Electronic Supporting Information for:

Crystal Photodimerization Reactions of Spatially Engineered Isocoumarin Assemblies

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Supporting Information

S1. Experimental Details

General Considerations. All chemicals and solvents were purchased from the Aldrich Chemical Co. or Acros Chemicals and used as received without further purification unless stated otherwise. ^{1}H NMR and ^{13}C NMR spectral data were recorded with a 400 MHz Bruker Avance spectrometer using TopSpin v.3.2 and referenced using the solvent residual signal as internal standard. The chemical shift values are expressed as δ values (ppm) and the value of coupling constants (*J*) in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; and br, broad.

Synthetic Procedures

Compounds **6**, **8**, and **9** were prepared using parallel procedures as described previously.[1]

Dimethyl 2-(2-methoxy-2-oxo-ethyl)benzoate (8). 

A 500 mL rd-bottom flask was charged with homophthalic acid (30.001 g, 0.166 mol), MeOH (140 mL, 0.593 mol), and concentrated HCl (6 mL, 0.408 mol) and the mixture was stirred at reflux for 72 hours. The MeOH was removed under *vacuo* (rotary evaporator) and the remaining mixture was placed in a 500 mL separatory funnel with saturated $NaHCO_3$ (100 mL) and extracted with 2x50 mL CH_2Cl_2. The combined organic layers were washed with deionized water (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, and then reduced under *vacuo* (rotary evaporator) to give **8** as a yellow oil (31.724 g, 0.152 mol, 91.6%). ^{1}H NMR (400 MHz, acetone-*d*6): δ 8.02 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar-H); 7.49 (dt, *J* = 7.50, 1.4 Hz, 1H, Ar-H); 7.37 (dt, *J* = 7.68, 1.3 Hz, 1H, Ar-H); 7.26 (d, *J* = 7.56 Hz, 1H, Ar-H); 4.01 (s, 2H, C_{sp3}-H); 3.87 (s, 3H, CH_3); 3.70 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 167.6, 136.1, 132.5, 132.4, 131.2, 129.7, 127.6, 52.1, 52.1, 40.6.

Dimethyl 1-oxoisochromene-3,4-dicarboxylate. 

Sodium metal (0.502 g, 21.833 mmol, 1.52 eqv.) was isolated from a mineral oil solution, washed with ~5 mL of hexanes, and added to a 250 mL rd-bottom flask purged with nitrogen gas. The flask was chilled to 0°C under a nitrogen atmosphere followed by the addition of 7.0 mL of anhydrous methanol. The contents were stirred to form a clear yellow solution. The hexanes were removed *via* a mechanical vacuum pump (10^{-3} torr) and the residue suspended in 30 mL of dry benzene. Two solutions consisting of dimethyl homophthalate (**8**) (2.983 g, 14.342 mmol, 1.0 eqv.) dissolved in benzene (4 mL) and dimethyl oxalate (2.233 g, 18.923 mmol, 1.32 eqv.) dissolved in benzene (4 mL) were mixed together and added over one hour using an addition funnel. The mixture was stirred at room temperature for an additional 18 hours under nitrogen atmosphere to form a bright yellow homogenous solution. 2M HCl (10 mL) was then added to the mixture and stirred for 5 minutes to give a heterogenous mixture consisting of a white solid and yellow solution. The organic layer was separated and washed with distilled water (20 mL), dried

1. a) Seitz, M.; Pluth; M. D.; Raymond, K. M. *Inorg. Chem*. **2007**, *46*, 351-353. b) M. Seitz, Department of Chemistry and Biochemistry, Ruhr-University Bochum, Bochum, Germany. Personal communication, December 2010.

