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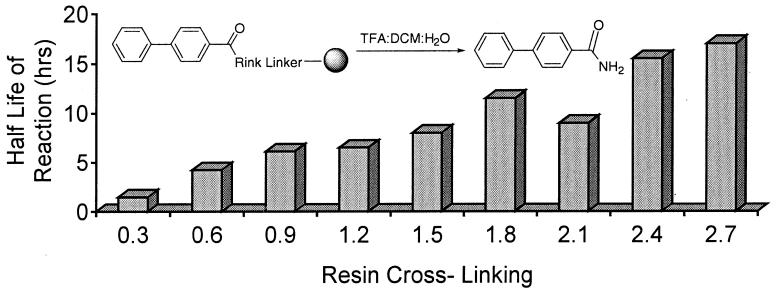

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Articles

Influence of Resin Cross-Linking on Solid-Phase Chemistry

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A range of PS-DVB resins were prepared by suspension polymerization with styrene, *p*-chloromethyl styrene, and DVB. Yields of polymerization increased (from 40% to almost 80%) with increasing cross-linking. The beads exhibited the expected swelling characteristics, with the 0.3% resin swelling to almost 9 times its dry volume in $CHCl_3$. Kinetics of cleavage of the dye Methyl Red from the range of Rink linked resins showed rate enhancements of up to 500% between the 6.0 and the 0.3% cross-linked resins. Total synthesis of Kawaguchipeptin B was carried out on the resins, and their performance during the syntheses was investigated. Contrary to expectations, the purities of the cyclic peptide product increased with increasing resin cross-linking doubling from the 0.3−6.0% resin. A Suzuki reaction showed the half-lives of reaction increased with increasing resin cross-linking with an 11-fold increase in half-life between the 0.3−2.7% resin. Surprisingly, we observed very little reaction in the case of the 3.0 and 6.0% cross-linked resins.

Introduction

Although solid-phase chemistry has over the past decade seen a dramatic increase in activity and application,[1a−e] attention has been focused almost exclusively on traditional 1−2% divinyl benzene (DVB) polystyrene cross-linked supports.[2] Considering the limitations of these materials, including the necessity of extensive washings throughout the synthesis, and other handling issues, we decided to investigate in a systematic manner a wider range of other DVB cross-linked solid supports (0.3−6.0%). We were aware of other studies, certainly in the early days of solid-phase peptide synthesis (SPPS), looking at a limited range of solid supports.[3] However, chemistries in relation to small organic molecule synthesis[4] are fundamentally different to the demands of peptide synthesis, especially with regard to the overall sizes of the compounds being prepared. In this paper we sought to define the relationship between cross-linking in a polymeric support and its overall effect on selected chemical reactions.

The chemistries we investigated involved the preparation of the natural product Kawaguchipeptin B, [5,6] an 11-mer cyclic peptide, as well as a Suzuki coupling reaction and the release under acidic conditions of a range of compounds from a linker bound to the resin.

Results and Discussion

Initial studies involved the preparation of 11 different polystyrene (PS)-DVB cross-linked resins from 0.3 to 6.0% DVB by traditional suspension polymerization methods[7a−d] and loaded with chloromethyl sites by the incorporation of 4-chloromethylstyrene (CMS) in the suspension polymerization mixture. There are a number of variables which must be considered when altering the cross-linking ratios; thus the relative amounts of styrene, DVB, and CMS and their relative incorporation ratios all needed to be taken into account during the synthesis. In our case, the incorporation of CMS used in the polymerization mixtures was such as to give a real loading of 0.5 mmol/g. A typical protocol used styrene and DVB (see Experimental Section), CMS (2.4 mL), poly vinyl alcohol (PVA) (2.5 g, 87−89% hydrolyzed, Mr 85−150 kDa), and benzoyl peroxide (0.25 g) suspended in water (1000 mL) and stirred for 6 h at 80 °C.

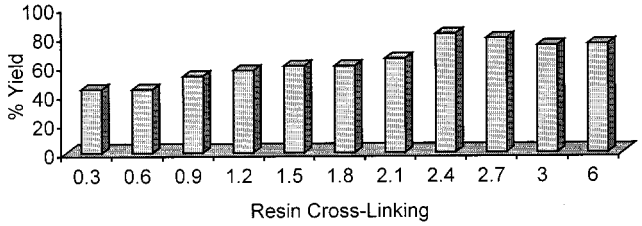

Figure 1. Relationship between the crude yield of the polymerization reaction and cross-linking of the solid support.

It was observed that the crude yield of the polymerization was dependent on the amount of cross-linking agent added to the reaction (Figure 1).

