

*Supporting Information for*

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

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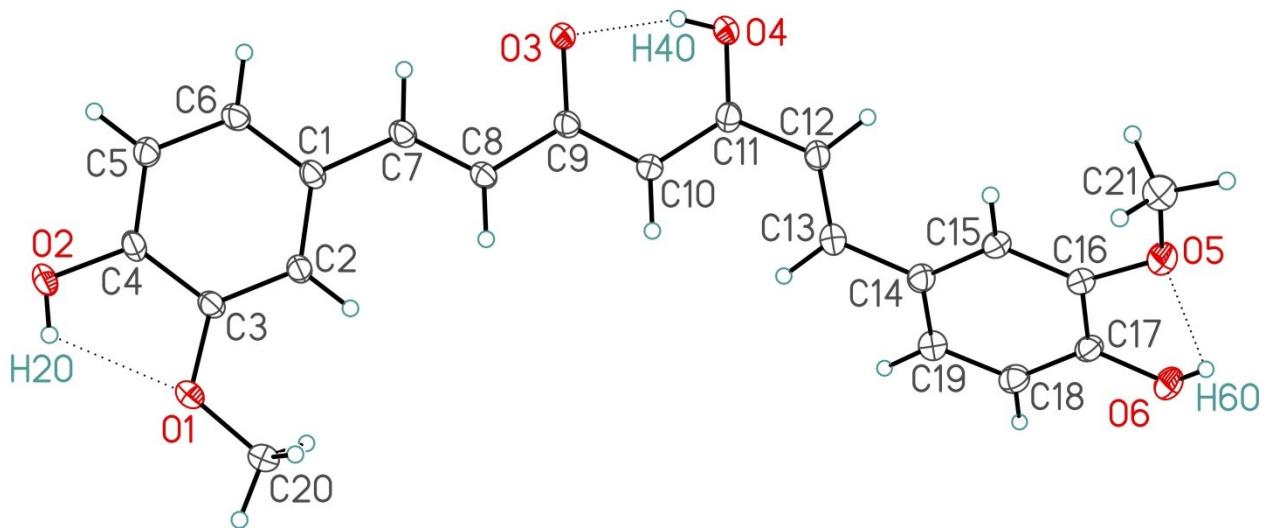
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## 1.0 Single-Crystal X-ray Diffraction

### 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.

Crystal Parameter	Form I	Form I reported by Parimita et al. <sup>1</sup>
Space group	<i>P</i> 2/ <i>n</i>	<i>P</i> 2/ <i>n</i>
System	monoclinic	monoclinic
<i>a</i> /Å	12.6264(2)	12.707(3)
<i>b</i> /Å	7.11013(16)	7.2186(14)
<i>c</i> /Å	19.9560(4)	19.880(4)
$\beta$	95.0882(7)	95.384(4)
<i>V</i> /Å <sup>3</sup>	1784.50(4)	1815.6(7)
<i>D</i> <sub>calcd</sub> /g·cm <sup>-3</sup>	1.371	1.384
<i>Z</i>	4	4
<i>T</i> /K	173	290
Goodness-of-fit	1.063	

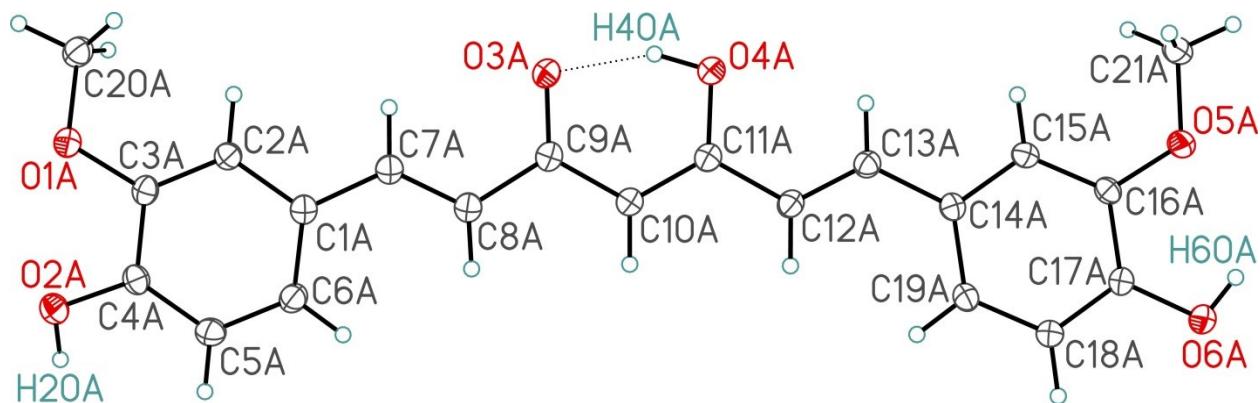
**Table S2.** Hydrogen-bond Interactions for Form I of Curcumin.

