Influence of Chemical Functionality on the Rate of Polymer-Induced Heteronucleation

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SI 1. Synthesis of functionalized Merrifield Resin

All chemicals were obtained and used without further purification. Merrifield Resin, phenol, and 4-hydroxyacetophenone were purchased from Sigma Aldrich; 4-aminophenol and 4-hydroxyacetaphenone were purchased from Acros Organics; acetaminophen was purchased from MP Biomedicals; methyl-acetaminophen was purchased from EnamineStore; and cesium carbonate was purchased from Alfa Aesar.

Merrifield's peptide resin (150 mg) and a phenol (2.5 mmol) were added to a 100 mL round bottom flask containing cesium carbonate (3.5 mmol). Under an inert nitrogen atmosphere, 15 mL dimethylacetamide was then added and the reaction was held at 85 °C overnight. The resulting resin was then thoroughly washed with DMF, DMF:H_2O, H_2O, and methanol and allowed to dry overnight to evaporate any residual solvent.

Although in theory no physical changes should occur upon functionalization, in reality, abrasion due to stirring during functionalization does have a slight effect on resin shape. Because resin swells in organic solvent upon functionalization, it becomes more susceptible to breakage. As a result, smaller pieces of polymer were filtered through a 0.063 mm mesh and discarded prior to crystallization experiments.

SI 2. Raman spectroscopy of functionalized Merrifield Resin

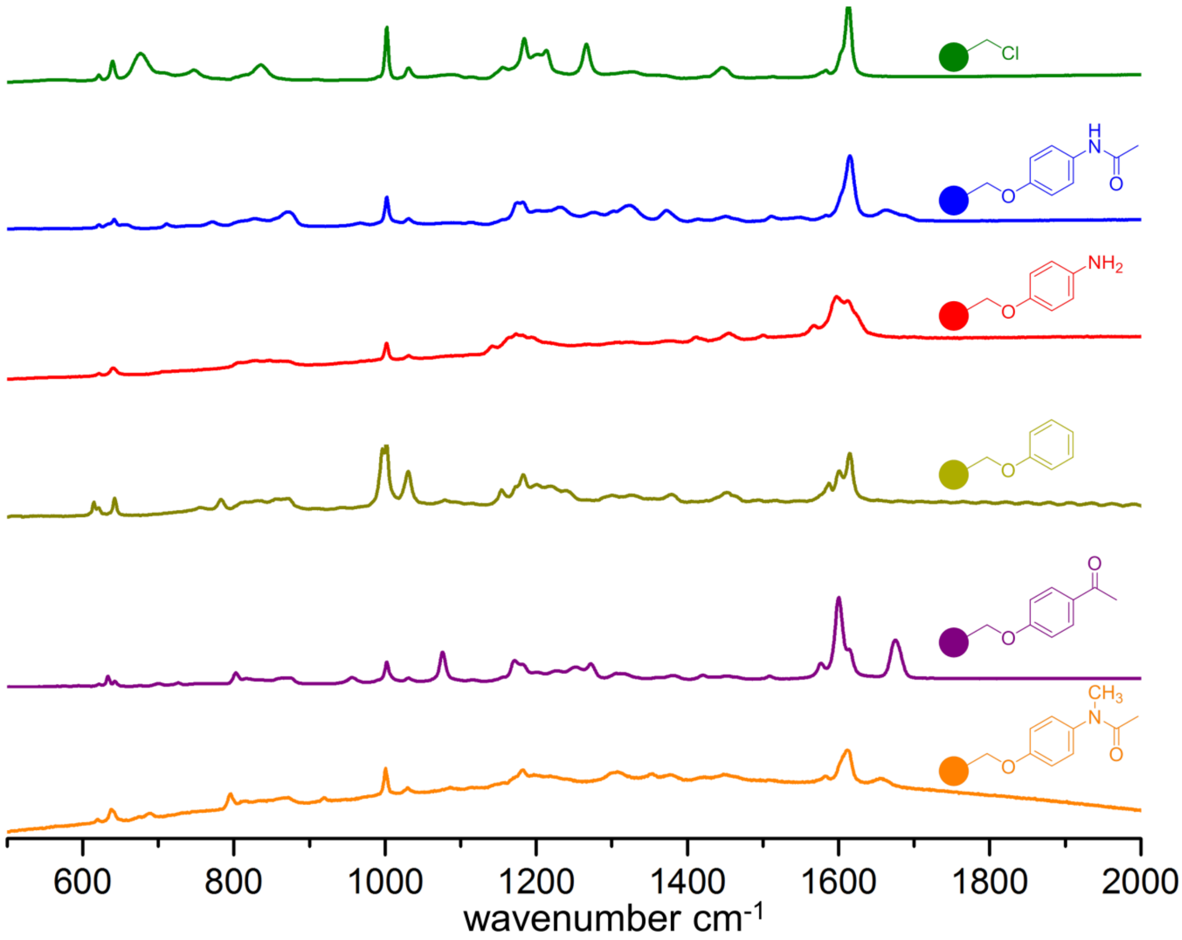


Figure S1. Raman spectra of functionalized Merrifield Resins. Each colored plot corresponds with the functionalized resin pictured at the right in the diagram.

