Substituent Effects on Benzoic Acid Activity

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Introduction

Materials and Methods

Scheme 1 illustrates the synthesis of 2,5-dihydroxybenzoic acid by phenylester cleavage of 2-hydroxy-5-acetoxybenzoic acid. The starting material is reacted with sodium hydroxide and hydrogen peroxide in aqueous solution. A detailed description of this synthesis is provided in the appendix.

Scheme 1. Synthesis of 2,5-dihydroxybenzoic acid.

The synthesis of 2,6-dihydroxybenzoic acid is outlined in Scheme 2. 2,6-Dihydroxybenzoic acid is prepared by carboxylation of 1,3-dihydroxybenzene and a detailed description of this synthesis is provided in the appendix.

Scheme 2. Synthesis of 2,6-dihydroxybenzoic acid.

The $pK_a$ values of the three disubstituted benzoic acids were determined by the capillary zone electrophoresis method. All analyses were made on a Hewlett-Packard Model G1600A 3DCE system equipped with diode array detector. A fused silica capillary i.d. 50 ixm was from Agilent Technologies. The effective and total lengths of the capillary were 645 mm and 560 mm, respectively. Injection was made hydrostatically at 30 mbar for 10 s and detection was by indirect UV at 254 nm. The applied separation voltage was
30 kV (anode at detection side) and the current varied between 19 to 9 IxA as a response to changes in pH and ionic strength. The temperature was 25° C.

Water was the solvent used in the experimental determination of all of these pK_a values. Their measured pK_a values are listed in Table 1. The pK_a values for the two mono-substituted benzoic acids, as well as benzoic acid itself, were previously determined.\(^{1,2}\)

**Table 1.** pK_a Values of Substituted Benzoic Acids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Number</th>
<th>pK_a Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic Acid</td>
<td>1</td>
<td>4.19</td>
<td>1</td>
</tr>
<tr>
<td>2-hydroxybenzoic acid</td>
<td>2</td>
<td>2.93</td>
<td>1</td>
</tr>
<tr>
<td>3-hydroxybenzoic acid</td>
<td>3</td>
<td>4.08</td>
<td>2</td>
</tr>
<tr>
<td>2,3-dihydroxybenzoic acid</td>
<td>4</td>
<td>2.91</td>
<td>This work</td>
</tr>
<tr>
<td>2,5-dihydroxybenzoic acid</td>
<td>5</td>
<td>2.95</td>
<td>This work</td>
</tr>
<tr>
<td>2,6-dihydroxybenzoic acid</td>
<td>6</td>
<td>1.22</td>
<td>This work</td>
</tr>
</tbody>
</table>

**Results and Discussion**

**Conclusion**

**Supplemental Material Available:** Details of the syntheses of 2,5- and 2,6-dihydroxybenzoic acid and results of their characterization by mass spectrometry, \(^1\)H- and \(^13\)C-NMR, and IR spectroscopy. The appendix can be obtained by contacting the authors.

**References**


Supporting Information

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Table of Contents

Synthesis of 2,5-dihydroxybenzoic acid................................. 3
Mass Spectrum of 2,5-dihydroxybenzoic acid.......................... 4
$^{13}$C NMR spectrum of 2,5-dihydroxybenzoic acid.................... 5
$^1$H NMR spectrum of 2,5-dihydroxybenzoic acid..................... 6
IR spectrum of 2,5-dihydroxybenzoic acid............................... 7
Synthesis of 2,6-dihydroxybenzoic acid................................. 8
Mass Spectrum of 2,6-dihydroxybenzoic acid.......................... 9
$^{13}$C NMR spectrum of 2,6-dihydroxybenzoic acid.................... 10
$^1$H NMR spectrum of 2,6-dihydroxybenzoic acid..................... 11
IR spectrum of 2,6-dihydroxybenzoic acid............................... 12
Synthesis of 2,5-dihydroxybenzoic acid

The following is the specific procedure followed for the 1 step, 1 stage synthesis of 2,5 dihydroxybenzoic acid. All reagents were purchased from the Aldrich Chemical Company. The 2-hydroxy-5-acetylbenzoic acid is combined with a 3% solution of sodium hydroxide/hydrogen peroxide. This results in a deacylation, cleavage, another deacylation, oxidation, and an oxidative cleavage to result with the final acid in a 63% yield.
Mass Spectrum of 2,5-dihydroxybenzoic acid

The spectrum was obtained at a source temperature of 200°C and a sample temperature of 0°C. The DIRECT was set at 75 eV.
$^{13}$C NMR spectrum of 2,5-dihydroxybenzoic acid

The spectrum was obtained at 25.16 MHz at a sample dilution of 0.260 g : 1.5 mL D$_2$O.
\(^1\)H NMR spectrum of 2,5-dihydroxybenzoic acid

The spectrum was obtained at 89.56 MHz at a sample dilution of 0.047g : 0.5 mL DMSO-\(d_6\).
IR spectrum of 2,5-dihydroxybenzoic acid

The spectrum was obtained using the nujol mull method of obtaining infrared spectroscopy.
**Synthesis of 2,6-dihydroxybenzoic acid**

The following is the specific procedure followed in order to synthesis 2,6-dihydroxybenzoic acid. All reagents were purchased from the Aldrich Chemical Company. Carbon dioxide reacts with 1,3 dihyrdoxybenzene in 1 step with the application of 3 separate stages. In the first stage the reagents are placed in the solvent AcNMe₂ at 135°C. Following this K₂CO₃ at 140-160°C is added to the mixture. The mixture is then heated to 155-160°C and rests for 6-7 hours. In the final stage Acid hydrogenates the reagents followed by reflux for 1 hour.
Mass Spectrum of 2,6-dihydroxybenzoic acid

The spectrum was obtained at a source temperature of 170°C and a sample temperature of 120°C. The DIRECT was set at 75 eV.
$^{13}$C NMR spectrum of 2,6-dihydroxybenzoic acid

**Figure 6.** The following spectrum was obtained at 25.16 MHz at a sample dilution of 0.034g : 0.5 mL DMSO-d$_6$. 
$^1$H NMR Spectrum of 2,6-dihydroxybenzoic acid

The spectrum was obtained at 89.56 MHz at a sample dilution of 0.034g : 0.5 mL DMSO-$d_6$. 
IR spectrum of 2,6-dihydroxybenzoic acid

The spectrum was obtained using the nujol mull method of obtaining infrared spectroscopy.
Citation for Synthesis of 2,5-dihydroxybenzoic acid


Citation for Synthesis of 2,6-dihydroxybenzoic acid


Citation for pKa determination procedure