Electronic Supplementary Information

Conformational preferences in a series of α-hydroxy ketone derivatives: Interplay of conformational energies and lattice cohesive energies

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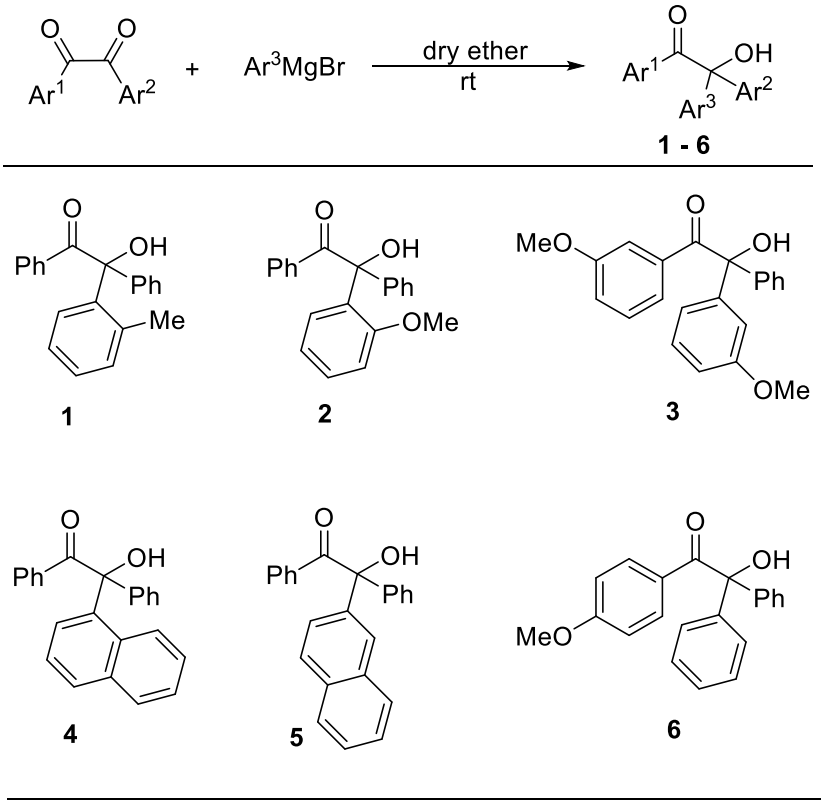
General experimental procedure for the preparation of α-hydroxy ketones (1 - 6)

A solution of 1,2-diaryl-1,2-diketone (2-5 mmol) in dry ether (50 mL) was placed in a round bottom flask (RBF). To this solution, freshly prepared arylmagnesium bromide (1.2 equiv.) was added dropwise through septum under N_2 atmosphere. The contents were stirred at room temperature, and progress of the reaction was monitored by TLC analysis. After stirring the contents for appropriate time period, reaction was quenched with saturated solution of NH_4Cl. The crude product was extracted with ethyl acetate, washed with 10% Na_2CO_3 and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate and hexane (1:9) as eluting solvents to obtain α-hydroxy ketones (**1-6**) as white solid.



Scheme S1. Synthesis of various α-hydroxy ketones (**1-6**).

Table S1. Crystallographic refinement details of the six compounds.

Identification code	**1**	**2**	**3**
Empirical formula	$C_{21}H_{18}O_2$	$C_{21}H_{18}O_3$	$C_{22}H_{20}O_4$
Formula weight	302.35	318.35	348.38
Temperature/K	293(1)	100(1)	298(1)
Crystal system	monoclinic	monoclinic	monoclinic
Space group	C2/c	$P2_1/c$	$P2_1/n$
a/Å	14.9249(6)	12.1162(6)	8.3589(3)
b/Å	11.7152(4)	8.6650(5)	10.1168(3)
c/Å	19.1338(7)	15.2466(8)	21.3108(7)
α/°	90	90	90
β/°	104.921(4)	94.663(4)	99.806(3)
γ/°	90	90	90
Volume/$Å^3$	3232.7(2)	1595.39(14)	1775.83(10)
Z	8	4	4
$\rho_{calc}g/cm^3$	1.242	1.325	1.303
μ/mm^{-1}	0.079	0.088	0.089
F(000)	1280.0	672.0	736.0
Crystal size/mm^3	0.22 × 0.15 × 0.11	0.24 × 0.16 × 0.11	0.26 × 0.17 × 0.15
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.776 to 49.988	6.262 to 49.994	6.378 to 49.99
Index ranges	$-17 \le h \le 16$, $-12 \le k \le 13$, $-22 \le l \le 22$	$-13 \le h \le 14$, $-10 \le k \le 10$, $-17 \le l \le 18$	$-9 \le h \le 9$, $-11 \le k \le 12$, $-25 \le l \le 21$
Reflections collected	10333	11859	19686
Independent reflections	2719 [R_{int} = 0.0694, R_{sigma} = 0.0481]	2778 [R_{int} = 0.0529, R_{sigma} = 0.0446]	3061 [R_{int} = 0.0680, R_{sigma} = 0.0387]
Data/restraints/parameters	2719/0/209	2778/0/217	3061/0/235
Goodness-of-fit on F^2	1.112	1.069	1.104
Final R indexes [I>=2σ (I)]	R_1 = 0.0547, wR_2 = 0.1856	R_1 = 0.0533, wR_2 = 0.1293	R_1 = 0.0464, wR_2 = 0.1218
Final R indexes [all data]	R_1 = 0.0745, wR_2 = 0.2481	R_1 = 0.0653, wR_2 = 0.1352	R_1 = 0.0657, wR_2 = 0.1318
Largest diff. peak/hole / e $Å^{-3}$	0.31/-0.32	0.28/-0.21	0.12/-0.19

Identification code	**4**	**5**	**6**
Empirical formula	$C_{24}H_{18}O_2$	$C_{24}H_{18}O_2$	$C_{21}H_{18}O_3$
Formula weight	338.38	338.38	318.35
Temperature/K	293	293	293
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1$
a/Å	8.6118(3)	9.0420(4)	6.0013(2)
b/Å	16.6368(8)	18.3274(5)	16.6234(6)
c/Å	12.4195(6)	11.5796(4)	8.3924(3)
α/°	90	90	90
β/°	100.260(4)	110.560(4)	91.974(3)
γ/°	90	90	90
Volume/$Å^3$	1750.92(14)	1796.70(12)	836.75(5)
Z	4	4	2
$\rho_{calc}g/cm^3$	1.284	1.251	1.264
μ/mm^{-1}	0.080	0.078	0.084
F(000)	712.0	712.0	336.0
Crystal size/mm^3	0.25 × 0.15 × 0.14	0.28 × 0.17 × 0.13	0.26 × 0.15 × 0.14
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.668 to 49.992	6.552 to 50	6.794 to 50
Index ranges	$-10 \le h \le 10$, $-19 \le k \le 19$, $-14 \le l \le 14$	$-10 \le h \le 10$, $-20 \le k \le 21$, $-13 \le l \le 13$	$-6 \le h \le 7$, $-19 \le k \le 18$, $-9 \le l \le 9$
Reflections collected	13125	20986	6217
Independent reflections	3057 [R_{int} = 0.1546, R_{sigma} = 0.0813]	3149 [R_{int} = 0.0664, R_{sigma} = 0.0414]	2625 [R_{int} = 0.0433, R_{sigma} = 0.0428]
Data/restraints/parameters	3057/0/235	3149/9/235	2625/1/217
Goodness-of-fit on F^2	1.081	1.126	0.989
Final R indexes [I>=2σ (I)]	R_1 = 0.0747, wR_2 = 0.2048	R_1 = 0.0589, wR_2 = 0.1585	R_1 = 0.0398, wR_2 = 0.0979
Final R indexes [all data]	R_1 = 0.0944, wR_2 = 0.2336	R_1 = 0.0906, wR_2 = 0.1759	R_1 = 0.0442, wR_2 = 0.1014
Largest diff. peak/hole / e $Å^{-3}$	0.23/-0.28	0.38/-0.25	0.12/-0.14
Flack parameter			**-0.3(10) ***

