Crystal Structure and Absolute Configuration of the Hydrobromide Salt of (-)-2-exo-Aminonorbornane-2-carboxylic Acid

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Abstract: The configuration of one of the four isomers of 2-aminonorbornane-2-carboxylic acid (C₇H₈O₂N) has been determined to be (1R,2R,4S) by X-ray crystallography, utilizing anomalous scattering. The hydrobromide salt of this isomer, (-)-2-exo-aminonorbornane-2-carboxylic acid, crystallizes in space group P2₁2₁2, with four molecules per unit cell of dimensions a = 6.986, b = 22.669, and c = 6.150 Å. The structure was determined by the heavy atom method and refined to a final R factor of 0.04. The bond angles and distances in the bicycloheptane ring agree well with those observed in other norbornane compounds, but the location of the carboxyl group in the endo position is counter to certain chemical predictions. Determination of the absolute configuration relates this norbornane amino acid to (-)-norbornanone (1R).

The unnatural amino acid, 2-aminonorbornane-2-carboxylic acid, or BCH,¹ has been prepared by both the Strecker and the Bucherer syntheses,² and shown to possess several interesting biological activities. BCH inhibits the Na⁺-independent transport of nonpolar amino acids across cell membranes,³ like leucine, it acts as an insulin-releasing factor in the rat,⁴ and it inhibits the flavoprotein amino acid oxidases.⁵ The chemical syntheses from (+)-norbornanone yield a mixture of four isomers, the (-) and (+) enantiomers of the exo-amino (I and II) and endo-amino forms. The geometric isomers have been separated by column chromatography,⁵,⁶ the isomer eluted first being designated a-BCH. Resolution of the enantiomers of both a- and b-BCH has permitted the demonstration that the biological potency of these compounds depends on both the geometric and absolute configurations of the molecule.⁴ Although the insulin-releasing activity and the uptake into Escherichia coli cells are restricted to the levorotatory b-BCH, the stereospecificity displayed by other bioassay systems is not absolute.⁴,⁶

Efforts to establish the geometric configurations of the a- and b-BCH isomers by degradation to the known norbornane carboxylic acids⁷ proved unsuccessful.⁶ The assignments of configuration in the analogous cy-clohexane amino acids, based on pK values, spectra, and reactivities, have been the subject of some disagreement.⁸,⁹ Moreover, the differences in pK and in reactivity between exo-amino- and endo-amino-BCH are not large.⁴ We therefore undertook the crystal structure analysis of one of the a-BCH isomers in order to determine its configuration. For comparison with the amino acid whose activity is mimicked by BCH, the absolute configuration is also essential, and has been determined by the use of anomalous scattering. To ensure that the observed intensity differences would be sufficiently large, a good anomalous scatterer was incorporated into the structure by conversion of (–)-a-BCH to the hydrobromide salt, which was prepared and crystallized for us by H. Tager.

The initial Fourier map of a-BCH, based on phases calculated from the bromine positions, showed that, contrary to the predictions from the pK values for the carboxyl and amino groups, a-BCH possesses an endo carboxyl group. The absolute configuration of (–)-a-BCH has been established as structure I (1R,2R,4S); refinement of this structure resulted in a final R factor of 0.04. In the accompanying paper,⁴ Tager and Christensen report the identification of the two isomers of b-BCH.

Experimental Section

Unit cell parameters and other physical data are included in Table I. The hkl and Friedel-related hkl intensities were measured using a diffractometer with Weissenberg geometry. Integrated intensities were calculated from counts accumulated during stepwise θ scans, and background correlations were reduced by employing balanced filters. An intensity was considered to be unobserved whenever contiguous counts in the peak region were not significantly greater than the adjacent background noise level.¹° Correcions for relative absorption were computed from measurements of the crystal dimensions.¹¹,¹² As a final check on the absolute configuration, intensities of a selected set of reflections were also determined with a four-circle diffractometer (Table VI).