D–H···A	D–H/Å	H···A/Å	D···A/Å	$\angle$ D–H···A /deg
O2–H2O···O1	0.81(3)	2.20(3)	2.6736(17)	118(3)
O3–H3O···O4	0.77(3) <sup>a</sup>	1.74(3)	2.4558(16)	156(5)
O4–H4O···O3	0.77(3) <sup>a</sup>	1.74(3)	2.4558(15)	156(5)
O6–H6O···O3 <sup>b</sup>	0.76(3)	2.11(3)	2.807(2)	152(2)
O6–H6O···O5	0.76(3)	2.29(2)	2.700(2)	115(2)

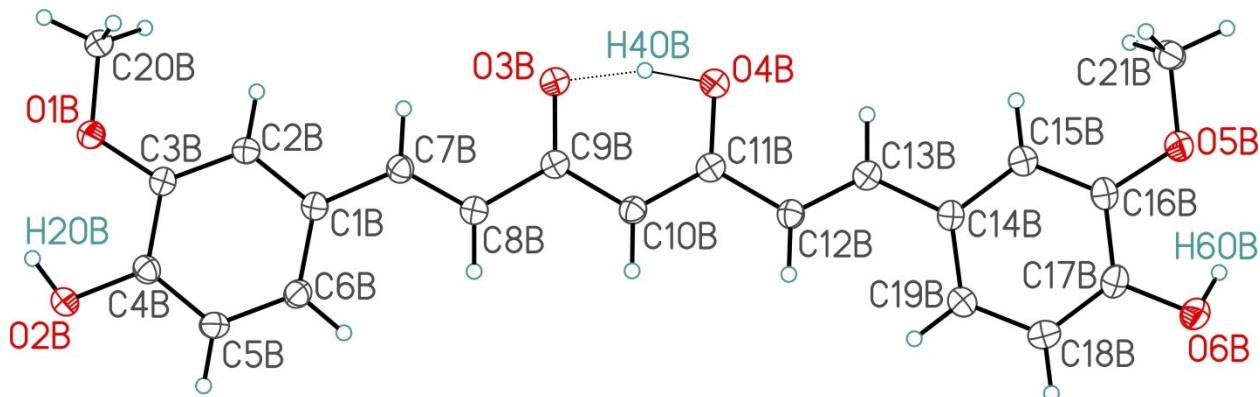
<sup>a</sup> The O3–H3O and O4–H4O distances were constrained to be equal (within 0.03 Å) during refinement.

<sup>b</sup> Intermolecular hydrogen bond at  $\frac{1}{2} + x, \bar{y}, -\frac{1}{2} + z$ .

## 1.2 Form II



Molecule A



Molecule B

**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.

Crystal Parameter	Form II	Form II reported by Sanphui et al. <sup>2,a</sup>
Space group	Pca2 <sub>1</sub>	Pca2 <sub>1</sub>
a/Å	35.4456 (5)	35.417 (3)
b/Å	7.84979 (10)	7.7792 (7)
c/Å	12.69296 (16)	12.6482 (11)
V/Å <sup>3</sup>	3531.70 (8)	3484.7 (5)
D <sub>calcd</sub> /g·cm <sup>-3</sup>	1.386	1.404
Z	8/2	8/2
T/K	173	100
Goodness-of-fit	1.061	1.083

a. Similar parameters were reported by Parameswari et al. in a later study.<sup>3</sup>

**Table S4.** Hydrogen-bond Interactions for Form II of Curcumin.

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

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

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

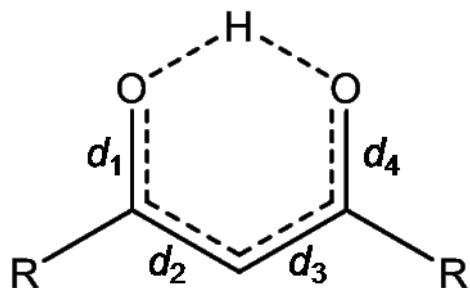
<sup>c</sup> Intermolecular hydrogen bond at  $\frac{1}{2} + x$ ,  $1 - y$ ,  $z$ .