* Since structure 6 exhibited a high value of uncertainty in the Flack parameter, a twin refinement was performed considering the possibility of racemic twinning, with a twin law [-1 0 0 0 -1 0 0 0-1]. The refinement resulted in a small BASF value of 0.1 (15). However, the high standard uncertainty associated with the value makes it difficult to conclude on the

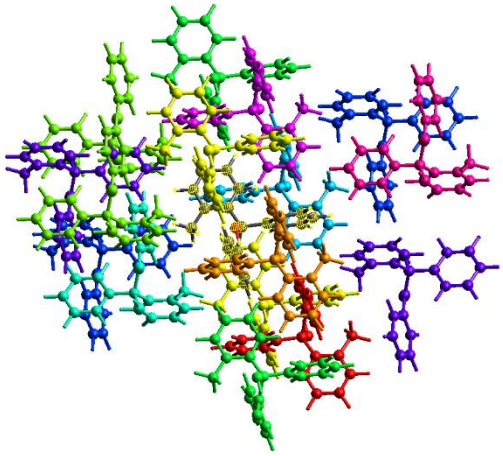
exact percentage of the twin domain. Importantly, the refinement R factors or residual peaks do not improve with the twin refinement.

Table S2. The pairwise intermolecular interaction energies are given along with the estimate of the lattice cohesive energies

Structure 1:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x+1/2, -y+1/2, -z	7.46	B3LYP/6-31G(d,p)	-9.2	-1.7	-42.4	21.8	-34.3
	1	-x, -y, -z	7.35	B3LYP/6-31G(d,p)	-9.1	-2.3	-31.7	26.7	-22.4
	2	x+1/2, y+1/2, z	9.49	B3LYP/6-31G(d,p)	-5.6	-1.9	-14.9	7.1	-15.9
	2	-x+1/2, y+1/2, -z+1/2	10.67	B3LYP/6-31G(d,p)	-0.5	-0.1	-5.1	1.2	-4.3
	2	x+1/2, y+1/2, z	9.49	B3LYP/6-31G(d,p)	-2.9	-1.2	-8.7	3.7	-9.3
	1	-x, y, -z+1/2	7.39	B3LYP/6-31G(d,p)	-3.2	-0.8	-39.0	23.0	-23.7
	1	-x, -y, -z	5.18	B3LYP/6-31G(d,p)	-23.4	-2.2	-82.7	64.6	-58.5
	2	x, -y, z+1/2	10.66	B3LYP/6-31G(d,p)	0.2	-0.1	-4.3	0.6	-3.2
	2	x+1/2, -y+1/2, z+1/2	10.57	B3LYP/6-31G(d,p)	-3.0	-0.3	-10.4	6.2	-8.7
	1	-x+1/2, -y+1/2, -z	8.24	B3LYP/6-31G(d,p)	0.1	-1.0	-22.9	9.3	-14.9
	1	-x, y, -z+1/2	11.75	B3LYP/6-31G(d,p)	-1.3	-0.2	-9.4	4.6	-6.9



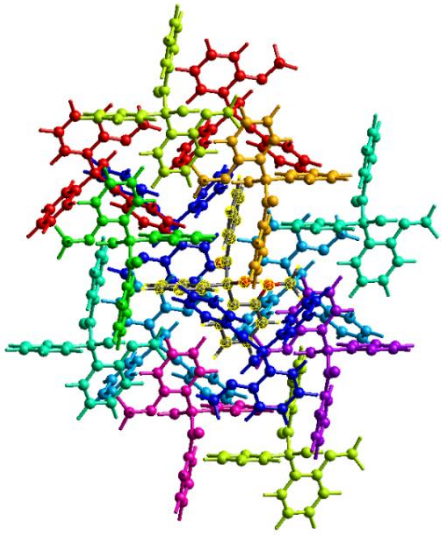
Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Structure 2:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

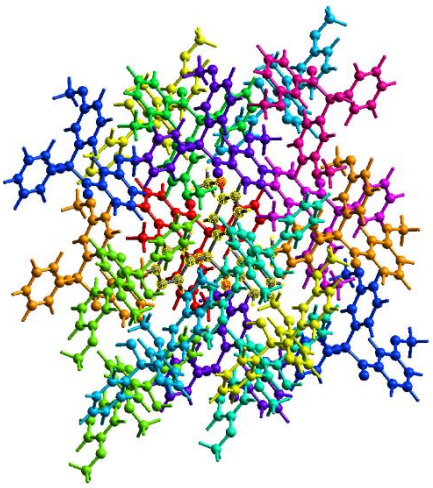
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	-x, y+1/2, -z+1/2	9.13	B3LYP/6-31G(d,p)	-5.5	-1.1	-27.6	18.4	-19.3
	1	-x, -y, -z	8.17	B3LYP/6-31G(d,p)	-9.7	-1.5	-32.6	25.9	-23.7
	2	x, y, z	12.12	B3LYP/6-31G(d,p)	3.2	-0.2	-7.2	0.0	-3.1
	1	-x, -y, -z	9.12	B3LYP/6-31G(d,p)	-3.7	-0.7	-30.5	17.0	-20.5
	2	x, y, z	8.67	B3LYP/6-31G(d,p)	-8.5	-2.0	-31.3	23.7	-23.2
	2	-x, y+1/2, -z+1/2	7.70	B3LYP/6-31G(d,p)	-12.6	-4.1	-33.4	18.3	-34.2
	2	x, -y+1/2, z+1/2	7.68	B3LYP/6-31G(d,p)	1.1	-0.9	-14.0	7.9	-6.8
	1	-x, -y, -z	7.60	B3LYP/6-31G(d,p)	-15.9	-3.3	-41.9	19.9	-43.5
	1	-x, -y, -z	8.61	B3LYP/6-31G(d,p)	-2.9	-0.8	-29.2	14.9	-19.9



Structure 3:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

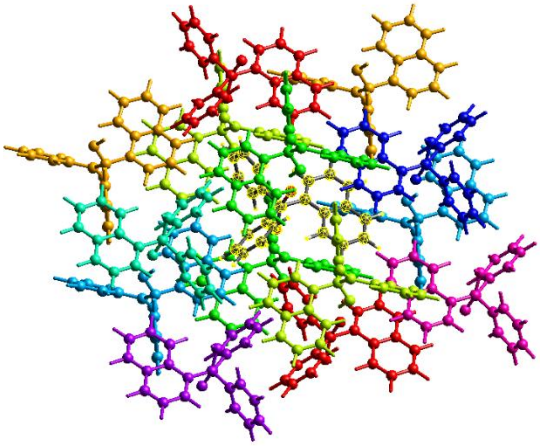
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, -z	5.02	B3LYP/6-31G(d,p)	-93.5	-19.7	-99.2	129.8	-119.6
	2	x, y, z	8.36	B3LYP/6-31G(d,p)	-2.1	-0.8	-25.6	10.8	-18.5
	2	x+1/2, -y+1/2, z+1/2	10.99	B3LYP/6-31G(d,p)	-2.5	-0.4	-2.8	0.1	-5.3
	2	-x+1/2, y+1/2, -z+1/2	10.89	B3LYP/6-31G(d,p)	-4.0	-0.8	-14.1	6.0	-13.4
	1	-x, -y, -z	8.40	B3LYP/6-31G(d,p)	-10.0	-2.7	-46.2	30.0	-34.3
	2	-x+1/2, y+1/2, -z+1/2	8.33	B3LYP/6-31G(d,p)	-4.6	-2.8	-24.6	13.5	-20.0
	2	x+1/2, -y+1/2, z+1/2	12.30	B3LYP/6-31G(d,p)	-0.5	-0.3	-5.8	0.0	-5.9
	2	x, y, z	13.12	B3LYP/6-31G(d,p)	0.6	-0.1	-3.4	0.0	-2.4
	2	x, y, z	10.12	B3LYP/6-31G(d,p)	-0.4	-0.4	-10.6	4.4	-7.2
	1	-x, -y, -z	8.73	B3LYP/6-31G(d,p)	-17.1	-3.2	-59.0	37.8	-48.5
	1	-x, -y, -z	11.02	B3LYP/6-31G(d,p)	-0.5	-0.1	-3.1	0.1	-3.2



