

Probing the Reactivity of Solid Supports via Hammett Relationships

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Abstract: A high-throughput technique for elucidating Hammett relationships on solid supports and its application to the comparison of various commercially available solid supports is reported. Specifically, we report the use of competition experiments to derive Hammett relationships for the displacement of a solid-supported pentafluorophenyl (pfp) ester with four para-substituted anilines (*p*-MeO, *p*-Me, *p*-F, *p*-Cl) and aniline. By taking advantage of the unique physical properties of the solid supports, we were able to conduct competition experiments with seven different solid supports in a single reaction vessel. This enabled us to generate 35 Hammett plots from only 10 reaction vessels. These studies revealed the strong dependence of the Hammett reaction constant ρ on both the solid support and solvent used in the ester displacement reaction. Interestingly, the ρ values obtained for reactions conducted on poly(ethylene glycol)-grafted polystyrene (PS-PEG) resin closely matched the corresponding solution-phase ρ values, a result which supports the supposition that molecules attached to PS-PEG exhibit “solution-like” behavior. Moreover, changing the solvent from DMF to CH₂Cl₂ greatly reduced the support-to-support variation in ρ , suggesting that the degree of solvation or “swelling” of the solid support greatly influences the chemical environment around the solid-support substrate.

Introduction

In recent years, the synthesis of nonpeptidic organic molecules on polymer-based solid supports^{1,2} has attracted a great deal of interest in the synthetic community, due mainly to the ease with which large numbers of compounds can be synthesized and purified in parallel. The throughput advantages offered by solid-phase synthesis are offset by a number of disadvantages: (1) Many solution-phase reactions have not been exemplified on the solid phase, effectively limiting the synthetic options available to the solid-phase chemist. (2) Every molecule synthesized on the solid phase bears an artifact (or “trace”) reflecting its point of attachment to the solid support. (3) The role of the solid support in the solid-phase reaction is not well understood, and this situation is further complicated by solvent effects which affect the physical properties of the solid support.

Current research in the field of solid-phase synthesis has largely addressed the first two items in the above list: many solution-phase reactions have been effectively transferred to the solid phase,^{1,3} and numerous methods have been developed for attaching molecules to the solid support.^{1,4} In contrast, studies of the solid support itself have primarily focused on the physical

properties of the polymer^{2,5} (for instance, swelling behavior in various solvents⁶) rather than the role that the support plays in a chemical reaction. This is not to suggest that the extent to which a solid support swells in a given solvent is unimportant, but there are a number of interesting solid supports (i.e., macroreticular^{2,7} and pellicular^{2,8} solid supports) for which swelling is simply not a meaningful measurement.

We have had a long-standing interest in carrying out solid-phase syntheses on pellicular solid supports, such as crowns,⁹ in which a functionalized polymer is grafted to a chemically inert “base” polymer. Pellicular solid supports offer a number of advantages over microreticular polymers (e.g., polystyrene resin beads), particularly in ease of handling, but their physical properties are difficult to measure, in part because they do not exhibit the same swelling behavior as resin. This prompted us to investigate new methods for evaluating the reactivity of solid supports, and we have found that the information gleaned from a Hammett plot for a given solid-phase reaction can be utilized to address this issue while providing the chemist with valuable quantitative information about a reaction’s sensitivity to substituent effects.¹⁰

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(10) Portions of this work were presented at the International Kyoto Conference on Organic Synthesis—The 14th Nozaki Conference, Kyoto, Japan, November 9, 1999.

The Hammett equation (eq 1)¹¹ is a powerful tool for

$$\log(k/k^0) = \sigma\rho \quad (1)$$

measuring the sensitivity of the rate of a reaction (ρ) to electronic substituent effects (σ). In the case of solid-phase synthesis, the value of ρ is useful information because a given reaction will generally be repeated with a series of functionally related reactants bearing an electronically diverse set of substituents. For example, in the synthesis of a combinatorial library¹² the ideal reaction would have $\rho = 0$, signifying that individual reaction rates would be insensitive to the range of electronic properties inherent to the monomer set. It has been demonstrated¹³ that ρ is influenced by various reaction conditions such as temperature and solvent. In the case of solid-phase synthesis, it has been postulated¹⁴ that the solid support serves as a cosolvent, and thus the chemical properties of the solid phase may also affect ρ .

The direct measurement of reaction rates on a solid support is technically demanding,¹⁵ and so we elected to measure relative rates via competition experiments in which an equimolar mixture of two reagents is reacted with a solid-supported substrate. Solid-phase competition experiments have been utilized to measure the relative reactivity of amino acids in amide bond formation,¹⁶ but the logical extension of this technique to determine Hammett relationships has not been reported. It has been our experience that the use of a solid support expedites a competition experiment when compared to a similar solution-phase experiment: the solid support simplifies the removal of large excesses of the reactants (necessary to maintain approximately constant concentrations through the course of the reaction) and facilitates product purification. Moreover, multiple solid supports may be reacted in the same flask (vide infra) to eliminate "flask-to-flask" variance, a major source of experimental error.