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

<sup>e</sup>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).<sup>4</sup>



**Figure S3.** Resonance assisted hydrogen bonding structure for the keto-enol region of a  $\beta$ -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.

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

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.

$d_1$		$d_2$		$d_3$		$d_4$		$q_1$		$q_2$		O3-H/\text{\AA}		O4-H/\text{\AA}		O3-O4/\text{\AA}		Ref
A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	
1.335	1.323	1.375	1.378	1.420	1.420	1.277	1.276	-0.058	-0.047	-0.043	-0.042	0.921	1.014	1.687	1.527	2.536	2.497	3 <sup>a</sup>
1.312	1.329	1.372	1.374	1.415	1.413	1.273	1.273	-0.039	-0.056	-0.043	-0.039	0.94	0.95	1.58	1.64	2.528	2.498	2 <sup>a</sup>
1.331	1.311	1.378	1.388	1.417	1.414	1.269	1.289	-0.062	-0.022	-0.039	-0.026	0.911	1.110	1.682	1.421	2.530	2.501	this work <sup>b</sup>

a. Measured at 100 K.

b. Measured at 173 K.

### 3.0 Additional Tables

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

Solvent	Number of Crystallization Steps	Curcumin Polymorph Form	Color
Ethanol 95%	2	II	Dark orange crystals
Acetonitrile	1	I	Red crystals
Acetonitrile seeded with form I/form II mixture	3	I	Dark red crystals
Methanol seeded with form I/form II mixture	3	I	Dark red crystals
Methanol:acetonitrile 1:1	1	I	Orange crystals
Ethanol 95%, 4-hydroxypyridine	1	No solid to characterize	Yellow solution
Ethanol 95% 4,6-dihydroxy-5-nitropyrimidine	1	No solid to characterize	Yellow solution

**Table S8.** Experimental and CASTEP-computed  $^{13}\text{C}$  and  $^1\text{H}$  Solid-state NMR Chemical Shifts for Form II of Curcumin.<sup>a</sup>

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

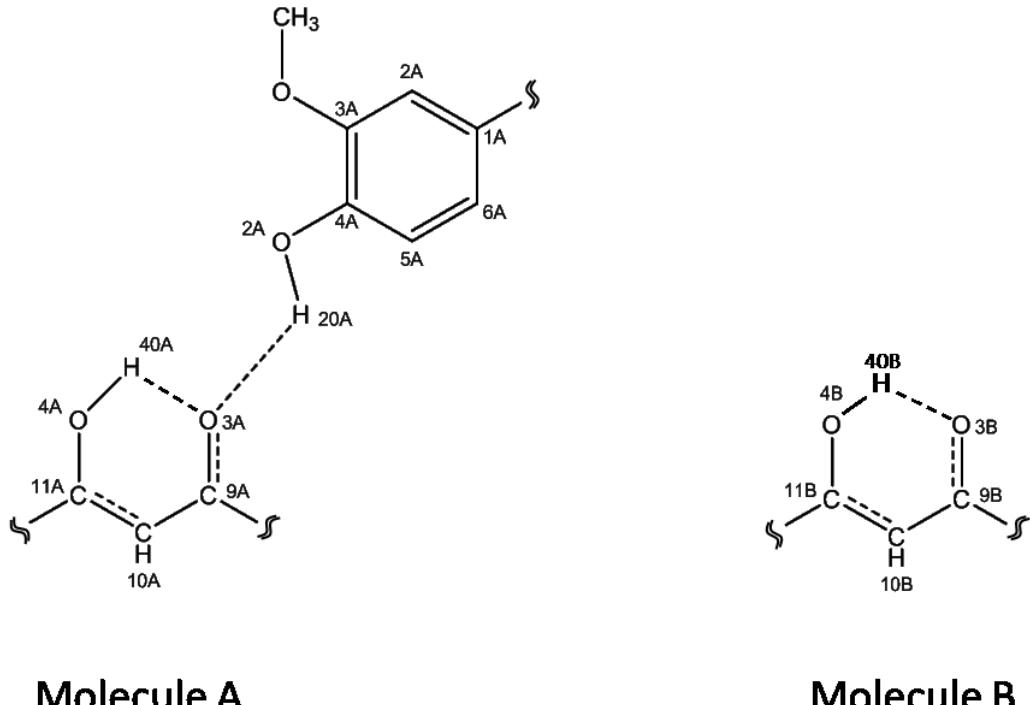
a. See Figure S2 for atom designation.