Structure 4:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	8.61	B3LYP/6-31G(d,p)	-7.0	-1.1	-34.5	20.1	-25.8
	2	-x, y+1/2, -z+1/2	11.60	B3LYP/6-31G(d,p)	-1.6	-0.2	-10.1	6.7	-6.5
	2	x, -y+1/2, z+1/2	9.70	B3LYP/6-31G(d,p)	-2.4	-0.5	-17.1	6.2	-13.9
	2	x, -y+1/2, z+1/2	6.24	B3LYP/6-31G(d,p)	-27.2	-7.1	-37.3	37.4	-43.4
	1	-x, -y, -z	9.21	B3LYP/6-31G(d,p)	-7.4	-1.2	-38.5	24.0	-27.4
	2	-x, y+1/2, -z+1/2	9.24	B3LYP/6-31G(d,p)	-3.9	-0.7	-28.0	17.2	-18.5
	1	-x, -y, -z	8.10	B3LYP/6-31G(d,p)	-7.7	-4.6	-45.3	21.7	-37.5
	1	-x, -y, -z	12.84	B3LYP/6-31G(d,p)	-1.7	-0.1	-4.4	0.0	-5.7
	1	-x, -y, -z	12.07	B3LYP/6-31G(d,p)	-1.6	-0.3	-10.9	0.0	-11.4

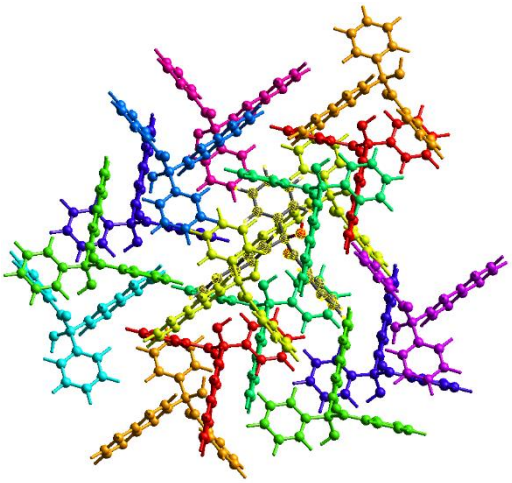


Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Structure 5:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

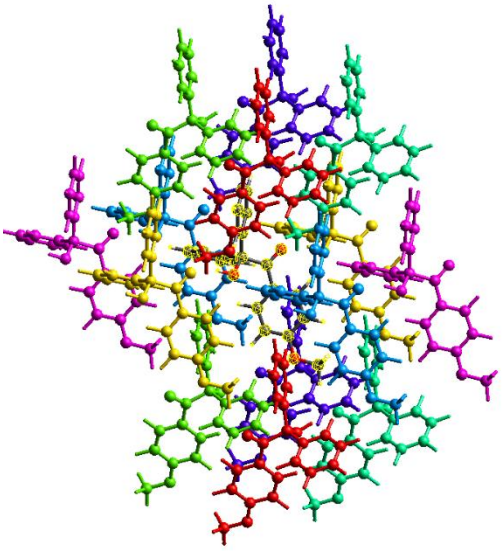
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, -y+1/2, z+1/2	8.92	B3LYP/6-31G(d,p)	-7.7	-1.6	-40.7	24.2	-29.7
	2	x, y, z	11.93	B3LYP/6-31G(d,p)	-0.5	-0.1	-3.6	0.2	-3.6
	2	x, y, z	9.04	B3LYP/6-31G(d,p)	-3.9	-2.1	-17.9	10.0	-15.0
	2	-x, y+1/2, -z+1/2	12.07	B3LYP/6-31G(d,p)	-2.4	-0.2	-9.3	0.0	-10.9
	2	x, -y+1/2, z+1/2	5.88	B3LYP/6-31G(d,p)	-32.1	-6.5	-49.8	48.0	-52.5
	1	-x, -y, -z	12.72	B3LYP/6-31G(d,p)	-3.3	-0.1	-5.9	0.0	-8.7
	1	-x, -y, -z	8.52	B3LYP/6-31G(d,p)	-4.9	-0.7	-30.9	15.7	-22.9
	2	-x, y+1/2, -z+1/2	9.74	B3LYP/6-31G(d,p)	-3.8	-0.5	-21.1	9.7	-16.7
	1	-x, -y, -z	10.55	B3LYP/6-31G(d,p)	-0.9	-0.6	-12.0	2.3	-10.3
	1	-x, -y, -z	12.19	B3LYP/6-31G(d,p)	-0.3	-0.3	-6.1	0.0	-5.9



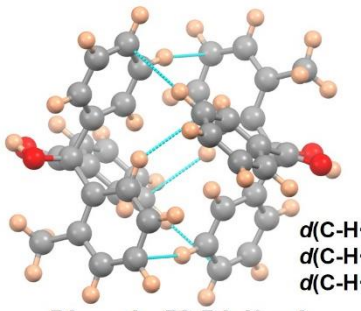
Structure 6:

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

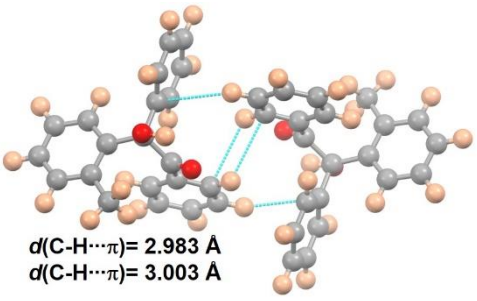
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	-x, y+1/2, -z	10.83	B3LYP/6-31G(d,p)	0.4	-0.4	-10.7	2.5	-7.6
	2	x, y, z	6.00	B3LYP/6-31G(d,p)	-44.9	-10.9	-36.5	57.9	-51.6
	2	-x, y+1/2, -z	9.02	B3LYP/6-31G(d,p)	-6.8	-1.4	-35.1	20.6	-26.0
	2	-x, y+1/2, -z	11.04	B3LYP/6-31G(d,p)	-7.7	-2.2	-20.8	11.5	-20.7
	2	x, y, z	8.39	B3LYP/6-31G(d,p)	-6.8	-1.4	-23.6	18.2	-17.6
	2	-x, y+1/2, -z	9.08	B3LYP/6-31G(d,p)	-4.6	-0.9	-29.3	13.4	-22.8
	2	x, y, z	10.48	B3LYP/6-31G(d,p)	-1.1	-0.4	-6.2	1.2	-6.1



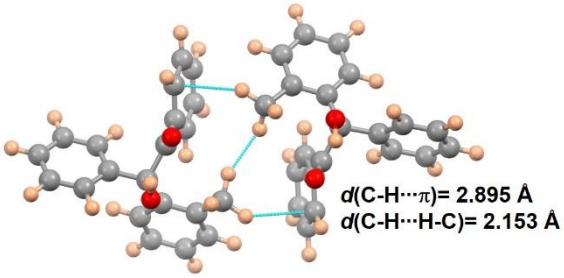
Dominant molecular pairs in structure 1:



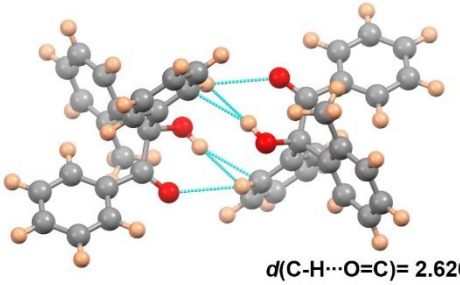
Dimer I: -58.5 kJ/mol



Dimer II: -34.3 kJ/mol

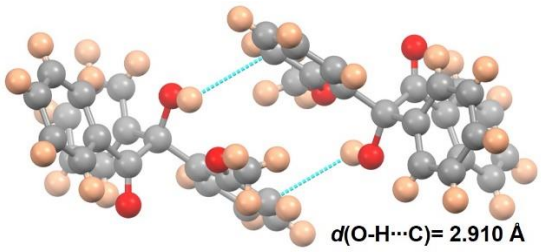


Dimer III: -23.7 kJ/mol

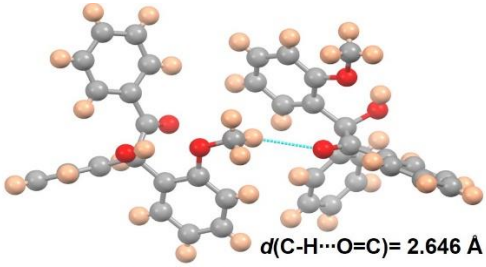


Dimer IV: -22.4 kJ/mol

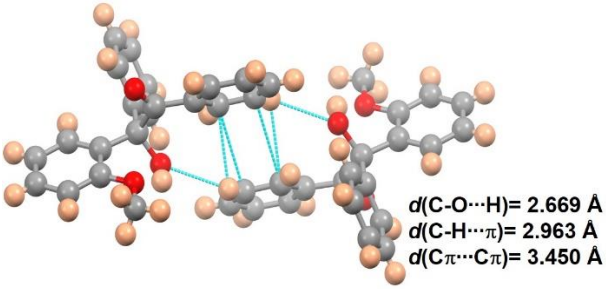
Dominant molecular pairs in structure 2:



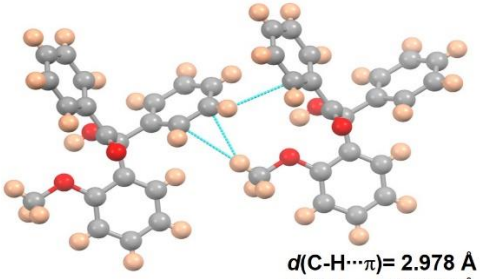
Dimer I: -43.5 kJ/mol



Dimer II: -34.2 kJ/mol

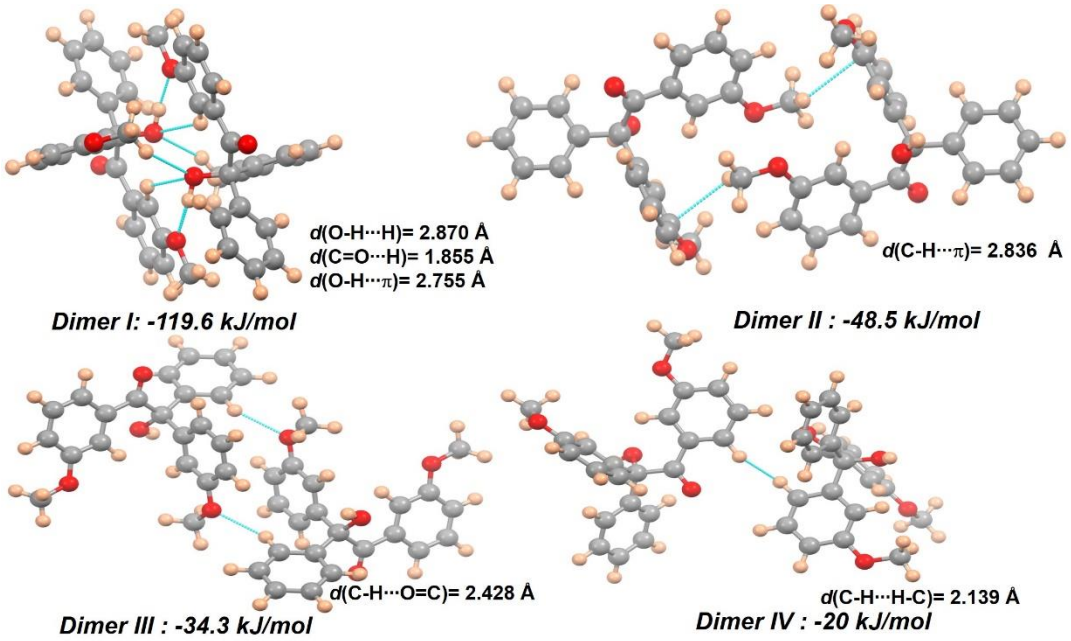


Dimer III: -23.7 kJ/mol

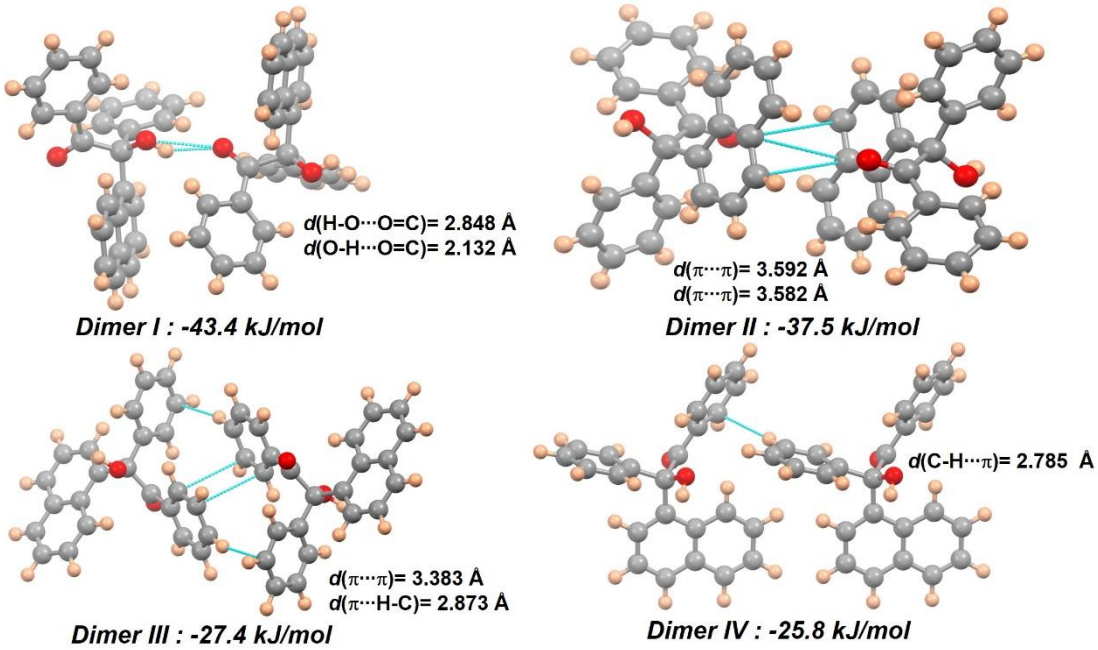


Dimer IV : -23.2 kJ/mol

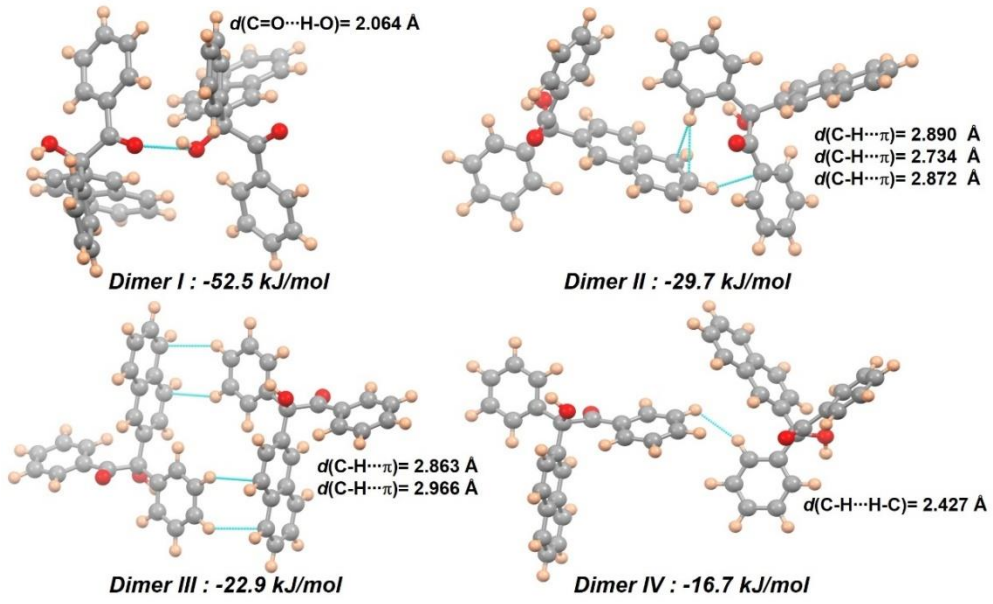
Dominant molecular pairs in structure 3



Dominant molecular pairs in structure 4:



Dominant molecular pairs in structure 5:



Dominant molecular pairs in structure 6:

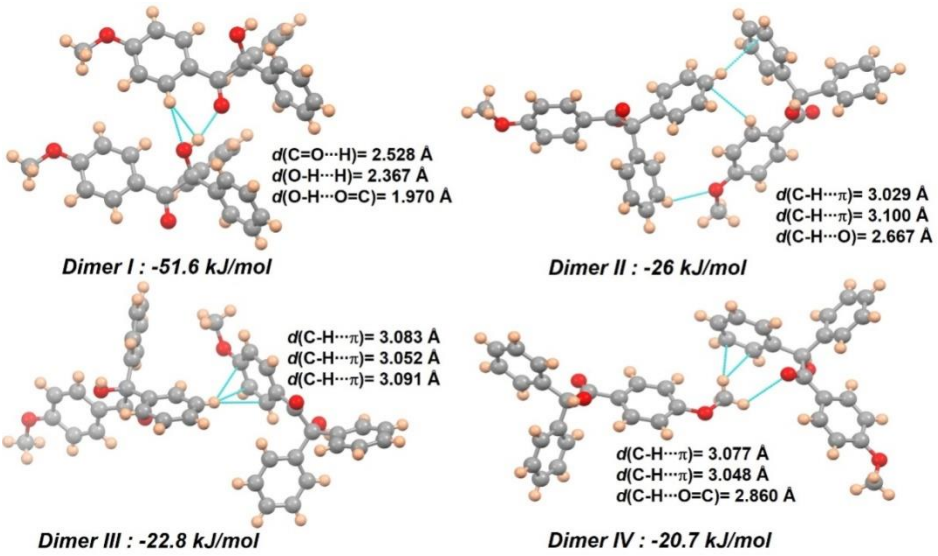
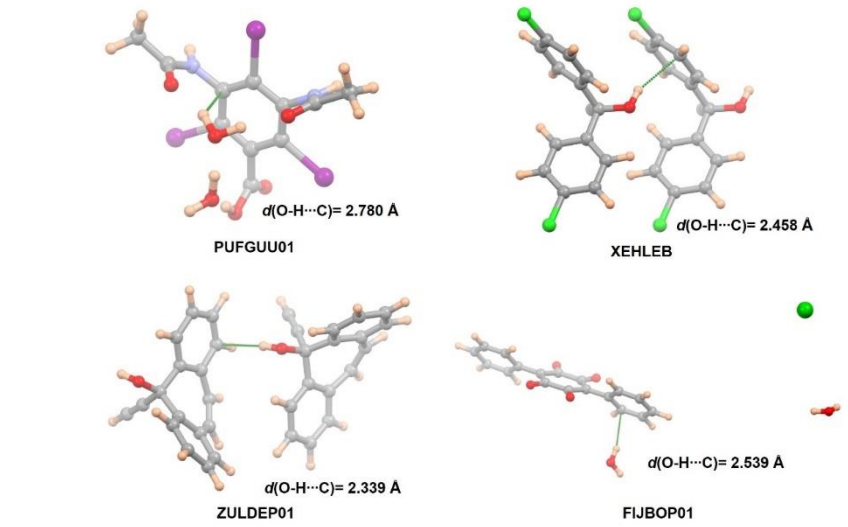


Figure S1. Intermolecular interactions and the corresponding interaction energies of molecular pairs in the six crystal structures

Cambridge Structure Database (CSD) analysis

Table S3. A survey of the O-H··· π interaction distances in the CSD for crystal structures refined using neutron diffraction data (Some examples are shown in the figure below).

CSD refcode	d(O–H···π) (Å)
FIJBOP01	2.539
IVUZUW02	2.551
PUFGUU01	2.642
REBYEE02	2.698
SAFJEO11	2.391
XEHLEB	2.458
ZULDEP01	2.679



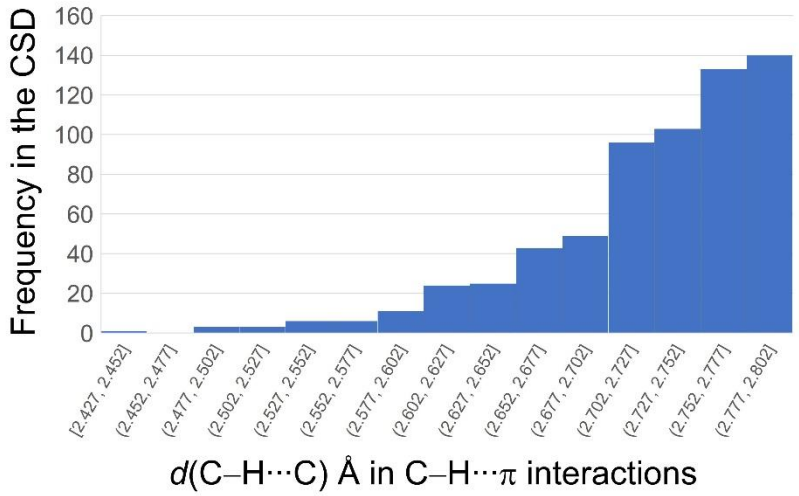


Figure S2. Distribution of the C-H··· π interaction distances in the CSD for crystal structures refined using neutron diffraction data.

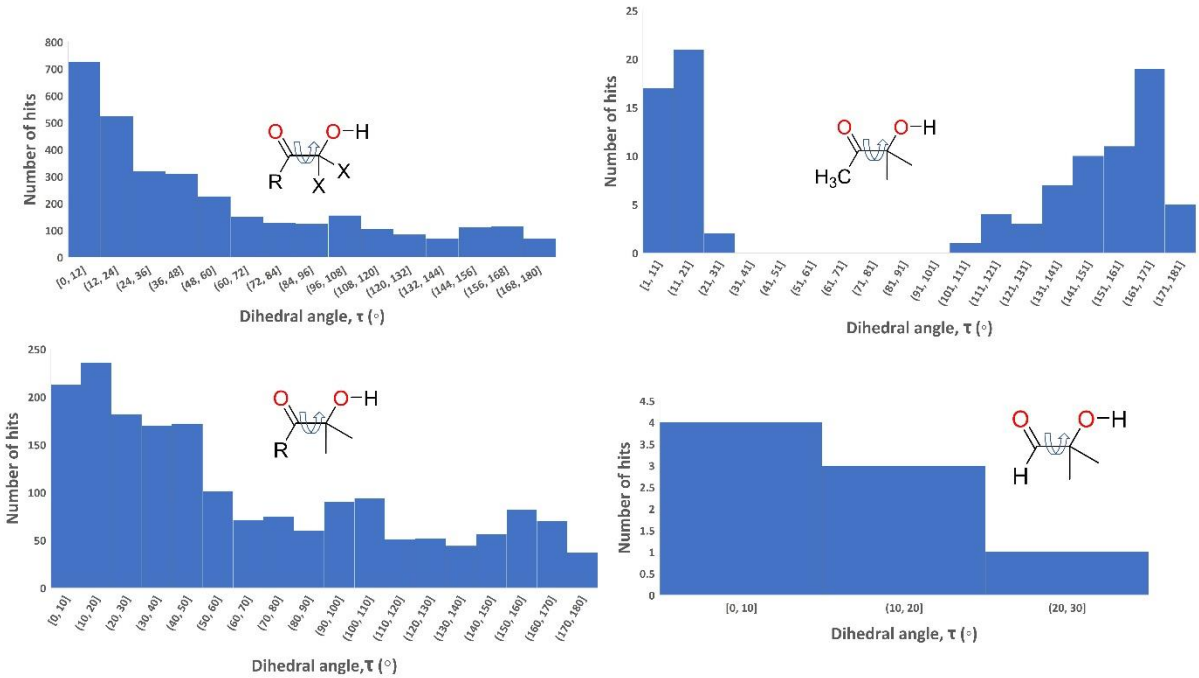


Figure S3: Torsional search in the CSD with the substructure chemical diagram and histogram showing the distribution of torsional angle.