Results and Discussion

Our initial investigations focused on amide bond formation via displacement of a solid-supported pentafluorophenyl (pfp) ester by a series of anilines. A variety of Knorr-modified Rink linker-equipped¹⁷ solid supports were used, as described in Table 1. With the exception of PTFE tubes,¹⁸ all of the solid supports are commercially available.¹⁹ The solid supports were selected to test a range of support types (e.g., crowns and resin), polymer types, and loading levels. We kept the linker portion of the polymers constant so that the solid supports would be chemically identical from the linker amide outward.

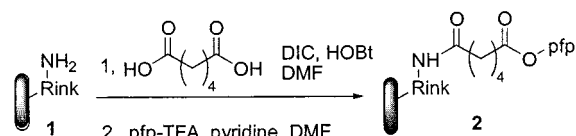
As previously mentioned, each synthetic step was carried out with all of the solid supports combined in a single reaction vessel. This is possible because crowns, tubes, and lanterns are all macroscopic supports that can be easily separated from one another. The microscopic PS and PS-PEG resin beads were

Table 1. Chemical Descriptions for Solid Supports Utilized in Competition Experiments

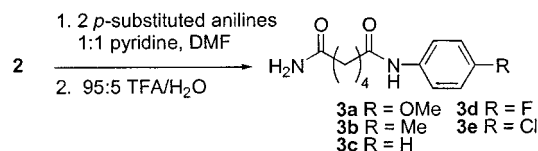
abbreviation	base polymer ^a	graft ^a	loading ^b
MA/DMA crowns	PE	MA/DMA	7.6 $\mu\text{mol/crown}$
LLPS crowns	PE	PS	8.0 $\mu\text{mol/crown}$
HLPS crowns	PE	PS	26.0 $\mu\text{mol/crown}$
PS lanterns	PE	PS	35.0 $\mu\text{mol/lantern}$
PTFE tubes	PTFE	PS	35.0 $\mu\text{mol/tube}$
PS resin	PS	None	0.53 mmol/g
PS-PEG resin	PS	PEG	0.20 mmol/g

^a MA/DMA = methacrylic acid/dimethyl acrylamide copolymer; PE = poly(ethylene); PS = poly(styrene); PTFE = poly(tetrafluoroethylene); PEG = 3000–4000 MW poly(ethylene glycol). ^b As reported by the manufacturer.

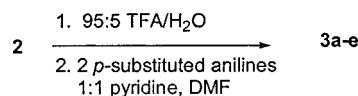
Scheme 1



Solid Phase Competition Experiments:



Solution Phase Competition Experiments:



placed in individual MiniKans and combined with the macroscopic supports. A general synthesis of the solid-supported pfp-ester is outlined in Scheme 1. Adipic acid was coupled to Rink-functionalized solid support **1** under standard conditions. The resulting acid was converted to the pfp-ester **2** with pfp-trifluoroacetate in DMF with pyridine as base.²⁰ In each competition experiment, pfp-ester **2** was treated with a 0.5 M solution of two anilines in 1:1 pyridine–DMF for 24 h. We utilized five anilines for these experiments: *p*-anisidine, *p*-toluidine, aniline, *p*-fluoroaniline, and *p*-chloroaniline. All possible combinations of these five anilines were used for a total of 10 competition experiments.²¹ The resulting binary mixtures of aromatic amides **3a–e** were cleaved off the solid supports with 95:5 TFA/H₂O. Product ratios and yields²² were determined by ¹H NMR with 2,5-dimethylfuran (DMFu) as an internal standard for quantitation,²³ and the identities of the amides were confirmed by LC/MS analysis. Similar competition experiments were conducted in the solution phase. Treatment of **2** with 95:5 TFA/H₂O provided the corresponding pfp-ester

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(21) The number of experiments required to conduct a "combinatorial" Hammett experiment can be expressed by the equation $N(N-1)/2$, where N is the number of analogues to be studied.

(22) In all cases, yields exceeded 85% (based on initial polymer loading).

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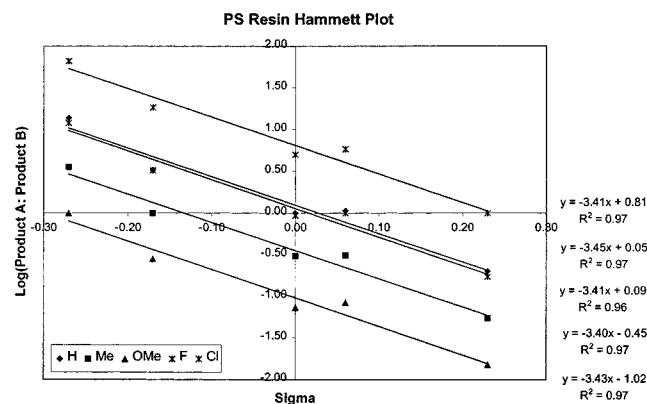
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(19) Specific information regarding the commercial sources and catalog numbers for the solid supports can be found in the Experimental Section.