b. *fgo*: fully geometry optimized from original X-ray structure

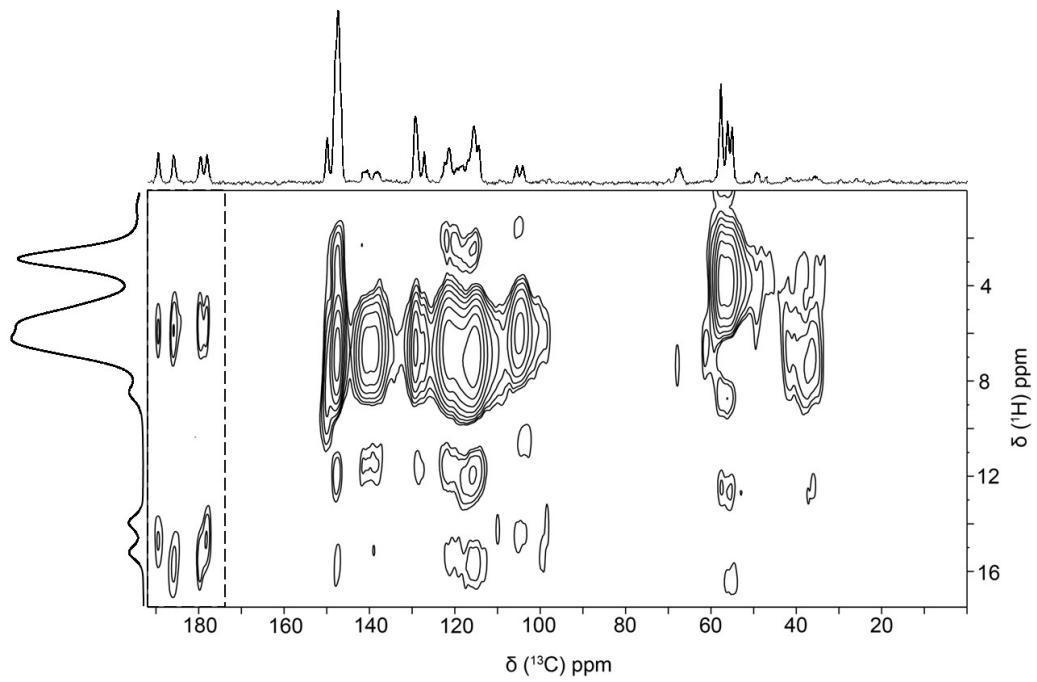
c. *hgo*: only the H positions from the original structure optimized