over anhydrous $MgSO_4$, and concentrated under *vacuo* (rotary evaporator) to yield a yellow oil. The oil was heated at 100°C for 2 hours and upon cooling to room temperature formed a light-yellow solid. This mixture was allowed to stand for 16 hours and then refluxed in 10 mL of reagent grade methanol for 30 minutes. After cooling to room temperature, the resulting solid was collected by vacuum filtration and washed with MeOH to give dimethyl 1-oxoisochromene-3,4-dicarboxylate as colorless needles (1.844 g, 7.043 mmol, 50.07%). Mp 128-133°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (dd, *J* = 8.0, 0.8 Hz, 1H, Ar-H); 7.85 (dt, *J* = 8.0, 0.8 Hz, 1H, Ar-H); 7.71 (dt, *J* = 8.0, 0.8 Hz, 1H, Ar-H); 7.54 (dd, *J* = 8.0, 0.8 Hz, 1H, Ar-H); 4.00 (s, 3H, CH_3); 3.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 160.1, 159.2, 140.81, 135.5, 132.7, 131.2, 130.3, 125.5, 121.9, 119.0, 53.4 (2C).

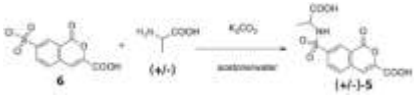
1-Oxoisochromene-3-carboxylic acid (9).

To a 250 mL rd-bottom flask was charged with conc. HCl (60 mL, 1.643 mol) and heated to 110°C. Dimethyl 1-oxoisochromene-3,4-dicarboxylate (4.483 g, 17.113 mmol) was then added portionwise and the mixture was allowed to stir at reflux for 22 hours. The resulting white solid and yellow solution was cooled to room temperature and the solid was collected by vacuum filtration. The solid was further dried using a mechanical vacuum pump (10^{-3} torr), and then heated over a hot water bath at 50-60°C for 1 hour to give isocoumarin **9** as an off-white solid (2.843 g, 14.953 mmol, 87.37%). Mp 218-223°C; ^{1}H NMR (400 MHz, acetone-*d*6): δ 8.21(dd, *J* = 0.6, 6.8 Hz, 1H, Ar-H);7.87 (dt, *J* = 1.3, 7.3 Hz, 1H, Ar-H); 7.81 (dd, *J* = 1.2, 7.8 Hz, 1H, Ar-H) 7.71 (dt, *J* = 1.2, 7.2 Hz, 1H, Ar-H); 7.60 (s, 1H, C_{sp2}-H). ^{13}C NMR (100 MHz, acetone-d6): δ 161.4, 161.3, 144.5, 136.3, 136.2, 131.8, 130.3, 129.0, 123.7, 113.0.

3-Carboxy-7-chlorosulfonylisocoumarin (6).

To a nitrogen gas purged 100 mL rd-bottom flask at -4°C was charged with chlorosulfonic acid (40 mL, 601.524 mmol, 38.0 eqv.). 3-Carboxyisocoumarin (**9**) (3.003 g, 15.805 mmol, 1.0 eqv.) was then added to a 100 mL rd-bottom flask portionwise for 1 hour. The yellow homogenous solution was heated at 120-130°C for 7 hours using a sand bath to give a dark-brown solution that was cooled to room temperature and added dropwise onto ice (~ 70.0 g) with stirring. The resulting white solid was washed with ice water and vacuum filtered, dissolved in acetone (10 mL), dried with anhydrous $MgSO_4$, and reduced under *vacuo* (rotary evaporator) to give isocoumarin **6** as a white solid (0.734 g, 2.543 mmol, 16.08%). ^{1}H NMR (400 MHz, acetone-*d*6): δ 8.80 (d, *J* = 2.2 Hz, 1H, Ar-H); 8.59 (dd, *J* = 8.5 Hz, 2.2 Hz, 1H, Ar-H); 8.30 (d, *J* = 8.5 Hz, 1H, Ar-H); 7.85 (s, 1H, C_{sp2}-H). ^{13}C NMR (100 MHz, acetone-*d*6): δ 160.9, 160.0, 147.6, 145.5, 142.4, 133.1, 131.5, 129.2, 124.7, 111.6.