Table 2. Product Ratios Obtained from PS Resin Following Two Sets of Ten Competition Experiments

aniline (X)	sigma (σ_p)	log(ratio) <i>p</i> -OMe/X	log(ratio) <i>p</i> -Me/X	log(ratio) H/X	log(ratio) <i>p</i> -F/X	log(ratio) <i>p</i> -Cl/x
<i>p</i> -OMe	-0.27	0	0	-0.55	-0.52	-1.14
<i>p</i> -Me	-0.17	0.55	0.52	0	-0.52	-0.58
H	0.00	1.14	1.14	0.52	0.58	0
<i>p</i> -F	0.06	1.08	1.14	0.51	0.50	-0.03
<i>p</i> -Cl	0.23	1.82	1.82	1.26	1.32	0.70

**Figure 1.** The “combinatorial” Hammett plot for one set of competition experiments conducted with PS resin.

which, following removal of TFA in vacuo, was treated with the aforementioned 10 mixtures of anilines in 1:1 pyridine–DMF. After 24 h, the solution was concentrated and the excess anilines were removed by cation exchange chromatography.

For a given reaction, a “traditional” Hammett experiment will compare a standard benzene derivative (typically the H-substituted derivative) to every member of a series of substituted benzene derivatives. In contrast, the “combinatorial” Hammett experiments reported herein comprise 10 competition experiments (carried out in duplicate²⁴) in which all possible binary combinations of five anilines are compared. For example, Table 2 lists the product ratios obtained from the two sets of competition experiments conducted with PS resin. The data from one set of PS resin experiments were used to construct a Hammett plot, as shown in Figure 1. This Hammett plot and the Hammett plot corresponding to the second set of PS resin competition experiments provide a total of 10 linear free energy relationships, the slopes of which are used to calculate an average ρ value and the standard error. In the case of PS resin, the average ρ was -3.45 ± 0.01 . Similar plots were generated for the six other solid supports present in each reaction vessel, and an average ρ value was obtained for each support. A total of 70 data points were generated from 10 solid-phase experiments, enabling us to construct 35 Hammett relationships and calculate seven average ρ values. In contrast, the 10 solution-phase experiments generated 10 data points and one average ρ value.²⁵

The ρ values obtained from each Hammett plot are summarized numerically in Table 3. It is in this context that the value of the “combinatorial” Hammett plot becomes apparent. Because each ρ value is derived from the best fit for a straight line through five data points, a certain amount of experimental error is inevitable. For example, the “H” column in Table 3

(24) The solution-phase and PS lantern competition experiments were carried out only once, while the MA/DMA crown and LLPS crown competition experiments were carried out in triplicate.

(25) It is worth noting that the solution-phase competition experiments could be carried out in the same flask as the solid-phase experiments, but technical considerations (i.e., isolating the desired amide products from over 100 equiv of each substituted aniline) prompted us to conduct the solution-phase experiments separately.

highlights the variability between the two ρ values obtained for each solid support, even though the difference between solid supports is evident (cf. LLPS crowns and PS-PEG resin). It is interesting to note that the “H” column contains the data which would be provided by a “traditional” Hammett plot conducted in duplicate. In the case of LLPS crowns, the average ρ value for the “H” column is -3.52 ± 0.11 . This ρ value is in perfect agreement with the ρ value calculated using the “combinatorial” Hammett approach, but the error is four times larger. Since we are using these ρ values to compare a number of solid supports to one another, both the value for ρ and its associated error affect the quality of the comparison.

Figure 2 graphically depicts the average ρ values obtained for each solid support and in solution. In general, the data demonstrate the dependence of ρ on the type of solid support. With the exception of PS-PEG resin all supports afforded a significantly higher absolute value for ρ than the corresponding solution-phase reaction. The strong agreement between the PS-PEG resin and solution-phase ρ values supports the anecdotal evidence that the poly(ethylene glycol) spacer in PS-PEG imparts “solution-like” reactivity to the solid support.^{5b,5c,26} The other solid supports appeared to group together, although it is noteworthy that the ρ value for HLPS crowns was significantly lower than the ρ values obtained for PS resin, MA/DMA crowns, and LLPS crowns. In general, we were surprised by the large differences in ρ between the three crown-based supports, in that the ρ values appear to correlate more strongly with the grafting density (cf. LLPS and MA/DMA: their loadings are very similar, but their grafts are chemically very different) and less strongly with the chemical structure of the graft (cf. LLPS and HLPS: their grafts are chemically identical, but HLPS has 3 \times the loading of LLPS). It is not clear why a higher grafting density would result in a lower absolute value of ρ . Our subsequent experiments explored the effect of the solvent on ρ in solution and for three solid supports: MA/DMA crowns, HLPS crowns, and PS-PEG resin.

As described in Figure 3, changing the solvent from DMF to CH_2Cl_2 had a significant effect on ρ for both solid- and solution-phase reactions. It is interesting that the change in ρ varied from support to support, with PS-PEG showing the smallest change and MA/DMA crowns showing the largest. As is the case with reactions conducted in DMF, the ρ values for PS-PEG and the solution phase in CH_2Cl_2 are in close agreement. Overall, it appears that CH_2Cl_2 attenuates the effect of the solid support on ρ , minimizing the differences between solid- and solution-phase ρ values. The source of this “leveling effect” may be related to the increased swelling of PS-based supports in CH_2Cl_2 relative to DMF, thereby exposing a greater proportion of the solid support to solvent.²⁷ Whatever the cause, these results provide strong evidence that the interaction between a solvent