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

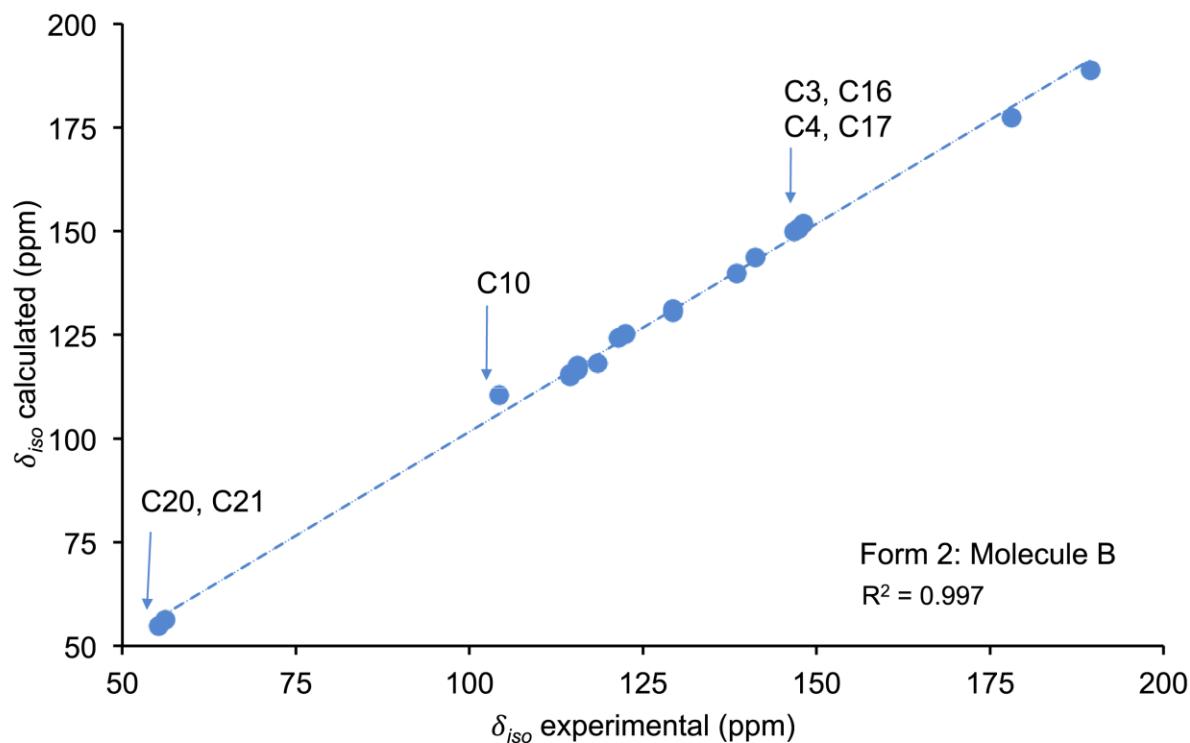
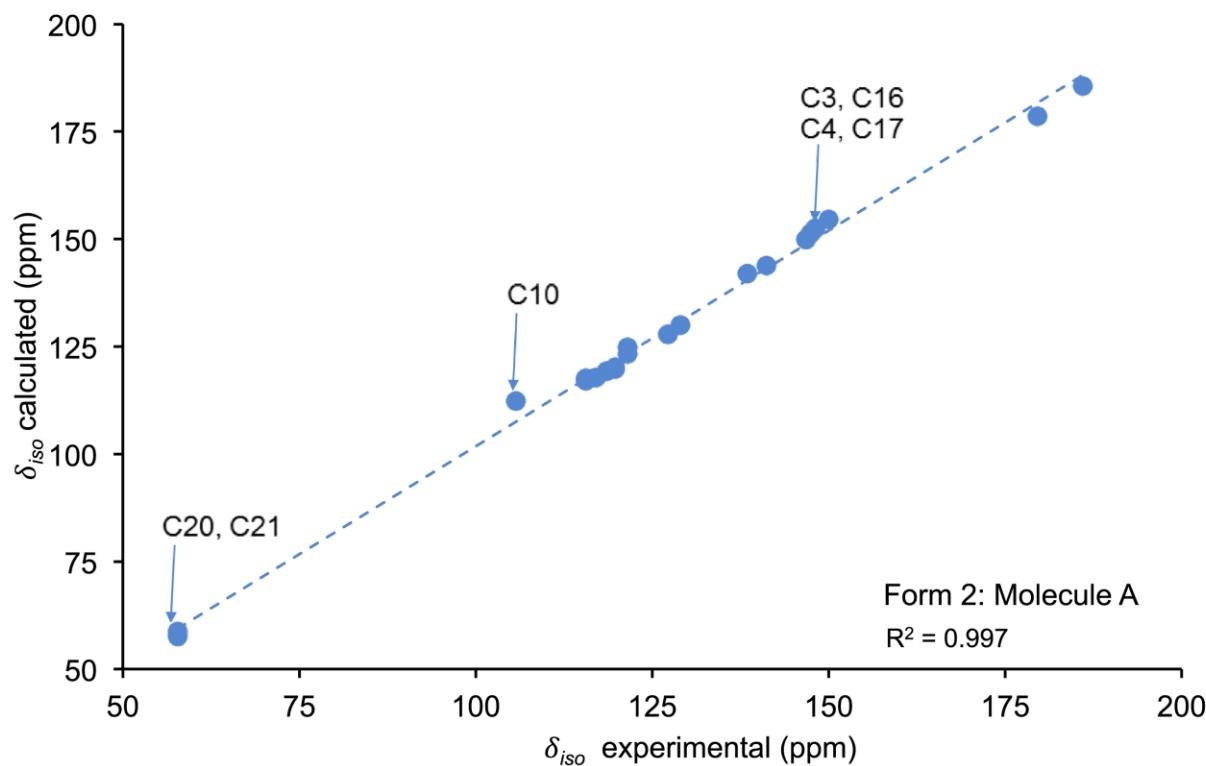
## 4.0 Additional Figures



**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,  $r(O3A, O4A) = 2.530 \text{ \AA}$  and  $r(O3A, O2A) = 2.633 \text{ \AA}$ . For molecule B,  $r(O9B, O10B) = 2.501 \text{ \AA}$ .



**Figure S5.** Complete  $^{13}\text{C}$ - $^1\text{H}$  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

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