The yields of synthesis increased with increasing cross-linking ratio, with the 0.3% resin giving a yield of only 42% whereas the 2.1−6% resins consistently yielded almost 80%. Since increasing cross-linking confers upon a growing

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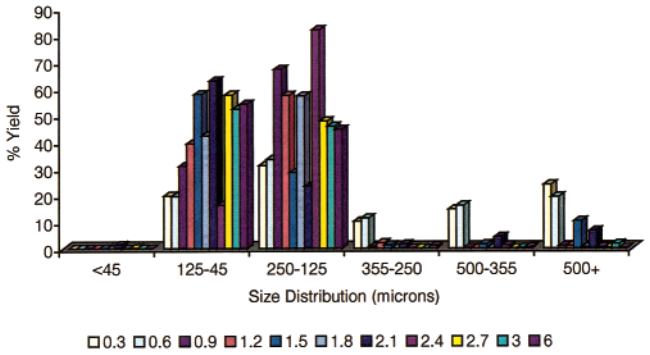


Figure 2. Size distribution of the 0.3−6.0% cross-linked beads following suspension polymerization.

polymer increasing insolubility in the medium, it follows that a higher proportion of soluble polymer will remain in the cases of the lowest cross-linked resins, and given the fact that these will be washed out of the resins by the workup procedure, the yields of reaction will increase with increasing resin cross-linking. In all cases, the size distribution of the beads used in synthesis was carefully controlled by stirring, and the beads were sieved to give the distribution shown in Figure 2. The polymerizations were optimized to produce beads of predominately 45−250 μm in diameter by alteration of the stirring speed during the preheat equilibration phase of the polymerization cycle (see Experimental Section). Of these beads the 45−125 μm beads were used in the subsequent studies.

Swelling studies[8] were carried out on each of 11 different DVB cross-linked polystyrene resins, and the data are shown in Figure 3. The trends were as expected, with the 0.3% cross-linked material swelling by up to 9 times its volume in $CHCl_3$. This material was quite prone to deformation but its swelling properties were remarkable, the beads becoming almost transparent once solvated. The 6.0% beads, once swollen, retained their spherical opaque character. The trends were uniform across the series, with the lower cross-linked materials swelling to a greater proportion than the more highly cross-linked resins.

Cleavage of Methyl Red from the Resins. The resins were all converted to the aminomethyl resins **(1)** and loaded

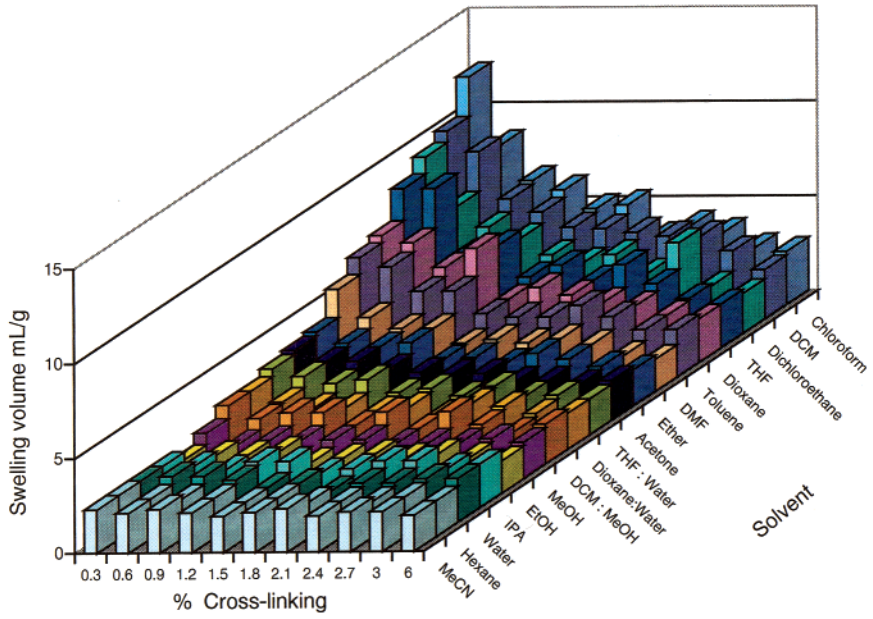
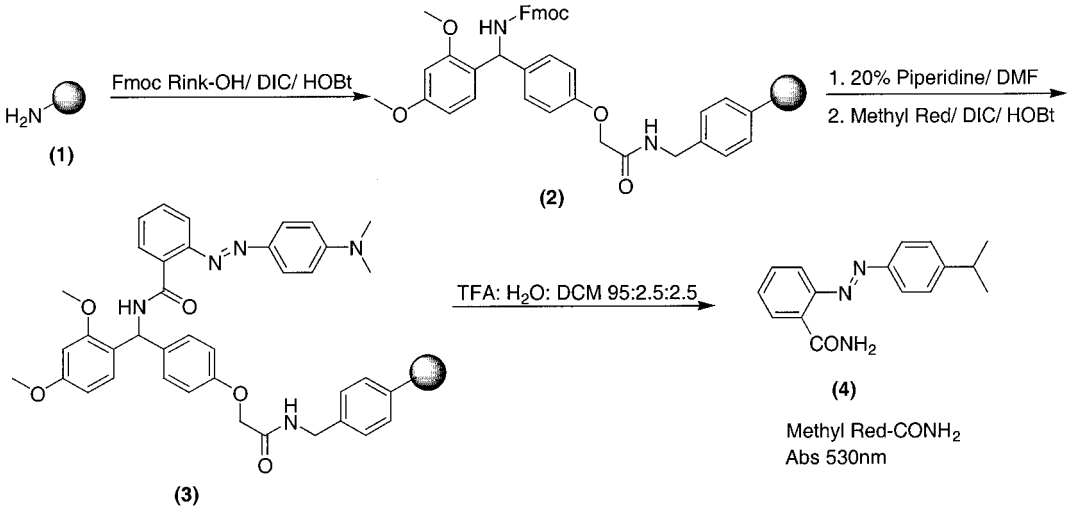