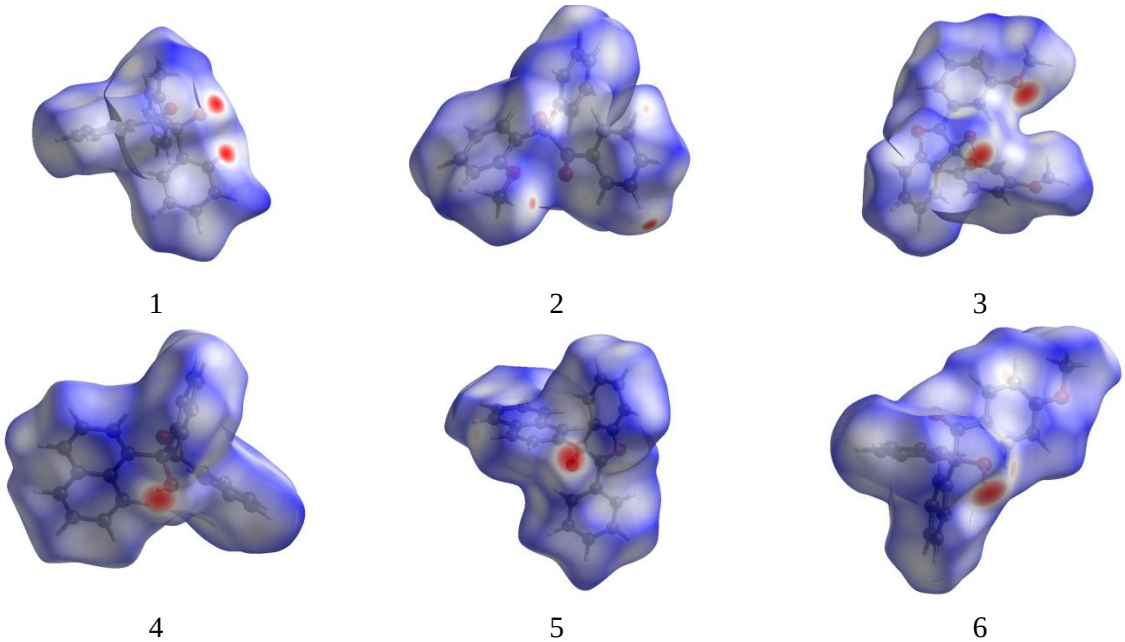
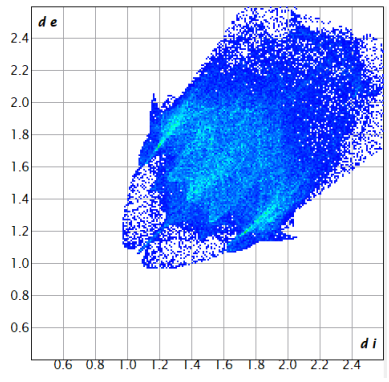
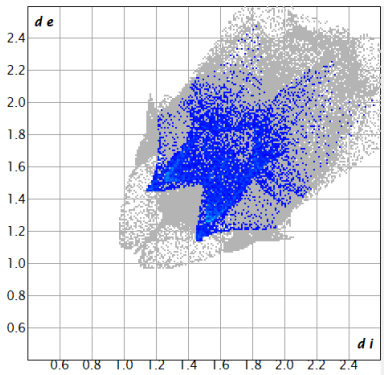


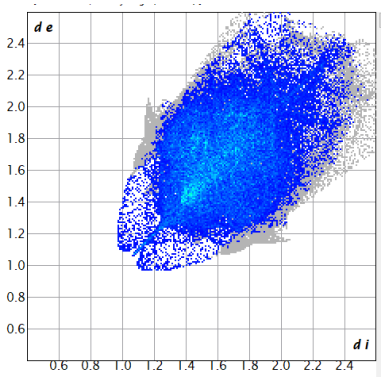
Figure S4. Hirshfeld surfaces of structures 1-6 , with dnorm mapped on the surfaces.



