Supporting Information for

Capturing Elusive Polymorphs of Curcumin: A Structural Characterization and Computational Study

Maria A. Matlinska, † Roderick E. Wasylishen,* † Guy M. Bernard, † Victor V. Terskikh, ‡ Andreas Brinkmann, § and Vladimir K. Michaelis †

† Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2

‡ Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5

§ Metrology, National Research Council Canada, 1200 Montreal Road, Ottawa, Ontario, Canada, K1A 0R6

Corresponding Author

* Telephone: +1-780-492-4336, email: roderick.wasylishen@ualberta.ca
Table of Contents

1.0 **Single-Crystal X-ray Diffraction**
   
   1.1 **Form I**
   - Figure S1. Perspective view of form I of curcumin.
   - Table S1. Comparison of crystal parameters of form I obtained in this work and reported previously.
   - Table S2. Hydrogen-bond interactions for form I of curcumin.

   1.2 **Form II**
   - Figure S2. Perspective views of the two crystallographically-independent molecules for form II of curcumin.
   - Table S3. Comparison of crystal parameters of form II obtained in this work with those reported in the literature.
   - Table S4. Hydrogen-bond interactions for form II of curcumin.

2.0 **Resonance Assisted Hydrogen Bonding**
   - Figure S3. Resonance assisted structure for the keto-enol region of a β-diketone.
   - Table S5. Interatomic distances and calculated $q$ values for the keto-enol region of form I of curcumin.
   - Table S6. Interatomic distances and calculated $q$ values for the keto-enol region of form II of curcumin.

3.0 **Additional Tables**
   - Table S7. Crystallization conditions and resulting curcumin polymorphs.
   - Table S8. Experimental and CASTEP-computed $^{13}$C and $^1$H solid-state NMR chemical shifts for form II of curcumin.

4.0 **Additional Figures**
   - Figure S4. Hydrogen bonding interactions in the carbonyl region for form II of curcumin.
   - Figure S5. Complete $^{13}$C-$^1$H HETCOR spectrum for solid curcumin, form II, acquired at 21.1 T.
   - Figure S6. Plot of experimental vs computed (CASTEP) $^{13}$C NMR chemical shifts for molecules A and B of form II curcumin.

5.0 **References**
1.0 Single-Crystal X-ray Diffraction

1.1 Form I

Figure S1. Perspective view of form I of curcumin, showing the labeling scheme used below and in the manuscript. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.
Table S1. Comparison of Crystal Structural Parameters of Form I Obtained in this work and Reported Previously.

<table>
<thead>
<tr>
<th>Crystal Parameter</th>
<th>Form I</th>
<th>Form I reported by Parimita et al.¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>$P2/n$</td>
<td>$P2/n$</td>
</tr>
<tr>
<td>System</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>$a$/Å</td>
<td>12.6264(2)</td>
<td>12.707(3)</td>
</tr>
<tr>
<td>$b$/Å</td>
<td>7.11013(16)</td>
<td>7.2186(14)</td>
</tr>
<tr>
<td>$c$/Å</td>
<td>19.9560(4)</td>
<td>19.880(4)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>95.0882(7)</td>
<td>95.384(4)</td>
</tr>
<tr>
<td>$V$/Å³</td>
<td>1784.50(4)</td>
<td>1815.6(7)</td>
</tr>
<tr>
<td>$D_{calcd}$/g∙cm⁻³</td>
<td>1.371</td>
<td>1.384</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>$T$/K</td>
<td>173</td>
<td>290</td>
</tr>
<tr>
<td>Goodness-of-fit</td>
<td>1.063</td>
<td></td>
</tr>
</tbody>
</table>

Table S2. Hydrogen-bond Interactions for Form I of Curcumin.

<table>
<thead>
<tr>
<th>D–H⋯A</th>
<th>D–H/Å</th>
<th>H⋯A/Å</th>
<th>D⋯A/Å</th>
<th>$\angle$D–H⋯A /deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2–H2O⋯O1</td>
<td>0.81(3)</td>
<td>2.20(3)</td>
<td>2.6736(17)</td>
<td>118(3)</td>
</tr>
<tr>
<td>O3–H3O⋯O4</td>
<td>0.77(3)⁺</td>
<td>1.74(3)</td>
<td>2.4558(16)</td>
<td>156(5)</td>
</tr>
<tr>
<td>O4–H4O⋯O3</td>
<td>0.77(3)⁺</td>
<td>1.74(3)</td>
<td>2.4558(15)</td>
<td>156(5)</td>
</tr>
<tr>
<td>O6–H6O⋯O3⁺</td>
<td>0.76(3)</td>
<td>2.11(3)</td>
<td>2.807(2)</td>
<td>152(2)</td>
</tr>
</tbody>
</table>

a The O3–H3O and O4–H4O distances were constrained to be equal (within 0.03 Å) during refinement.

b Intermolecular hydrogen bond at $\frac{1}{2} + x, y, -\frac{1}{2} + z$. 

