.4 mmol of racemic substrate in dry CH\textsubscript{2}Cl\textsubscript{2}(7 mL) and dry DMSO(0.2 mL). After stirring for 3-20 h, a reaction mixture was washed successively with water, saturated aq. NaHCO\textsubscript{3} and brine followed by drying(MgSO\textsubscript{4}) and evaporation to give crude diastereomeric esters and amides which were submitted to \textsuperscript{1}H NMR inspection.

Table 2 Comparison of Optical Purity Determination by Optical Rotation and \textsuperscript{1}H NMR Integration (100 MHz)

<table>
<thead>
<tr>
<th>(R)- and (S)- Composition %e.e. \textsuperscript{a}</th>
<th>Diastereomeric ratio of CPYRO-OH by weight</th>
<th>ester and amide %d.e. by \textsuperscript{1}H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl 50:50 1.2</td>
<td>50.5:49.5</td>
<td>1.0</td>
</tr>
<tr>
<td>mandelate 80:20 58.7</td>
<td>79.5:20.5</td>
<td>59.0</td>
</tr>
<tr>
<td>95: 5</td>
<td>95.8: 4.2</td>
<td>91.6</td>
</tr>
<tr>
<td>Methyl 50:50 0</td>
<td>50.8:49.2</td>
<td>1.6</td>
</tr>
<tr>
<td>leucinate 70:30 40.5</td>
<td>69.5:30.5</td>
<td>39.0</td>
</tr>
<tr>
<td>90:10</td>
<td>89.8:10.4</td>
<td>79.2</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by specific rotation, [\alpha]D\textsuperscript{a} (c=1, CH\textsubscript{2}Cl\textsubscript{2}).

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