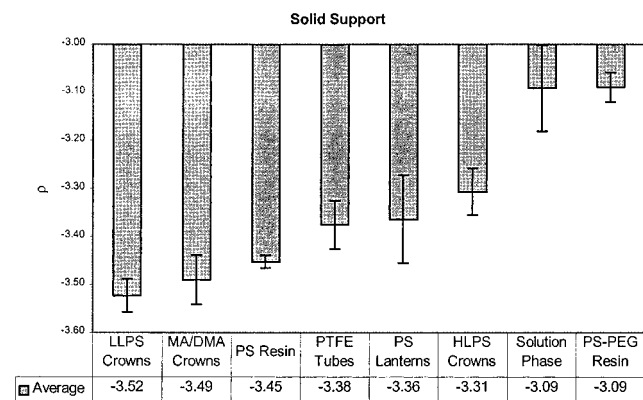
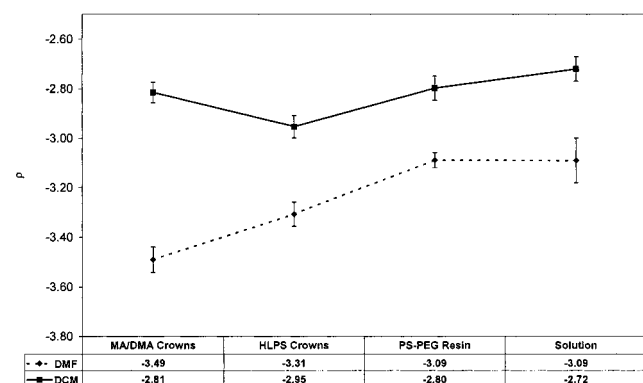
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Table 3. ρ Values Obtained from Hammett Plots for Seven Solid Supports and in Solution

resin	<i>p</i> -OMe		<i>p</i> -Me		H	<i>p</i> -F		<i>p</i> -Cl		av ρ	standard error ^a	
LLPS crowns ^b	-3.78	-3.81	-3.57	-3.46	-3.40	-3.63	-3.54	^c	-3.79	-3.70	-3.52	0.03
MA/DMA crowns ^b	-3.50	-3.81	-3.24	-3.66	-3.65	-3.30	-3.52	-3.40	-3.34	-3.94	-3.49	0.05
PS resin	-3.50	-3.43	-3.45	-3.40	-3.49	-3.41	-3.53	-3.45	-3.46	-3.41	-3.45	0.01
PTFE tubes	-3.10	-3.44	-3.51	-3.41	-3.21	-3.61	-3.45	-3.44	-3.19	-3.40	-3.38	0.05
PS lanterns ^d	-3.34		-3.19		-3.70		-3.38		-3.21		-3.36	0.09
HLPS crowns	-3.11	-3.21	-3.45	-3.30	-3.54	-3.48	-3.40	-3.24	-3.14	-3.21	-3.31	0.05
solution phase ^d	-3.24		-2.80		-3.12		-3.31		-2.99		-3.09	0.09
PS-PEG resin	-3.07	-2.84	-3.11	-3.31	-3.21	-3.00	-2.94	-3.08	-3.12	-2.99	-3.09	0.03

^a Standard error = $\sigma(N^{1/2})$, where σ = standard deviation and N = number of observations. ^b A third set of competition experiments were carried out and included in the average (see Supporting Information for data). ^c Hammett plot not constructed due to missing data. ^d Only one set of competition experiments were conducted.

**Figure 2.** Average ρ values obtained for seven solid supports and in solution.**Figure 3.** The effect of solvent on ρ .

and a solid support is highly synergistic, and lead us to conclude that these reaction variables should not be evaluated independently.²⁸

In conclusion, we have established a straightforward and efficient method for the determination of Hammett relationships for reactions conducted on a solid support. This methodology can be used to quickly determine ρ values for a given reaction using a variety of solid supports and experimental conditions. A key aspect of this work is the ability to mix multiple solid supports in a single reaction vessel: it is theoretically possible to repeat the competition experiments reported herein in which 50 different solid supports are present in each reaction flask, and these 10 experiments would afford 500 data points. In addition, an obvious extension to these efforts is the systematic variation of the electronic properties of the solid-supported substrate, which in combination with the aforementioned competition experiments would allow us to simultaneously establish Hammett relationships for the solid-phase substrate and solution-phase reagent.

Experimental Section

General. Reagents and solvents were obtained from commercial suppliers and were used as received unless otherwise noted. Solid supports were obtained from the following sources: LLPS crowns (no longer commercially available); HLPS crowns (catalog No. SP-PS-I-RAM), MA/DMA crowns (catalog No. SP-MD-I-RAM), and PS lanterns (catalog No. SP-PS-D-RAM) were purchased from Chiron Technologies, Pty. Ltd., Clayton, Victoria, Australia. PTFE tubes (no longer commercially available) and MiniKans (catalog No. MK-I096) were purchased from IRORI, La Jolla, CA. PS-PEG resin (catalog No. 01-64-0060) and PS resin (catalog 01-64-0038) were purchased from Novabiochem, San Diego, CA. Concentration in vacuo refers to the removal of volatile solvents under vacuum with a Savant centrifugal concentrator. A "wash" of a polymer refers to rinsing the polymer with DMF (3 \times 10 mL), MeOH (3 \times 10 mL), and CH₂Cl₂ (3 \times 10 mL). ¹H NMR spectra were obtained with Varian 300, 400, and 500 MHz instruments using DMSO-*d*₆ as the solvent and with data reported (multiplicity, number of hydrogens, coupling constants in hertz) relative to tetramethylsilane (0.00 ppm). All ¹³C NMR were proton decoupled and were obtained on a Varian spectrometer at 100.6 MHz with DMSO-*d*₆ as the solvent with data reported relative to DMSO.