S4
1.2 Form II

Figure S2. Perspective views of the two crystallographically-independent molecules for form II of curcumin showing the atom labeling scheme used below and in the manuscript. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.
Table S3. Comparison of Crystal Parameters of Form II Obtained in this Work with those Reported in the Literature.

<table>
<thead>
<tr>
<th>Crystal Parameter</th>
<th>Form II</th>
<th>Form II reported by Sanphui et al.$^{2,a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>Pca2$_1$</td>
<td>Pca2$_1$</td>
</tr>
<tr>
<td>$a$/Å</td>
<td>35.4456 (5)</td>
<td>35.417 (3)</td>
</tr>
<tr>
<td>$b$/Å</td>
<td>7.84979 (10)</td>
<td>7.7792 (7)</td>
</tr>
<tr>
<td>$c$/Å</td>
<td>12.69296 (16)</td>
<td>12.6482 (11)</td>
</tr>
<tr>
<td>$V$/Å$^3$</td>
<td>3531.70 (8)</td>
<td>3484.7 (5)</td>
</tr>
<tr>
<td>$D_{\text{calc}}$/g·cm$^{-3}$</td>
<td>1.386</td>
<td>1.404</td>
</tr>
<tr>
<td>$Z$</td>
<td>8/2</td>
<td>8/2</td>
</tr>
<tr>
<td>$T$/K</td>
<td>173</td>
<td>100</td>
</tr>
<tr>
<td>Goodness-of-fit</td>
<td>1.061</td>
<td>1.083</td>
</tr>
</tbody>
</table>

a. Similar parameters were reported by Parameswari et al. in a later study.$^{3}$
Table S4. Hydrogen-bond Interactions for Form II of Curcumin.

<table>
<thead>
<tr>
<th>D–H⋯A</th>
<th>D–H/Å</th>
<th>H⋯A/Å</th>
<th>D⋯A/Å</th>
<th>∠D–H⋯A/deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2A–H2OA⋯O3A</td>
<td>0.848(14)e</td>
<td>1.84(2)</td>
<td>2.633(2)</td>
<td>155(4)</td>
</tr>
<tr>
<td>O4A–H4OA⋯O3A</td>
<td>0.91(4)</td>
<td>1.68(4)</td>
<td>2.530(2)</td>
<td>154(4)</td>
</tr>
<tr>
<td>O6A–H6OA⋯O5A</td>
<td>0.832(14)e</td>
<td>2.20(4)</td>
<td>2.714(2)</td>
<td>120(3)</td>
</tr>
<tr>
<td>O6A–H6OA⋯O1A</td>
<td>0.832(14)e</td>
<td>2.18(2)</td>
<td>2.920(2)</td>
<td>148(4)</td>
</tr>
<tr>
<td>O2B–H2OB⋯O1B</td>
<td>0.838(14)e</td>
<td>2.14(4)</td>
<td>2.652(3)</td>
<td>119(3)</td>
</tr>
<tr>
<td>O2B–H2OB⋯O6B</td>
<td>0.838(14)e</td>
<td>2.26(3)</td>
<td>2.924(3)</td>
<td>137(4)</td>
</tr>
<tr>
<td>O4B–H4OB⋯O3B</td>
<td>1.11(6)</td>
<td>1.42(6)</td>
<td>2.501(2)</td>
<td>162(6)</td>
</tr>
<tr>
<td>O6B–H6OB⋯O5A</td>
<td>0.837(14)e</td>
<td>2.26(3)</td>
<td>2.859(3)</td>
<td>129(3)</td>
</tr>
<tr>
<td>O6B–H6OB⋯O5B</td>
<td>0.837(14)e</td>
<td>2.18(4)</td>
<td>2.650(3)</td>
<td>116(3)</td>
</tr>
</tbody>
</table>

a Intermolecular hydrogen bond at $\bar{x}$, $1 - y$, $-\frac{1}{2} + z$.

b Intermolecular hydrogen bond at $\frac{1}{2} + x$, $\bar{y}$, $z$.

c Intermolecular hydrogen bond at $\frac{1}{2} + x$, $1 - y$, $z$.

d Intermolecular hydrogen bond at $-\frac{1}{2} + x$, $1 - y$, $z$.

e Distance constrained to a target value of 0.84(1) Å during refinement.
2.0  Resonance Assisted Hydrogen Bonding (RAHB).