Raman spectra were collected on a Renishaw inVia Raman Microscope using a 633 nm laser, 1800 lines/mm grating, 50 µm slit, and a RenCam CCD detector. Spectra was collected from 100-3800 cm-1 and analyzed using the WiRE 3.4 software package from Renishaw and OriginPro 9.1. Calibration was performed with a silicon standard.

SI 3. Induction times for acetaminophen crystallization in the presence of polymer heteronuclei

Table S1 shows induction time values for acetaminophen crystallization. Acetaminophen was verified to have crystallized in its monoclinic polymorph by Raman spectroscopy at the end of five cycles of crystallization. As mentioned in the manuscript text, vials that did not see crystallization over five heating/cooling cycles were removed from statistical analysis. It is possible that these vials did not yield crystals because of long induction times. However, their anomalous behavior is more likely the result of crystal formation on the closure of the vials lowering supersaturation in solution. In either case discarding these samples may lead to a moderate decrease in reported induction times but without bias. The ranking of heteronuclei in their ability to accelerate nucleation remains the same. The only resin which showed persistent lack of crystallization across an entire set of cycles was 4PH-MFR. This resin not only suffers from crystal formation on the closure of vials but also aggregation of highly hydrophobic resins. If heteronucleation occurred within the centers of aggregated polymer beads, such crystals are blocked from secondary nucleation and never cause a strong transmissivity drop. As a result, only 40 crystallization events for acetaminophen containing 4PH-MFR were used for analysis; that being said, even when these induction times are removed in statistical analysis, 4PH-MFR remains the weakest accelerant of heteronculeation.

Control	MFR	ACM-MFR	4AM-MFR	4AP-MFR	4PH-MFR	mACM-MFR
58.54	180.65	2.03	0.99	2.46	3.55	2.2
29.08	180.6	2	2.28	3.36	126.69	1.81
286.08	71.97	1.64	2.93	4.3	70.99	1.97

90.72	46.52	1.83	2.66	4.28	41.2	1.47
141.83	84.15	2.23	2.85	61.11	33.83	1.6
44.37	25.81	3.08	3.87	6.72	19.38	2.53
70.64	52.22	4.45	4.35	6.34	26.61	1.92
35.3	23.68	2.53	1.87	96.81	17.68	2.18
36.9	16.67	2.8	4.07	11.24	21.12	2.26
28.41	22.41	3.34	2.41	6.77	13.36	2.59
115.5	37.26	3.97	3.35	119.36	2	1.27
27.56	31.81	2.98	4.67	13.4	4.47	2.67
208.37	36.1	3.4	3.93	11.92	24.82	3.09
28.08	92.93	2.91	5.03	20.28	55.88	2.18
63	75.48	11.3	5.51	11.82	31.86	1.19
17.95	297.79	8.99	6.47	142.81	25.62	2.37
50.83	73.71	4.57	7.56	14.69	15.25	2.57
7.71	60.1	3.99	8.25	8.24	15.86	3.17
217.47	51.37	6.63	4.28	9.73	13.58	0.69
144.92	16.93	4.1	4.36	7.4	6.61	2.77
277.92	8.34	1.75	2.25	4.7	14.59	1.67
65.22	25.97	3.94	2.14	4.06	11.22	1.07
67.7	207.67	12.44	1.91	2.36	20.47	3.04
13.16	87.21	3.27	2.25	4.36	15.02	3.82
270.61	76.23	4.41	2.15	3.5	23.85	0.93
127.09	223.64	13.08	3.39	5.12	292.23	0.82
120.7	84.21	3.58	2.96	4.09	90.79	1.81
46.59	1.47	4.4	3.32	31.24	4.43	4.79
51.07	3.07	5.16	1.74	5.44	12.27	2.05
5.6	2.27	2.67	2.96	7.7	40.35	1.09

271.16	2.05	18.62	2.61	7.44	22.44	1.42
no crystals observed	2.99	6.95	3	34.66	no crystals observed	1.94
no crystals observed	3.54	5.42	1.72	15.13	no crystals observed	2.75
no crystals observed	1.41	6.58	2.13	4.57	no crystals observed	1.82
no crystals observed	12.39	8.03	2.8	6.83	no crystals observed	1.28
no crystals observed	6.03	4.27	1.96	3.07	no crystals observed	3.8
no crystals observed	7.09	16.77	2.26	4.01	no crystals observed	2.52
no crystals observed	7.83	5.24	2.12	2.57	no crystals observed	13.88
no crystals observed	10.06	7.59	2.37	3.35	no crystals observed	5.39
no crystals observed	23.08	7.89	13.51	4.12	no crystals observed	6.09
no crystals observed	8.39	0.98	2.33	2.39	no crystals observed	2.14
no crystals observed	8.23	12.01	4.63	6.13	no crystals observed	2.27
no crystals observed	17.44	3.04	2.96	3.2	no crystals observed	1.61
no crystals observed	5.82	11.51	2.07	4.15	no crystals observed	1.93
no crystals observed	5.15	6.74	3.36	3.51	no crystals observed	6.08
no crystals observed	6.43	6.05	1.71	3	no crystals observed	3.5
no crystals observed	9.38	4.77	4.75	3.59	no crystals observed	1.57