Pentafluorophenyl Esters (Method A). The Fmoc protected Rink amide solid support HLPS was treated with 2.5 mL of 20% piperidine in DMF for 1 h. The solid support was washed and treated with 2.5 mL of DMF containing 0.4 M diisopropylcarbodiimide (DIC), 0.4 M HOBt, and 0.44 M adipic acid for 16 h. After washing, the solid support was dried in a vacuum oven at 50 °C for 12 h. The solid support was then treated with a solution in DMF of 0.5 M pentafluorophenyl trifluoroacetate (pfp-TFA) and 0.5 M pyridine for 6 h. Washing yielded solid-supported pfp ester **2**. For characterization purposes, an HLPS crown was treated with 95:5 TFA-H₂O for 1 h. Concentration in vacuo of the resulting solution yielded the corresponding pentafluorophenyl ester as a white powder in 94% yield (based on initial HLPS crown loading) by ¹H NMR with DMFu quantitation. ¹H NMR (300 MHz, *d*₄-MeOH) δ 1.79 (m, 4H), 2.30 (t, J = 7.0, 2H), 2.79 (t, J = 7.0, 2H); HRMS calcd for C₁₂H₁₀NO₃F₅Na 334.0479, found 334.0486. All pfp-esters on different solid supports were synthesized and characterized in an analogous manner.

***p*-Anisidine Amide 3a.** The solid-supported pfp-ester **2** (synthesized via Method A) on an HLPS crown was treated with a solution of 2.5 mL of 1:1 DMF-pyridine containing 0.5 M *p*-anisidine and shaken for 12 h. The solid support was washed then treated with 2 mL of 95:5 TFA-H₂O for 1 h. The solid support was removed, and the solution concentrated in vacuo to give the amide **3a** as a white powder in 92% yield (based on initial HLPS crown loading) by ¹H NMR with DMFu quantitation. All subsequent amides were synthesized in an analogous

(28) Bing Yan's contribution to ref 2b (pp 447 and 448) also highlights the complex relationship between solid support and solvent.

manner. ^1H NMR (300 MHz, d_6 -DMSO) δ 1.44 (m, 4H), 2.05 (t, $J = 6.8$ Hz, 2H), 2.25 (t, $J = 6.8$ Hz, 2H), 3.70 (s, 3H), 6.69 (br s, 1H), 6.84 (d, $J = 8.9$ Hz, 2H), 7.23 (br s, 1H), 7.48 (d, $J = 8.9$ Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 25.5, 25.6, 35.6, 36.8, 55.8, 114.4, 121.2, 133.2, 155.6, 171.2, 174.8; HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}$ 273.1215, found 273.1212.

***p*-Toluidine Amide 3b.** Obtained as a white powder in 96% yield (based on initial HLPS crown loading) by ^1H NMR with DMFu quantitation. ^1H NMR (300 MHz, d_6 -DMSO) δ 1.49 (m, 4H), 2.05 (t, $J = 6.9$ Hz, 2H), 2.23 (s, 3H), 2.26 (t, $J = 6.8$ Hz, 2H), 6.69 (br s, 1H), 7.07 (d, $J = 8.1$ Hz, 2H), 7.23 (br s, 1H), 7.46 (d, $J = 8.3$ Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 21.1, 25.5, 25.6, 35.6, 36.9, 119.7, 129.7, 132.4, 137.5, 171.5, 174.8; HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ 257.1266, found 257.1260.

Aniline Amide 3c. Obtained as a white powder in 94% yield (based on initial HLPS crown loading) by ^1H NMR with DMFu quantitation. ^1H NMR (300 MHz, d_6 -DMSO) δ 1.50 (m, 4H), 2.04 (t, $J = 6.8$ Hz, 2H), 2.29 (t, $J = 6.8$ Hz, 2H), 6.70 (br s, 1H), 7.01 (t, $J = 7.3$ Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 2H), 7.30 (br s, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 9.85 (s, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 25.5, 25.6, 35.6, 36.8, 115.7, 115.9, 123.6, 129.3, 140.0, 171.8, 174.8; HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2\text{Na}$ 243.1109, found 243.1106.

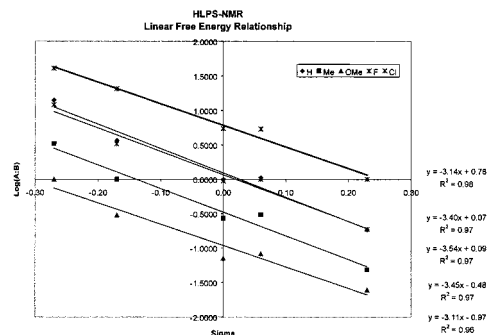
***p*-F aniline Amide 3d.** Obtained as a white powder in a 91% yield (based on initial HLPS crown loading) by ^1H NMR with DMFu quantitation. ^1H NMR (300 MHz, d_6 -DMSO) δ 1.47 (m, 4H), 2.05 (t, $J = 6.9$ Hz, 2H), 2.28 (t, $J = 6.9$ Hz, 2H), 6.70 (br s, 1H), 7.11 (t, $J = 8.8$ Hz, 2H), 7.23 (br s, 1H), 7.60 (dd, $J = 8.9, 5.1$ Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 25.5, 25.5, 35.6, 36.8, 115.7, 115.9, 121.3, 121.4, 136.4, 157.2, 159.6, 171.6, 174.8; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2\text{FNa}$ 261.1015, found 261.1015.