The degree of hydrogen bonding may be related to the structure of the keto-enol region (Figure S3).³

![Resonance assisted hydrogen bonding structure](image)

**Figure S3.** Resonance assisted hydrogen bonding structure for the keto-enol region of a β-diketone. The $d_i$ define the indicated bond lengths (see below).

The degree of resonance, and hence the strength of the hydrogen bond, may be assessed by measuring the differences between the two C-O bond lengths and between the two C-C bond lengths:

$$q_1 = d_4 - d_1$$

$$q_2 = d_2 - d_3$$

Tables S5 and S6 summarize the $d$ and $q$ values for forms I and II, respectively, of curcumin, as well as the reported O-H distances for the enolic regions of these molecules. $d_1$ was designated as the C-O bond with the attached proton (determined through inspection of reported crystal structures).
Table S5. Interatomic distances and calculated $q$ values for the keto-enol region of form I of curcumin.

<table>
<thead>
<tr>
<th>$d_1$/Å</th>
<th>$d_2$/Å</th>
<th>$d_3$/Å</th>
<th>$d_4$/Å</th>
<th>$q_1$</th>
<th>$q_2$</th>
<th>O3-H/Å</th>
<th>O4-H/Å</th>
<th>O3-O4/Å</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.313</td>
<td>1.402</td>
<td>1.392</td>
<td>1.315</td>
<td>0.002</td>
<td>0.010</td>
<td>–</td>
<td>–</td>
<td>2.446</td>
<td>5</td>
</tr>
<tr>
<td>1.304</td>
<td>1.390</td>
<td>1.402</td>
<td>1.282</td>
<td>−0.022</td>
<td>−0.012</td>
<td>1.26</td>
<td>1.28</td>
<td>2.455</td>
<td>1</td>
</tr>
<tr>
<td>1.298</td>
<td>1.403</td>
<td>1.397</td>
<td>1.303</td>
<td>0.005</td>
<td>0.006</td>
<td>1.07</td>
<td>1.44</td>
<td>2.441</td>
<td>2</td>
</tr>
<tr>
<td>1.298</td>
<td>1.390</td>
<td>1.401</td>
<td>1.285</td>
<td>−0.013</td>
<td>−0.011</td>
<td>1.36</td>
<td>–</td>
<td>2.454</td>
<td>6</td>
</tr>
<tr>
<td>1.302</td>
<td>1.388</td>
<td>1.393</td>
<td>1.291</td>
<td>−0.011</td>
<td>−0.005</td>
<td>0.80</td>
<td>1.716</td>
<td>2.459</td>
<td>7</td>
</tr>
<tr>
<td>1.289</td>
<td>1.385</td>
<td>1.390</td>
<td>1.276</td>
<td>−0.013</td>
<td>−0.005</td>
<td>0.82</td>
<td>≈1.75</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>1.298</td>
<td>1.405</td>
<td>1.400</td>
<td>1.305</td>
<td>0.007</td>
<td>0.005</td>
<td>1.118</td>
<td>1.378</td>
<td>2.439</td>
<td>9</td>
</tr>
<tr>
<td>1.291</td>
<td>1.385</td>
<td>1.428</td>
<td>1.289</td>
<td>−0.002</td>
<td>−0.043</td>
<td>1.258</td>
<td>1.310</td>
<td>2.487</td>
<td>10</td>
</tr>
<tr>
<td>1.306</td>
<td>1.397</td>
<td>1.406</td>
<td>1.294</td>
<td>−0.006</td>
<td>−0.009</td>
<td>0.764&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.763&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.456</td>
<td>this work</td>
</tr>
</tbody>
</table>

a. Two H sites each with 50 % occupation were determined in the refinement of the structure.

Table S6. Interatomic distances and calculated $q$ values for the keto-enol region of form II of curcumin.