7-(3-Hydroxy-2-methyl-3-oxo-propyl)sulfonyl-1-oxo-isochromene-3-carboxylic acid ((±)-5).



To a 250 mL rd-bottom flask was charged with DL-alanine (0.230 g, 2.583 mmol), 3-carboxy-7-chlorosulfonylisocoumarin (**6**) (0.466 g, 1.623 mmol), 50 mL of acetone, and 40 mL deionized water were added. The mixture was cooled to 0°C and stirred for an additional 10 minutes. To the white heterogeneous mixture was added K_2CO_3 (1.318 g, 9.554 mmol) dissolved in 75 mL of deionized water. The resulting yellow solution was stirred at 0°C for 4 hrs. The acetone was removed under *vacuo* (rotary evaporator) and the resulting aqueous layer was then cooled to 0°C and acidified to pH ~ 2 using 6M HCl.

The solution was then extracted with 3x25 mL of EtOAc, and the combined organic extracts were washed with 25 mL of deionized water, dried over anhydrous $MgSO_4$, and reduced under *vacuo* (rotary evaporator) to give isocoumarin ((±)-**5**) as a white solid (0.114 g, 0.334 mmol, 20.68%). Mp 233-236°C; ^{1}H NMR (400 MHz, acetone-*d6*): δ 8.68 (d, *J* = 1.9 Hz, 1H, Ar-H); 8.31 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar-H); 8.06 (d, *J* = 8.2, 1H, Ar-H); 7.74 (s, 1H, C_{sp2}-H); 7.28 (d, *J* = 8.7 Hz, 1H, NH); 4.11 (m, 1H, CH); 1.38 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, acetone-*d6*): δ 173.2, 161.1, 160.6, 146.2, 144.4, 139.4, 133.7, 130.0, 129.0, 123.9, 112.0, 52.5, 19.5.

S2. Crystal Growth. Recrystallization experiments of (±)-**5** were conducted *via* slow evaporation at room temperature using spectroscopic grade acetone to give X-ray quality crystals after 1-6 days.

S3. SCSC Photodimerization Reactions. Photoirradiation studies were conducted as previously described[2] and were carried out at room temperature (296 K) using a focused 200 W Xe(Hg) arc lamp (Newport Corp., 67005, 6292) equipped with a 360 nm optical edge filter (Newport Corp., CGA-360). Photodimerization conversion of (±)-**5** was assessed *via* X-ray diffraction of an irradiated single crystal that indicated quantitative conversion to photoproduct after 8 hours.

S4. X-ray Crystallography. Given the challenge of whole molecule disorder observed in crystals of unreacted (±)-**5**, four complete data sets were collected using two different CCD diffractometers. Each crystallographic study used a fresh crystal and close inspection and the group of data sets revealed very similar diffraction data. The lack of weak satellite reflections suggested the absence incommensurate behavior. One of these studies was selected for this contribution with the same crystal employed for both the initial X-ray and the SCSC transformation studies.

Crystallographic details for unreacted and photoirradiated (±)-**5** are summarized in Table S1. X-ray data were collected on a Bruker APEX II diffractometer using phi and omega scans with graphite monochromatic Cu $K\alpha$ (λ = 1.54178 Å) radiation. Data sets were corrected for Lorentz and polarization effects as well as absorption - SADABS/multi-scan.[3] The criterion for observed reflections is $I > 2\sigma(I)$. Lattice parameters were determined from least-squares analysis and reflection data. Empirical absorption corrections were applied using SADABS. Structures solved by direct methods and refined by full-matrix least-squares analysis on F^2 using X-SEED[4] equipped with SHELX-2014/7-XS[5]. All non-hydrogen atoms for the unreacted crystal phase were refined anisotropically unless specified by full-matrix least-squares on F^2 by the use of the SHELX-2014/7-XL[4] program.