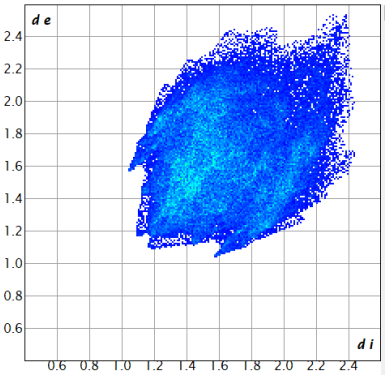
1



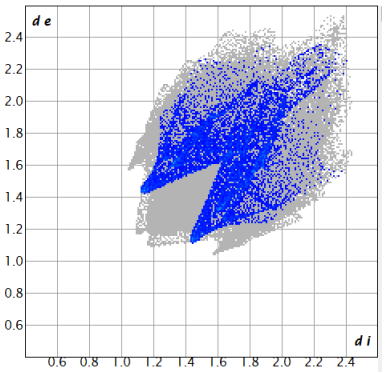
H···O contact=10.3%



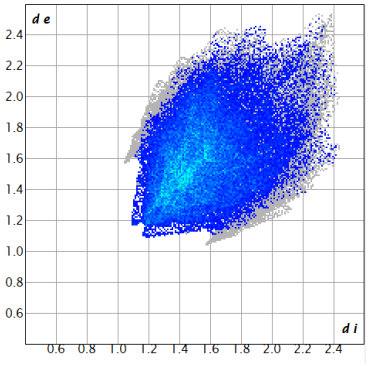
H···H contact=59.9%



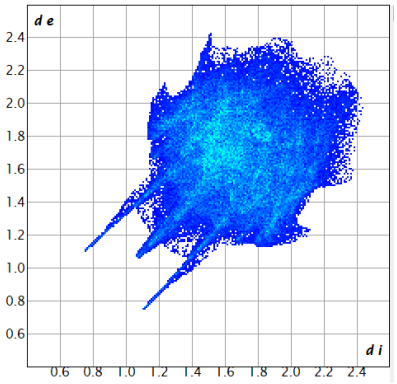
2



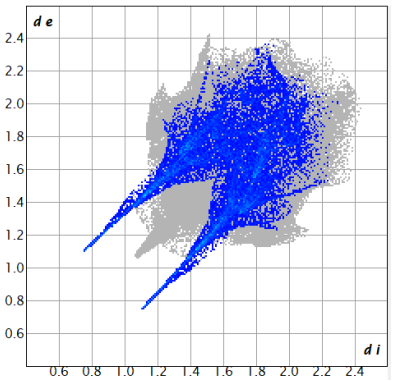
H···O contact=10.8%



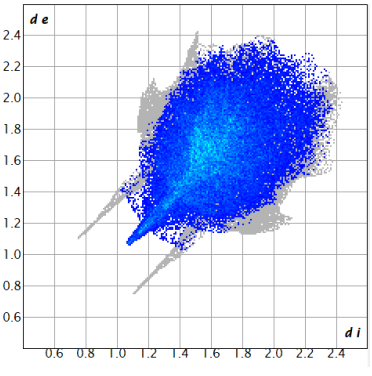
H···H contact=56.1%



3



H···O contact=18.9%



H···H contact=51.5%

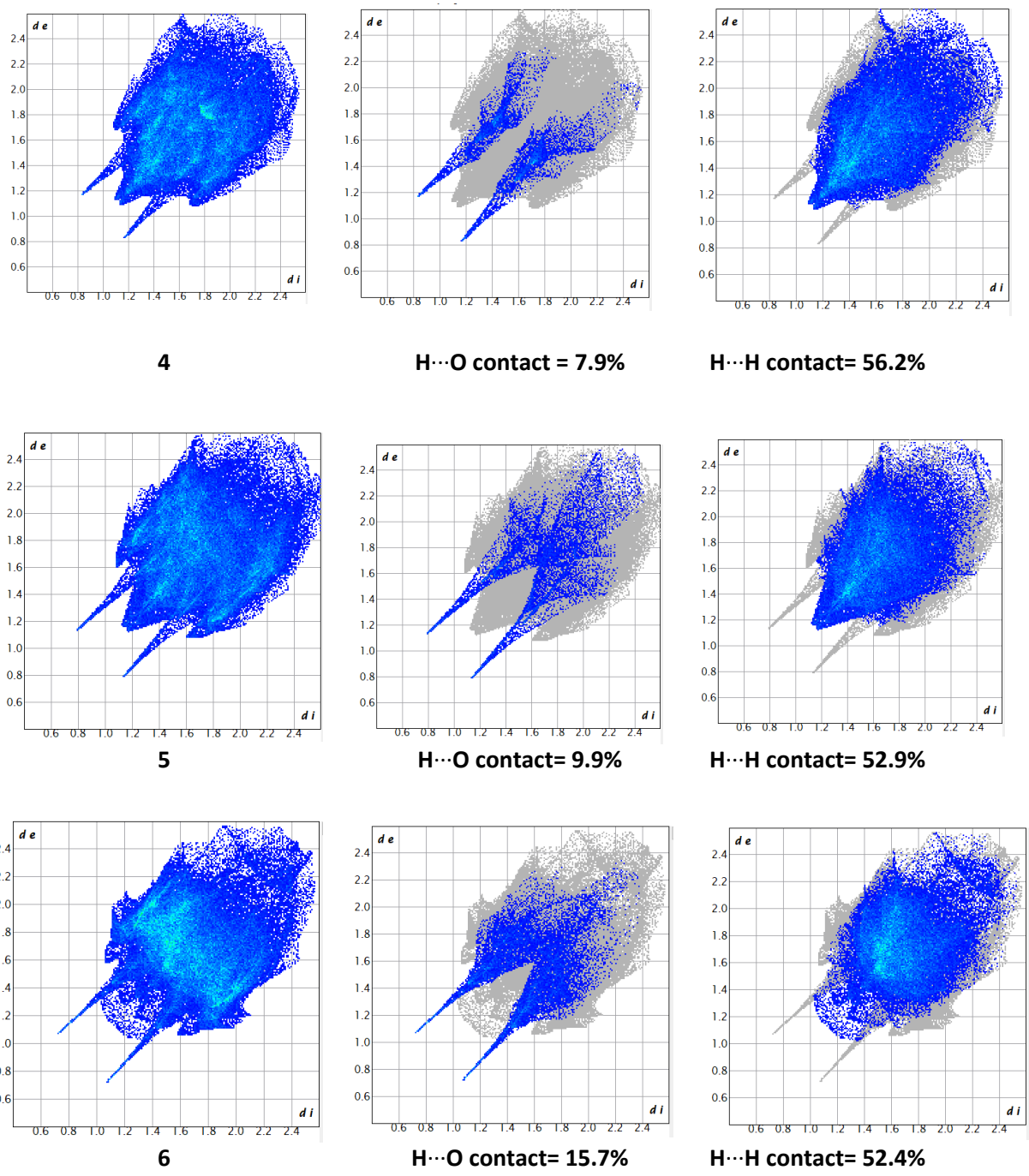


Figure S5. Finger print plots for different atom···atom contacts in the crystal structures.

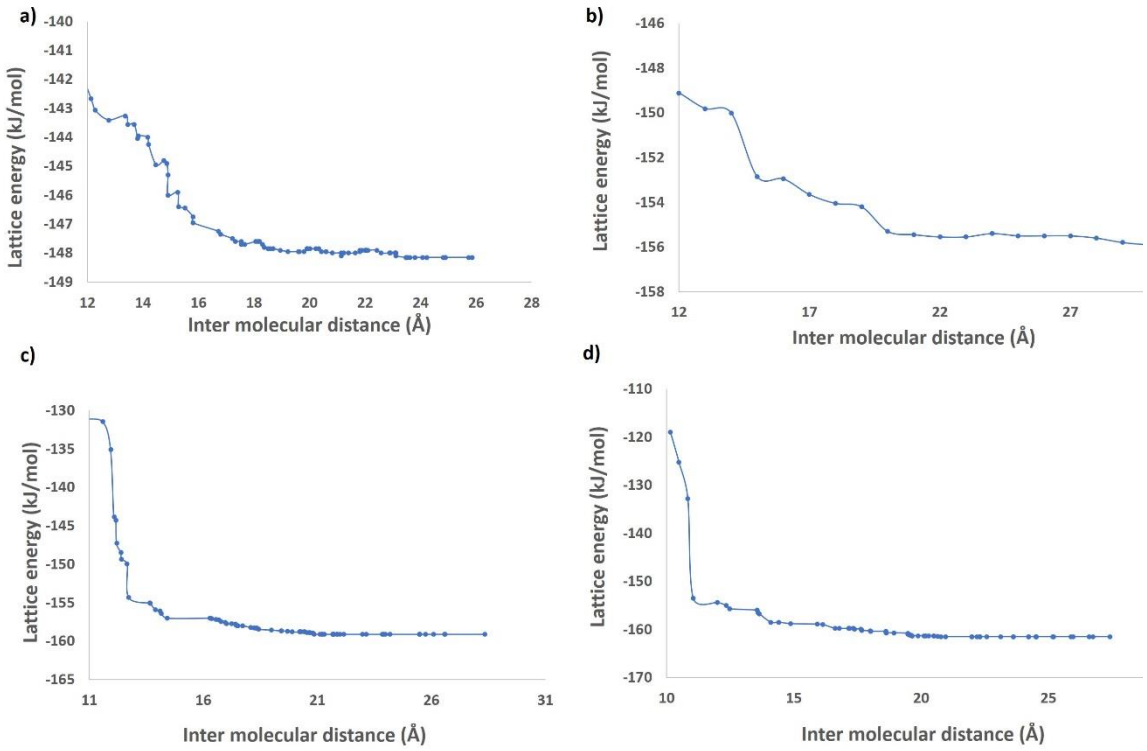


Figure S6. (a-d) The convergence of the pairwise interaction energy (I.E.) sum values at sufficientlylarge distances for the crystal structures of 2, 4, 5 and 6 (similar plots for 1 and 3 have been given in the main manuscript).

Conformational analysis of compounds 2-6.

Molecular conformational analysis was carried out by using Gaussian09 program at B3LYP/6-311G(d,p) level for structures 3-6. Molecular conformations were scanned for the torsional angle range of 360° rotations around the C–C bond across the hydroxy and carbonyl groups at the interval of 10° . The lowest energy value was set to the reference value of 0 and all other energy points were plotted with reference to this. For the structure 2, calculation convergence could not be achieved at B3LYP/6-311G(d,p) level. Hence, the conformational analysis was performed using the semi-empirical method PM6 for 2.