***p*-Cl Aniline Amide 3e.** Obtained as a white powder in a 95% yield (based on initial HLPS crown loading) by ^1H NMR with DMFu quantitation. ^1H NMR (300 MHz, d_6 -DMSO) δ 1.50 (m, 4H), 2.05 (t, $J = 7.0$ Hz, 2H), 2.29 (t, $J = 6.9$ Hz, 2H), 6.70 (br s, 1H), 7.23 (br s, 1H), 7.32 (d, $J = 8.9$ Hz, 2H), 7.61 (d, $J = 8.6$ Hz, 2H), 9.99 (s, 1H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 25.4, 25.5, 35.6, 36.9, 121.2, 127.1, 129.2, 138.9, 171.9, 174.8; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2\text{ClNa}$ 277.0744, found 277.0733.

General Procedure for the First Set of Solid-Phase Competition Experiments. To 10 scintillation vials was added an equimolar solution of two substituted anilines, each at 0.5 M in 1:1 DMF–pyridine, sufficient to provide 20 equiv of the anilines relative to the amount of solid-supported pfp-ester **2**. The two anilines in each vial were as follows: (1) aniline and *p*-methoxyaniline, (2) aniline and *p*-methylaniline, (3) aniline and *p*-fluoroaniline, (4) aniline and *p*-chloroaniline, (5) *p*-methoxyaniline and *p*-methylaniline, (6) *p*-methoxyaniline and *p*-fluoroaniline, (7) *p*-methoxyaniline and *p*-chloroaniline, (8) *p*-methylaniline and *p*-fluoroaniline, (9) *p*-methylaniline and *p*-fluoroaniline, and (10) *p*-fluoroaniline and *p*-chloroaniline. Equal amounts of the solid-supported pfp-ester **2** were then added to each vial and the resulting 10 suspensions were shaken for 24 h. Crowns, lanterns, and tubes were added as is while resins were first placed within IRORI Microkans. The solid supports were then washed and each support was individually treated with 95:5 TFA– H_2O for 1 h. Concentration in vacuo yielded a white solid containing a mixture of two amide products. The mixture was analyzed by ^1H NMR with DMFu internal standard at 5.0 mM concentration. In all cases, the combined yield of amide products exceeded 85%. Ratios of the two products were determined by integration of the relevant peaks for each amide product **3a–e**. The ratios were tabulated and used to construct Hammett plots. Following are the ratios determined for each competition experiment and the associated Hammett plot.

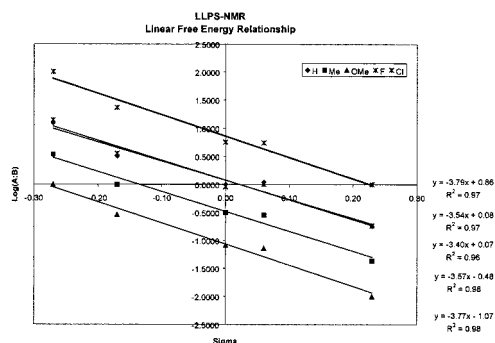
HLPS Crowns in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	1.75	24.73	0.07	14.13	-1.15	1.15
2	H	Me	137.17	506.60	0.27	3.69	-0.57	0.57
3	H	F	98.88	104.52	0.95	1.06	-0.02	0.02
4	H	Cl	1180.60	216.87	5.44	0.18	0.74	-0.74
5	OMe	Me	72.00	21.72	3.31	0.30	0.52	-0.52
6	OMe	F	407.83	33.55	12.16	0.08	1.08	-1.08
7	OMe	Cl	59.34	1.46	40.64	0.02	1.61	-1.61
8	Me	F	409.06	124.84	3.28	0.31	0.52	-0.52
9	Me	Cl	290.28	14.07	20.63	0.05	1.31	-1.31
10	F	Cl	55.80	10.39	5.37	0.19	0.73	-0.73