no crystals observed	no crystals observed	21.99	3.27	3.98	no crystals observed	4.72
no crystals observed	no crystals observed	4.42	3.25	2.7	no crystals observed	3.75
no crystals observed	no crystals observed	10.31	3.29	7.98	no crystals observed	4.75
no crystals observed	no crystals observed	105.36	3.86	6.44	no crystals observed	2.07
no crystals observed	no crystals observed	16.04	2.75	5.83	no crystals observed	8.04
no crystals observed	no crystals observed	5.57	4.64	6.98	no crystals observed	13.82
no crystals observed	no crystals observed	3.95	5.34	5.22	no crystals observed	7.31
no crystals observed	no crystals observed	10.22	4.83	1.91	no crystals observed	4.92
no crystals observed	no crystals observed	no crystals observed	3.59	no crystals observed	no crystals observed	no crystals observed
no crystals observed	no crystals observed	no crystals observed	9.63	no crystals observed	no crystals observed	no crystals observed
no crystals observed	no crystals observed	no crystals observed	7.23	no crystals observed	no crystals observed	no crystals observed
no crystals observed	no crystals observed	no crystals observed	8.03	no crystals observed	no crystals observed	no crystals observed
no crystals observed	no crystals observed	no crystals observed	3.14	no crystals observed	no crystals observed	no crystals observed

Table S1. Full listing of induction times (in minutes) for acetaminophen crystallization in the presence of insoluble heteronuclei. Values shaded in grey were discarded from statistical analysis—these represent cases where no crystallization occurred over five cycles for an individual vial.

SI 4. CSD Search Parameters

To estimate the extent of interaction between acetaminophen and functionalized Merrifield Resins, a CSD search identified materials containing an interaction between a phenolic hydroxy group (as an analogue to acetaminophen) and hydrogen bond accepting functionalities on four of the heteronuclei. The structures were limited to those containing intermolecular bonds (< 4 Å) between any phenolic hydroxy (regardless of other aromatic substituents) and each resin functionality as attached to a benzene ring (again, regardless of other substituents). Contacts were defined such that all bonds measured were intermolecular. Table S2 summarizes the average and standard error of bond lengths from materials collected in this search.

This interaction—hydroxy donating a hydrogen to the resin functionality—was selected as a model for acetaminophen heteronucleation considering prior work from the Matzger group. In Pfund et al.,[1] polymer heteronuclei for acetaminophen crystallization were designed to mimic either the acetamide or the phenolic ends of the pharmaceutical. Although these heteronuclei were not controlled for uniform topology, it was found that the acetamide polymer better promoted acetaminophen crystallization compared to the phenolic heteronucleus. In both the monoclinic and orthorhombic packing arrangements of acetaminophen, the acetamide end of the molecule forms a hydrogen bond with the phenolic hydroxy. These observations lead us to believe that acetaminophen aggregates most efficiently on a heteronucleus by way of dimer formation from its phenolic end, and for this reason, the CSD search probed bond distances between a phenolic hydroxy group and hydrogen-bond accepting functionalities on each resin.

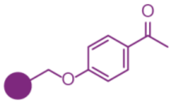
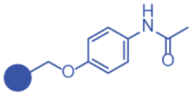
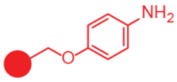
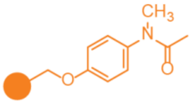
	 AP-MFR	 ACM-MFR	 AN-MFR	 MACM-MFR
Average bond distance to phenol (Å)	3.32 ± 0.01	3.09 ± 0.03	3.13 ± 0.02	3.05 ± 0.04
Number of hits	2515	329	480	156
Average bond distance to water (Å)	3.09 ± 0.02	3.06 ± 0.02	3.21 ± 0.001	3.04 ± 0.03
Number of hits	466	398	310	140
Average bond distance phenol to Nitrogen (Å)		3.37 ± 0.02		3.62 ± 0.03
Number of hits		244		48
Average bond distance water to Nitrogen (Å)		3.17 ± 0.02		3.63 ± 0.05
Number of hits		355		26

Table S2. Average intermolecular bond length to resin functionalities, shown with the standard error of measurement and the number of structures included in the averaging. Structures were constrained to those containing intermolecular contacts no more than 4 Å apart.

1. Pfund, L. Y.; Price, C. P.; Frick, J. J.; Matzger, A. J., *J. Am. Chem. Soc.* **2015,** *137* (2), 871-875.