<table>
<thead>
<tr>
<th>$d_1$</th>
<th>$d_2$</th>
<th>$d_3$</th>
<th>$d_4$</th>
<th>$q_1$</th>
<th>$q_2$</th>
<th>O3-H/Å</th>
<th>O4-H/Å</th>
<th>O3-O4/Å</th>
<th>Ref</th>
</tr>
</thead>
</table>
### 3.0 Additional Tables

**Table S7. Crystallization Conditions and Resulting Curcumin Polymorphs.**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Number of Crystallization Steps</th>
<th>Curcumin Polymorph Form</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol 95%</td>
<td>2</td>
<td>II</td>
<td>Dark orange crystals</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>1</td>
<td>I</td>
<td>Red crystals</td>
</tr>
<tr>
<td>Acetonitrile seeded with form I/form II mixture</td>
<td>3</td>
<td>I</td>
<td>Dark red crystals</td>
</tr>
<tr>
<td>Methanol seeded with form I/form II mixture</td>
<td>3</td>
<td>I</td>
<td>Dark red crystals</td>
</tr>
<tr>
<td>Methanol:acetonitrile 1:1</td>
<td>1</td>
<td>I</td>
<td>Orange crystals</td>
</tr>
<tr>
<td>Ethanol 95%, 4-hydroxypyridine</td>
<td>1</td>
<td>No solid to characterize</td>
<td>Yellow solution</td>
</tr>
<tr>
<td>Ethanol 95%, 4,6-dihydroxy-5-nitopyrimidine</td>
<td>1</td>
<td>No solid to characterize</td>
<td>Yellow solution</td>
</tr>
</tbody>
</table>
**Table S8.** Experimental and CASTEP-computed $^{13}$C and $^1$H Solid-state NMR Chemical Shifts for Form II of Curcumin.\(^a\)