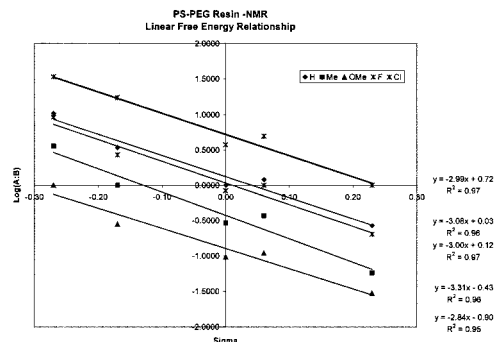
LLPS Crowns in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	0.66	8.08	0.08	12.24	-1.09	1.09
2	H	Me	13.18	41.99	0.31	3.19	-0.50	0.50
3	H	F	295.85	325.63	0.91	1.10	-0.04	0.04
4	H	Cl	15.50	2.76	5.62	0.18	0.75	-0.75
5	OMe	Me	16.15	4.69	3.44	0.29	0.54	-0.54
6	OMe	F	130.64	9.42	13.87	0.07	1.14	-1.14
7	OMe	Cl	35.11	0.35	100.31	0.01	2.00	-2.00
8	Me	F	22.48	6.34	3.55	0.28	0.55	-0.55
9	Me	Cl	14.60	0.63	23.17	0.04	1.37	-1.37
10	F	Cl	90.96	16.63	5.47	0.18	0.74	-0.74



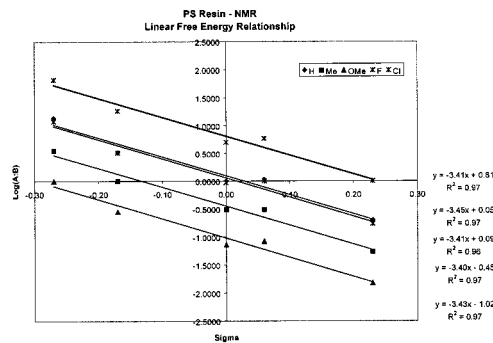
PS-PEG Resin in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	1.59	16.51	0.10	10.38	-1.02	1.02
2	H	Me	32.57	111.67	0.29	3.43	-0.54	0.54
3	H	F	75.41	90.09	0.84	1.19	-0.08	0.08
4	H	Cl	145.04	38.61	3.76	0.27	0.57	-0.57
5	OMe	Me	70.74	19.78	3.58	0.28	0.55	-0.55
6	OMe	F	21.64	2.37	9.13	0.11	0.96	-0.96
7	OMe	Cl	94.26	2.79	33.78	0.03	1.53	-1.53
8	Me	F	44.98	16.64	2.70	0.37	0.43	-0.43
9	Me	Cl	93.64	5.42	17.28	0.06	1.24	-1.24
10	F	Cl	5.09	1.03	4.94	0.20	0.69	-0.69



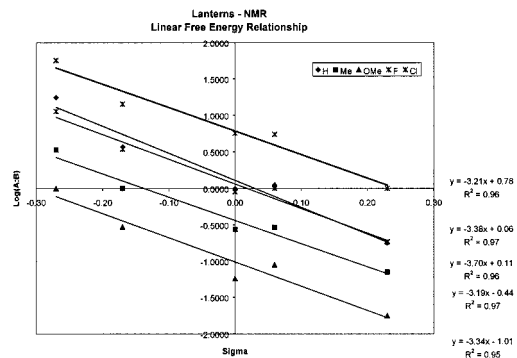
PS Resin in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	0.78	10.73	0.07	13.76	-1.14	1.14
2	H	Me	7.88	25.95	0.30	3.29	-0.52	0.52
3	H	F	44.49	47.61	0.93	1.07	-0.03	0.03
4	H	Cl	161.81	32.32	5.01	0.20	0.70	-0.70
5	OMe	Me	34.60	9.75	3.55	0.28	0.55	-0.55
6	OMe	F	72.79	6.11	11.91	0.08	1.08	-1.08
7	OMe	Cl	27.17	0.41	66.27	0.02	1.82	-1.82
8	Me	F	137.33	42.28	3.25	0.31	0.51	-0.51
9	Me	Cl	16.54	0.90	18.38	0.05	1.26	-1.26
10	F	Cl	50.16	8.58	5.85	0.17	0.77	-0.77



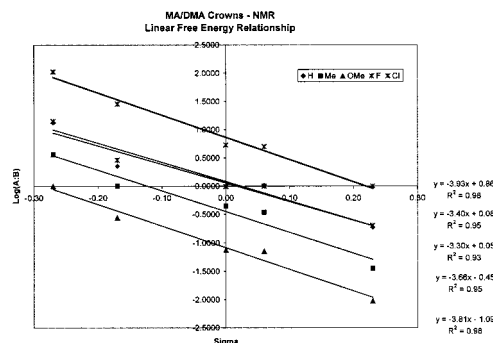
PS Lanterns in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	8.12	141.19	0.06	17.39	-1.24	1.24
2	H	Me	34.52	127.14	0.27	3.68	-0.57	0.57
3	H	F	38.14	42.57	0.90	1.12	-0.05	0.05
4	H	Cl	24.88	4.38	5.68	0.18	0.75	-0.75
5	OMe	Me	6.93	2.06	3.36	0.30	0.53	-0.53
6	OMe	F	556.21	49.48	11.24	0.09	1.05	-1.05
7	OMe	Cl	90.15	1.59	56.70	0.02	1.75	-1.75
8	Me	F	242.65	70.94	3.42	0.29	0.53	-0.53
9	Me	Cl	115.90	8.16	14.20	0.07	1.15	-1.15
10	F	Cl	92.06	16.94	5.43	0.18	0.74	-0.74