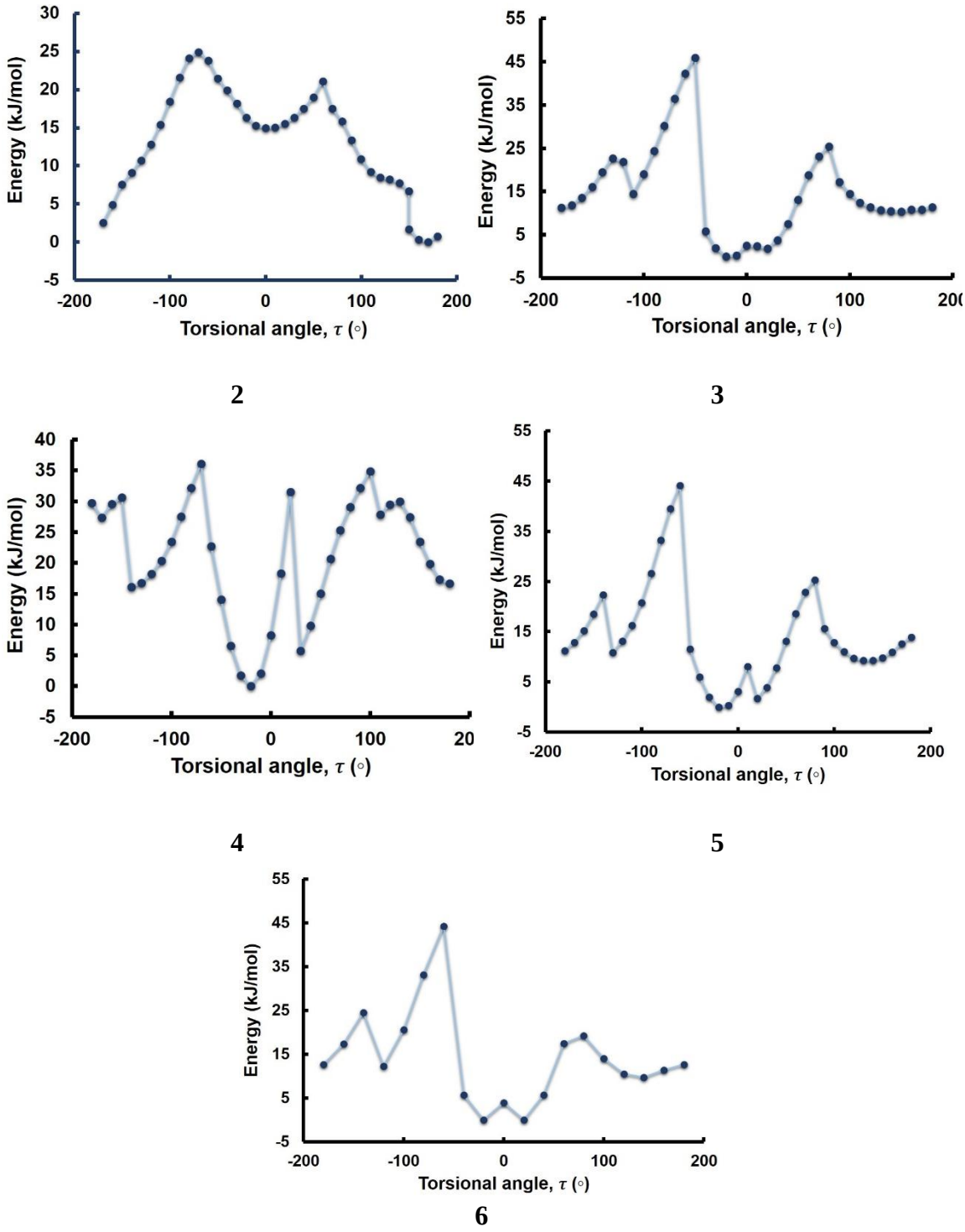


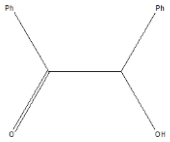
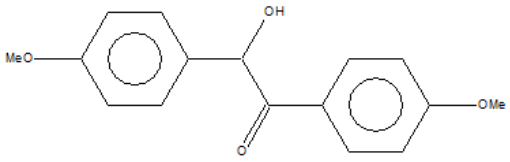
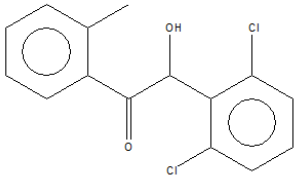
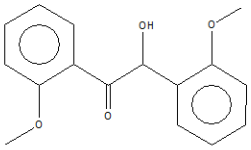
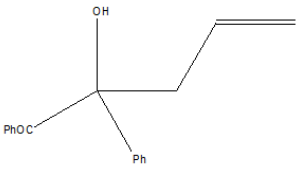
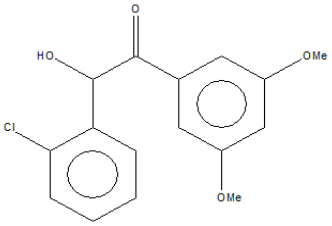
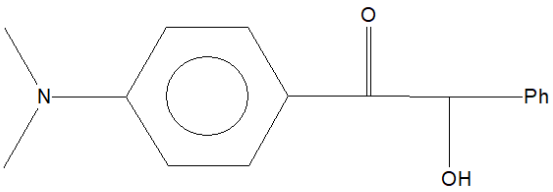
Figure S7. Torsional scan of energy for compounds **2-6.**

Table S4. Lattice energy estimation of a series of α-hydroxy ketones from the CSD (chemical diagrams are given below in Figure S8)

Crystal structure	Electrostatic	Dispersion	Repulsion	NNSE (kJ/mol)	Lattice energy (kJ/mol)	ΔE
BZOINN	-77.3	-112.6	62.8	-126.8	-142.0	-15.2
DAHSUA	-62.4	-135.7	58.7	-139.6	-150.0	-10.4
DEVRAX	-39.7	-113.2	46.6	-106.3	-113.5	-7.2
DMXBZO	-63.5	-122.3	48.6	-137.2	-141.7	-4.5
FUHZEQ	-55.7	-124.5	68.0	-112.3	-120.0	-7.7
KUTLUJ	-86.7	-154.2	86.3	-154.5	-161.5	-7
CUJTAC	-85.5	-141.7	72.8	-154.5	-174.1	-19.6
LOFLIB	-53.7	-163.8	68.8	-148.6	-159.9	-11.3
SIWDIL01	-83.2	-156.2	75.4	-163.9	-163.2	0.7

Table S5. Molecular conformations of a series of α-hydroxy ketones from the CSD and the conformational energy difference with the optimized geometry.

Crystal structure	Torsional angle (Crystal)	Optimized geometry (°)	Δτ (°)	ΔE_τ(kJ/mol)
BZOINN	25.96	14.04	11.92	-22.7
DAHSUA	15.06	15.56	-0.49	-0.03
DEVRAX	1.37	5.54	-4.17	-0.2
DMXBZO	4.07	2.18	1.88	-30.4
FUHZEQ	-136.49	-145.04	8.55	-0.4
KUTLUJ	20.42	13.65	6.77	-0.5
CUJTAC	28.38	14.64	13.73	-26.15
LOFLIB	140.55	149.86	-9.32	-0.44
SIWDIL01	10.80	11.49	-0.69	-0.31

CSD Code	Molecular Structure
BZOINN	
DAHSUA	
DEVRAX	
DMXBZO	
FUHZEQ	
KUTLUJ	
CUJTAC	

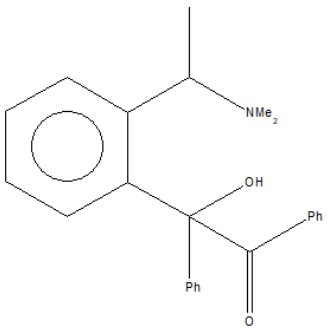
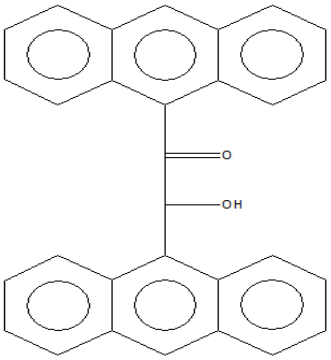
LOFLIB	
SIWDIL01	

Figure S8. Chemical diagrams of the compounds analyzed from the CSD, along with their CSD refcodes.