<table>
<thead>
<tr>
<th>$^{13}$C Assignment</th>
<th>Experimental $\delta_{\text{iso}}$/ppm</th>
<th>Computed, fgo$^b$ $\delta_{\text{iso}}$/ppm</th>
<th>Computed, hgo$^c$ $\delta_{\text{iso}}$/ppm</th>
<th>Computed, fgo-exp-acac$^d$ $\delta_{\text{iso}}$/ppm</th>
<th>Deviation Experimental - fgo-exp-acac$^d$ $\delta_{\text{iso}}$/ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule: A B</td>
<td>A B</td>
<td>A B</td>
<td>A B</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>127.2 129.4</td>
<td>127.8 130.5</td>
<td>127.1 129.8</td>
<td>127.8 130.5</td>
<td>−0.6 −1.1</td>
</tr>
<tr>
<td>C2</td>
<td>118.5 114.5</td>
<td>119.2 115.0</td>
<td>117.1 114.3</td>
<td>119.2 115.0</td>
<td>−0.7 −0.5</td>
</tr>
<tr>
<td>C3</td>
<td>147.4 146.8</td>
<td>151.3 149.9</td>
<td>149.7 149.0</td>
<td>151.4 149.8</td>
<td>−4.0 −3.0</td>
</tr>
<tr>
<td>C4</td>
<td>150.0 148.1</td>
<td>154.6 151.8</td>
<td>152.3 150.3</td>
<td>154.3 151.7</td>
<td>−4.3 −3.6</td>
</tr>
<tr>
<td>C5</td>
<td>115.6 114.5</td>
<td>117.6 115.6</td>
<td>116.1 114.2</td>
<td>117.5 115.6</td>
<td>−1.9 −1.1</td>
</tr>
<tr>
<td>C6</td>
<td>119.7 118.5</td>
<td>119.7 118.2</td>
<td>118.4 116.2</td>
<td>119.6 118.3</td>
<td>0.1 0.2</td>
</tr>
<tr>
<td>C7</td>
<td>141.2 141.2</td>
<td>143.8 143.7</td>
<td>141.5 143.6</td>
<td>143.4 143.7</td>
<td>−2.2 −2.5</td>
</tr>
<tr>
<td>C8</td>
<td>121.5 122.5</td>
<td>124.8 125.3</td>
<td>124.5 123.8</td>
<td>124.8 125.5</td>
<td>−3.3 −3.0</td>
</tr>
<tr>
<td>C9</td>
<td>186.0 189.5</td>
<td>185.6 188.8</td>
<td>185.0 189.4</td>
<td>182.7 188.1</td>
<td>3.3 1.4</td>
</tr>
<tr>
<td>C10</td>
<td>105.7 104.3</td>
<td>112.3 110.5</td>
<td>108.5 106.9</td>
<td>110.0 108.4</td>
<td>−4.3 −4.1</td>
</tr>
<tr>
<td>C11</td>
<td>179.6 178.1</td>
<td>178.6 177.3</td>
<td>176.5 175.5</td>
<td>176.2 175.7</td>
<td>3.4 2.4</td>
</tr>
<tr>
<td>C12</td>
<td>121.5 121.5</td>
<td>123.3 124.3</td>
<td>123.1 123.7</td>
<td>123.7 124.3</td>
<td>−2.2 −2.8</td>
</tr>
<tr>
<td>C13</td>
<td>138.5 138.5</td>
<td>142.0 139.8</td>
<td>140.1 138.8</td>
<td>141.7 140.0</td>
<td>−3.2 −1.5</td>
</tr>
<tr>
<td>C14</td>
<td>129.0 129.4</td>
<td>130.0 131.2</td>
<td>129.4 130.1</td>
<td>130.0 131.1</td>
<td>−1.0 −1.7</td>
</tr>
<tr>
<td>C15</td>
<td>117.0 115.6</td>
<td>117.8 116.6</td>
<td>115.4 116.2</td>
<td>117.6 116.6</td>
<td>−0.6 −1.0</td>
</tr>
<tr>
<td>C16</td>
<td>146.8 147.4</td>
<td>149.9 150.6</td>
<td>149.0 150.2</td>
<td>149.9 150.6</td>
<td>−3.1 −3.2</td>
</tr>
<tr>
<td>C17</td>
<td>148.1 147.4</td>
<td>152.5 150.5</td>
<td>150.6 148.2</td>
<td>152.2 150.6</td>
<td>−4.1 −3.2</td>
</tr>
<tr>
<td>C18</td>
<td>115.6 115.6</td>
<td>117.0 117.3</td>
<td>115.1 115.5</td>
<td>116.9 117.3</td>
<td>−1.3 −1.7</td>
</tr>
<tr>
<td>C19</td>
<td>119.7 115.6</td>
<td>120.1 117.6</td>
<td>118.5 116.0</td>
<td>120.0 117.6</td>
<td>−0.3 −2.0</td>
</tr>
<tr>
<td>C20</td>
<td>57.8 56.2</td>
<td>57.6 56.3</td>
<td>57.9 56.0</td>
<td>57.5 56.3</td>
<td>0.3 −0.1</td>
</tr>
<tr>
<td>C21</td>
<td>57.8 55.2</td>
<td>58.7 54.8</td>
<td>58.7 54.5</td>
<td>58.7 54.7</td>
<td>−0.9 0.5</td>
</tr>
<tr>
<td>H4</td>
<td>15.7 14.5</td>
<td>14.2 16.2</td>
<td>13.1 15.6</td>
<td>14.0 16.9</td>
<td>1.7 −2.4</td>
</tr>
</tbody>
</table>

\(a\). See Figure S2 for atom designation.

\(b\). fgo: fully geometry optimized from original X-ray structure

\(c\). hgo: only the H positions from the original structure optimized

\(d\). fgo-exp-acac: Initial structure from fgo structure apart from the keto-enol region which used the original X-ray structure; H position re-optimized
4.0 Additional Figures

Figure S4. Hydrogen bonding interactions in the carbonyl regions in molecules A and B of form II of curcumin. Note that significant intermolecular hydrogen bonding is only observed for molecule A. For molecule A, \( r(O3A,O4A) = 2.530 \, \text{Å} \) and \( r(O3A,O2A) = 2.633 \, \text{Å} \). For molecule B, \( r(O9B, O10B) = 2.501 \, \text{Å} \).
Figure S5. Complete $^{13}$C-$^1$H HETCOR spectrum for solid curcumin, form II, acquired at 21.1 T at a magic-angle spinning frequency of 18 kHz. For an expansion of the region within the dashed box, see Figure 3 of the manuscript. Note that the 1D spectra illustrated here were obtained in separate measurements.
Figure S6. Plots of experimental vs computed (CASTEP) $^{13}\text{C}$ NMR chemical shifts for molecules A and B of form II of curcumin.
5.0 References

1 Parimita, S. P.; Ramshankar, Y. V.; Suresh, S.; Row, T. N. G. Redetermination of curcumin: (1E,4Z,6E)-5-Hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one. Acta Crystallogr. 2007, E63, o860–o862.