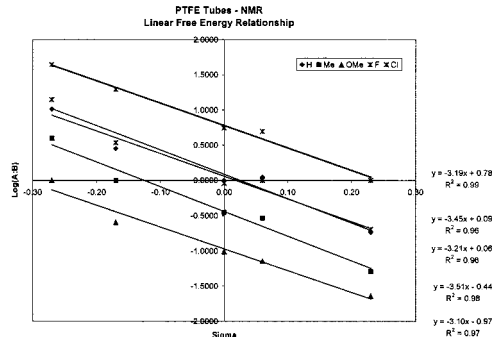
MA/DMA Crowns in 1:1 DMF:Pyridine – Run 1

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	1.16	15.47	0.07	13.34	-1.13	1.13
2	H	Me	0.16	0.36	0.44	2.25	-0.35	0.35
3	H	F	16.49	16.73	0.99	1.01	-0.01	0.01
4	H	Cl	4.79	0.90	5.32	0.19	0.73	-0.73
5	OMe	Me	19.47	5.41	3.60	0.28	0.56	-0.56
6	OMe	F	5.66	0.40	14.15	0.07	1.15	-1.15
7	OMe	Cl	75.35	0.71	106.13	0.01	2.03	-2.03
8	Me	F	2.31	0.80	2.89	0.35	0.46	-0.46
9	Me	Cl	5.40	0.19	28.42	0.04	1.45	-1.45
10	F	Cl	4.11	0.82	5.01	0.20	0.70	-0.70



PTFE Tubes in 1:1 DMF:Pyridine – Run 1

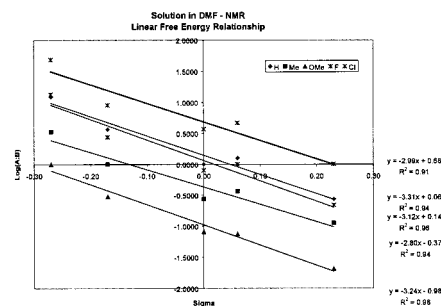
Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	15.75	161.41	0.10	10.25	-1.01	1.01
2	H	Me	75.04	211.27	0.36	2.82	-0.45	0.45
3	H	F	24.30	26.84	0.91	1.10	-0.04	0.04
4	H	Cl	144.59	26.30	5.50	0.18	0.74	-0.74
5	OMe	Me	35.37	9.03	3.92	0.26	0.59	-0.59
6	OMe	F	937.62	66.94	14.01	0.07	1.15	-1.15
7	OMe	Cl	13.61	0.31	43.90	0.02	1.64	-1.64
8	Me	F	1055.93	309.02	3.42	0.29	0.53	-0.53
9	Me	Cl	3398.20	173.75	19.56	0.05	1.29	-1.29
10	F	Cl	43.77	8.88	4.93	0.20	0.69	-0.69



General Procedure for the Solution Phase Competition Experiments. Ten vials were prepared, each containing 2 mL of a 0.5 M solution of two substituted anilines. The two anilines in each vial were as follows: (1) aniline and *p*-methoxyaniline, (2) aniline and *p*-methylaniline, (3) aniline and *p*-fluoroaniline, (4) aniline and *p*-chloroaniline, (5) *p*-methoxyaniline and *p*-methylaniline, (6) *p*-methoxyaniline and *p*-fluoroaniline, (7) *p*-methoxyaniline and *p*-chloroaniline, (8) *p*-methylaniline and *p*-fluoroaniline, (9) *p*-methylaniline and *p*-fluoroaniline, and (10) *p*-fluoroaniline and *p*-chloroaniline. Ten milligrams of pfp-ester (prepared as described in Method A) was then added to each vial and the vial was shaken for 24 h. Concentration in vacuo yielded a mixture of two amide products contaminated with excess anilines. The mixture was dissolved in DMF and passed over Dowex 50-W acidic ion exchange resin. Concentration in vacuo yielded the amide mixture. The mixture was analyzed by ¹H NMR with DMFu internal standard at 5.0 mM concentration. Ratios of the two products were determined by integration of the relative peaks. The ratios were tabulated and used to construct Hammett plots. Following are the ratios determined for each experiment and the associated Hammett plot.

Solution Phase in 1:1 DMF:Pyridine

Vial	A	B	A area	B Area	Ratio A/B	Ratio B/A	Log A/B	Log B/A
1	H	OMe	3.26	40.27	0.08	12.35	-1.09	1.09
2	H	Me	146.26	536.64	0.27	3.67	-0.56	0.56
3	H	F	5.60	7.05	0.79	1.26	-0.10	0.10
4	H	Cl	22.60	6.13	3.69	0.27	0.57	-0.57
5	OMe	Me	1.31	0.39	3.36	0.30	0.53	-0.53
6	OMe	F	374.45	27.95	13.40	0.07	1.13	-1.13
7	OMe	Cl	236.54	4.91	48.18	0.02	1.68	-1.68
8	Me	F	12.52	4.54	2.76	0.36	0.44	-0.44
9	Me	Cl	7.75	0.86	9.01	0.11	0.95	-0.95
10	F	Cl	70.78	15.21	4.65	0.21	0.67	-0.67



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Supporting Information Available: Raw data (tables of product ratios and Hammett plots) for the second and third sets of competition experiments conducted in 1:1 DMF/pyridine, and both sets of competition experiments conducted in 1:1 CH₂Cl₂/pyridine (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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