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5. H. N. Christensen and H. S. Tager, private communication.
clearly seen. The carboxyl group was in the endo configuration, demonstrating that (-)-a-BCH corresponds to either I or I1. For 80% of these 113 reflections, Table VI provides a quantitative comparison of the calculated and observed differences for selected reflections whose Bijvoet ratios were predicted to be large. The differences |\(F_{\text{calcd}}| - |\(F_{\text{obsd}}|\) were greater than 10% of \(|\(F_{\text{calcd}}| + |\(F_{\text{obsd}}|)/2\) for 113 reflections. The signs of the anomalous differences agreed with the assignment of \((-\alpha\)-BCH as structure I for 90% of these 113 reflections. Table VI provides a quantitative comparison of the calculated and observed differences for selected reflections whose Bijvoet ratios were predicted to be large.

Hydrogen Bonding. Each molecule makes four independent hydrogen bonds. Table VII presents the distances and angles between each of the possible hydrogen bonded pairs. There are four potential acceptor atoms, O2 II, Br II, Br III, and Br IV (Figures 1 and 2) situated about the nitrogen atom at distances assigned from the anomalous scattering differences, structure factors, \(F_{\text{calcd}}\), and \(F_{\text{obsd}}\) were calculated for I using the parameters of Tables II and III. The differences \(|\(F_{\text{calcd}}| - |\(F_{\text{obsd}}|\) were greater than 10% of \(|\(F_{\text{calcd}}| + |\(F_{\text{obsd}}|)/2\) for 113 reflections. The signs of the anomalous differences agreed with the assignment of \((-\alpha\)-BCH as structure I for 90% of these 113 reflections. Table VI provides a quantitative comparison of the calculated and observed differences for selected reflections whose Bijvoet ratios were predicted to be large.

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Figure 1. Stereoscopic drawing of (-)-a-BCH. This drawing was prepared by the program ORTEP. Thermal ellipsoids are scaled to enclose 50% probability. Hydrogen bonds connect O1 with Br and N with O2 II, Br II, and Br IV.

Discussion

Comparison of the bond distances and angles in I with those determined for other norbornane structures.

Table V. Bond Angles in Degrees

| C2-C1-C5 | 109.8 | C3-C4-C5 | 108.6 |
| C2-C1-C7 | 100.0 | C3-C4-C7 | 101.4 |
| C6-C1-C7 | 100.5 | C5-C4-C7 | 103.6 |
| C1-C2-C3 | 103.6 | C4-C5-C6 | 102.7 |
| C1-C2-N | 107.2 | C1-C6-C5 | 103.1 |
| C1-C2-C8 | 114.5 | C1-C6-C7 | 112.6 |
| N-C2-C3 | 110.5 | N-C2-C8 | 110.5 |
| N-C2-C7 | 104.9 | C1-C7-C4 | 94.2 |
| C8-C2-C3 | 116.0 | C2-C8-O1 | 112.6 |
| C2-C3-C4 | 102.8 | C2-C8-O2 | 121.8 |

- The central atom is the vertex. The estimated standard deviations in the angles ranged from 0.5 to 0.8 degrees.

Table VI. Comparison of Observed and Calculated Anomalous Differences for Selected Reflections

| Reflection | k | l | \(|F_+ - F_-|/|F_+ + F_-|\) | \(|F_+|_{\text{calc}}| |
|------------|---|---|----------------|----------------|
| 1 7 1      | 0.124 | 0.124 | 21.21 |
| 1 18 1     | -0.217 | -0.087 | 0.72 |
| 2 2 2      | 0.234 | 0.234 | 14.58 |
| 2 5 1      | -0.103 | -0.114 | 19.86 |
| 2 7 1      | -0.104 | -0.116 | 17.22 |
| 2 11 2     | -0.061 | -0.117 | 11.33 |
| 2 12 3     | 0.185 | 0.144 | 6.00 |
| 2 16 1     | 0.142 | 0.271 | 4.87 |
| 3 7 1      | 0.122 | 0.102 | 15.03 |
| 4 5 1      | -0.104 | -0.088 | 17.13 |