For unreacted (±)-**5**, the structure was modeled with two-part whole molecule disorder. The relative amounts of the two species in the lattice were determined from the occupancies of the two parts as 65:35. The sum of the occupancies were constrained to 1.0. H atoms (for OH and NH), where possible, were located in difference Fourier synthesis and refined isotropically with restrained O/N-H distances of 0.85(2) Å and U_{iso}=1.2U_{eq} of the attached O/N atom. The remaining H atoms were included in idealized geometric positions with U_{iso}=1.2U_{eq} of the atom to which they were attached (U_{iso}=1.5U_{eq} for methyl groups). Rigid body refinement using the SHELX RIGU command was applied to both isocoumarin fragments. The DFIX command was applied to the NH hydrogen atoms to give reasonable geometries.

2. Yan, Z.; Bolokowicz, A. J.; Collett, T. K.; Reeb, S. A.; Wiseman, J. D.; Wheeler, K. A. *CrystEngComm.* **2013**, *15*, 27-30.
3. G. M. Sheldrick, SADABS —Program for Area Detector Absorption Corrections, University of Göttingen, Göttingen, Germany, 2013.
4. Barbour, L. J. *J. Supramol. Chem*. **2001**, *1*, 189-191.
5. Sheldrick, G. M. *Acta Crystallogr., Sect. A: Fundam. Crystallogr.* **2008**, *64*, 112-122.

The electron density associated with carboxyl oxygen atoms of the alanine fragment was not localized or easily resolved and several models were tested. A model with three-component disorder was eventually selected and used in the refinement process of the crystal structure of unreacted (±)-**5**. The occupancy factors for these O atoms were initially refined and then fixed at a ratio of 40:35:25. Both FLAT and ISOR commands were used to restrain the carboxyl groups of this three-component disorder.

Upon UV irradiation of the crystal described above, the sample was crystallographically assessed using a similar solution and refinement strategies for unreacted (±)-**5**. A unit cell was determined using CELL_NOW[6] the data were corrected for absorption with TWINABS[7] using a two component model.

Table S1. Crystallographic data for Isocoumarin (±)-5

	(±)-**5**-unreacted	(±)-**5**-reacted
Crystal Data		
Empirical formula	$C_{13}H_{11}NO_8S$	$C_{13}H_{11}NO_8S$
Crystal System, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$
M_r	341.29	341.29
a, Å	11.5746(3)	11.4446(4)
b, Å	7.7435(2)	7.6479(3)
c, Å	16.5085(5)	16.9341(6)
α, deg	90	90
β, deg	107.394(2)	106.126(2)
γ, deg	90	90
V, (Å^3)	1411.96(7)	1423.87(9)
Z, *Z'*	4, 1	4, 1
D_{calc} (g cm^{-3})	1.605	1.592
μ (mm^{-1}), rad. type	2.479, Cu $K\alpha$	2.458, Cu $K\alpha$
F_{000}	704	704
temp (K)	100(2)	100(2)
Crystal form, color	plate, colorless	plate, colorless
Crystal size, mm	0.14 x 0.33 x 0.39	0.14 x 0.33 x 0.39
Data Collection		
Diffractometer	Bruker Apex II	Bruker Apex II
T_{min}/ T_{max}	0.445/0.729	0.606/0.753
No. of refls. (meas., uniq., and obs.)	8985/2448/2233	19222/2538/2127
R_{int}	0.0250	0.0363
θ_{max} (°)	67.732	67.799
Refinement		
R/R^2_ω (obs data)	0.0776/0.1947	0.0905/0.2201
R/R^2_ω (all data)	0.0823/0.1979	0.1014/0.2267
S	1.11	1.11
No. of refls.	2448	2538
No. of parameters and restraints	424, 280	331, 117
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.669/-0.556	0.409/-0.442
flack	-	-

6. Sheldrick, G. M. (2008). CELL_NOW. Version 2008/4. Georg-August-Universität Göttingen, Göttingen, Germany.
7. Sheldrick, G. M. TWINABS —Program for Area Detector Absorption Corrections of Twinned Data, University of Göttingen, Göttingen, Germany, 2013.