Three acceptors but vary from 90 to 124° for any of the three possible N-H-Br III interactions. Therefore the atoms to which nitrogen is hydrogen bonded are O2 III, Br II, and Br IV; Br III is an atom of close approach. The other hydrogen bond is between the hydroxyl oxygen O1 and the Br of the same asymmetric unit. Figures 2a and 2b show the crystal structure viewed down the a and -c axes, respectively. The molecules are laid down in hydrogen-bonded sheets perpendicular to the b axis. The sheets themselves are held together only by van der Waals forces.

by electron and X-ray diffraction reveals no strikingly unusual features in a-BCH. Thus the parameters in Tables IV and V lie within the expected ranges. The one-carbon bridge angle found in a-BCH, 94.2°, is comparable with the values 93.2 to 96.5° reported in a recent summary. The two-carbon bridge angles determined here vary between 102.7 and 103.6° and the bridgehead angles, C6-C1-C2 and C3-C4-C5, are 109.7 and 108.6°, respectively. These angles are in good agreement with those observed in 3-(N-benzyl-N-methylaminomethyl)-2-norbornanone and differ but marginally from the values determined for norbornane and 1,4-dichloronorbornane by electron diffraction. Recently it has been recognized that asymmetric substitution of the norbornane nucleus often produces a twist about the C1-C4 vector and thereby destroys the C8 symmetry of the bicycloheptane ring system. In (-)-a-BCH the loss of symmetry is just detectable in the bond lengths and angles, which differ by approximately 2σ across the mirror planes through the norbornane nucleus. For (-)-a-BCH - HBr the twist is S(-, -); the magnitude of the phase angle of pseudorotation, Δ, for the ring C1-C2-C3-C4-C7-C1

(21) Computations used the ORFE and ORTEP programs, obtained from the Oak Ridge National Laboratory, and written by W. R. Busing, K. O. Martin, and H. A. Levy, and by C. K. Johnson, respectively.
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the carboxyl group in crystalline \(a\)-BCH.

The exo- and endo-norbornane carboxylic acids and
amines were originally prepared and characterized by
\(a\)-BCH, this angle is 16'.

The angles at the carboxyl carbon follow the pattern of other acids, with the \(O-C-O\) angle near 125°, and the two \(O-C\) angles unequal,\(^\text{24}\)
although the disparity between the latter two angles is somewhat greater than the average. The extensive hy-
drogen bonding observed in crystalline BCH HB_r
is typical of amino acid salts. The hydrogen-bonded O
\(\cdots\) N distance of 2.86 \(\AA\) is close to the "normal"\(^\text{14}\)
value of 2.90 \(\AA\) and the N \(\cdots\) Br distances (Table VII)
may be compared with the 3.36 and 3.32 \(\AA\) reported for
leucine hydrobromide.\(^\text{21}\) The torsion angles about the
\(C_n(Carboxy)\) bond have been examined in several
amino acids and peptides. The absolute value of the
cis-cis angle \(O-C-C-C\) varies from 0° to about 70°, with a cluster of angles not far from zero.\(^\text{26}\) In
\(a\)-BCH, this angle is 16°. As a result, the plane of the
carboxyl group is approximately perpendicular to the
plane defined by \(C_1-C_2-C_3\) of the norbornane nucleus;
the interplanar angle is 80° 21'. The carboxyl proton
points away from the bicycloheptane ring. The hydro-
bonds to Br\(\text{-}\) and to the amino N of a neighboring
molecule undoubtedly stabilize this orientation
of the carboxyl group in crystalline \(a\)-BCH.

The exo- and endo-norbornane carboxylic acids and
amines are originally prepared and characterized by
Alder and coworkers.\(^\text{28}\) Subsequent identification of
exo and endo substituents has relied on the initial as-
signments and used a variety of techniques, especially
ir, and more recently, nmr. Solvolysis rates of exo-
and endo-norbornyl chlorides differ by several orders of
magnitude\(^\text{29}\) and can therefore be used to distinguish
these epimers. On the other hand, saponification rates
of the acid phthalates of exo- and endo-norbornone,\(^\text{23}\)
like the hydrolysis rates of exo- and endo-N-formyl-
BCH,\(^\text{a}\) are almost identical. In general, endo isomers
of norbornyl compounds prove to be less stable, and
the properties of endo substituents are more perturbed
by the ring system.\(^\text{24}\) On this basis, the \(pK\) values of
\(a\)- and \(b\)-BCH would suggest the tentative conclusion
that the a isomer possesses an exo-carboxyl group.\(^\text{4}\)
However, the structure analysis demonstrates that
the carboxyl group is endo and emphasizes the difficulties
of prediction in this series of compounds, especially
when the 2 position is disubstituted.

The absolute configurations of a number of norborn-
nane derivatives, including the \(exo\)- and \(endo\)-carbox-
ylic acids and the \(endo\)-amine, have been assigned by
chemical conversions relating them to other terpenoids
and ultimately to glyceraldehyde.\(^\text{27}\) Several previous
structure analyses of monoterpen derivatives\(^\text{27b}\)
have included the determination of absolute configura-
tion. Further configurational assignments have de-
hended upon application of the octant rules.\(^\text{29}\) By
the latter method, (\(-\)norbornanone (norecamphor)
was identified as 1R, in agreement with the chemical assign-
ment.\(^\text{29}\) A similar analysis of the ORD and CD spectra
of salicylidene derivatives of \(exo\)-3-phenyl-endol-2-nor-
bornanamines has established configurations for these
compounds and hence for the 3-phenyl-2-carboxylic
acids,\(^\text{20}\) and chemical reactions have referred the phenyl-
substituted series to norbornanone.\(^\text{31}\) The present
paper establishes that (\(-\)2-endo-carboxyl-2-exo-amino-
norbornane has the 1R configuration and therefore
unequivocally relates this amino acid to (\(-\)norbornanone
(1R). Chemical data reported in the accompany-
ing paper\(^\text{4}\) demonstrate that (\(-\)2-exo-carboxyl-2-
endo-aminonorbornane is also derived from (\(-\)nor-
bornanone. \(l\)-Leucine, \(d\)-valine, or \(d\)-isoleucine can
assume conformations which resemble (\(-\)\(a\)-BCH.

Given suitable restrictions of the rotation angles, any
of these carbon skeletons can be exactly superimposed
on \(l\): e.g., if \(C_3\) of d-isoleucine coincides with \(C_2\), then
\(C_2\) coincides with \(C_1\), the ethyl group with \(C_5\) and \(C_6\),
and the methyl with \(C_7\). The relative biological activ-
ities of the BCH isomers may be partly rationalized on
the basis of such comparisons.\(^\text{4}\)

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Michigan Medical School Fund for Computing.

Table VII. Possible Hydrogen Bonding Pairs\(^\text{a}\)

<table>
<thead>
<tr>
<th>Donor (D)</th>
<th>Acceptor (A)</th>
<th>Symmetry operation on A</th>
<th>Length, (\AA)</th>
<th>Angle, deg, C-D-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 N O2 III</td>
<td>1/2 - x, -y, -z + z</td>
<td>2.852</td>
<td>96.2</td>
<td></td>
</tr>
<tr>
<td>2 N Br II</td>
<td>1 + x, y, z</td>
<td>3.482</td>
<td>105.9</td>
<td></td>
</tr>
<tr>
<td>3 N Br IV</td>
<td>1 + x, y, -1 + z</td>
<td>3.483</td>
<td>109.1</td>
<td></td>
</tr>
<tr>
<td>4 N Br III</td>
<td>1/2 - x, -y, -z + z</td>
<td>3.349</td>
<td>168.4</td>
<td></td>
</tr>
<tr>
<td>5 N Br</td>
<td>x, y, z</td>
<td>3.098</td>
<td>114.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) The estimated standard deviation in the bond lengths ranged from 0.006 to 0.008 \(\AA\); those for the bond angles from 0.4° to 0.5°. This is an atom of close approach (see text).

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