Figure 3. Swelling of 0.3−6.0% DVB cross-linked PS resins in a number of different solvents.

Scheme 1. [2-[4-(Dimethylamino)phenyl-azo]benzoic Acid] Loading and Subsequent Cleavage



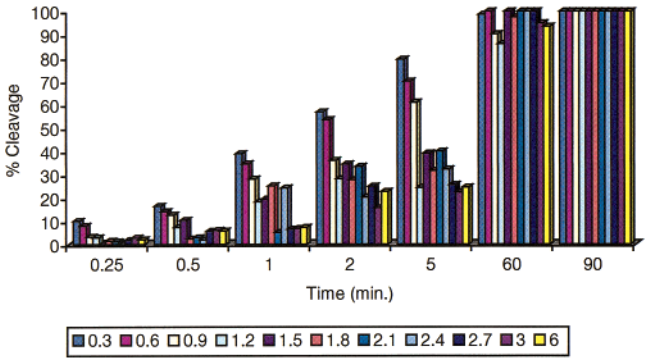


Figure 4. The effect of time on percent cleavage of Methyl Red carboxamide from the different cross-linked resins.

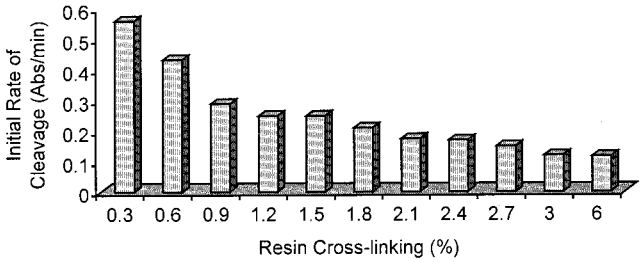


Figure 5. Initial rate of Methyl Red carboxamide cleavage reaction vs resin cross-linking.

with the Fmoc-Rink linker **(2)**.[9] The Fmoc group was removed, and the beads were coupled to the dye Methyl Red ([2-[4-(dimethylamino)phenyl-azo]benzoic acid]), to give **3** (Scheme 1).

The rate of release of the dye from **4** was measured by UV−vis spectroscopy following cleavage using a solution of TFA:H_2O:DCM (95:2.5:2.5) by periodically sampling aliquots of cleavage solution. The variation in cleavage rates between the 0.3% and 6.0% DVB beads was dramatic (Figure 4). Upon addition of the cleavage solution to the 0.3% resin, the beads and solvent turned, almost immediately, to a pink color, which darkened with time to full red (λ_{max} = 530 nm). In contrast, with the 6.0% resin the same overall color transitions were observed but over a much greater time scale.

By interpolation to time = 0 and differentiation it was observed that the initial rate of release of the dye from the 0.3% cross-linked resin was over 5 times that of the 6.0% cross-linked resin (Figure 5), indicating the ease of diffusion of the cleavage solution and dye in and out of the beads. Since each resin sample gave rise to the same maximal absorbance in the cleavage solution (also indicative of consistent loadings), this indicates that the dramatic variation in diffusion of cleavage solution and dye in to and out of the beads is totally based on the cross-linking of the polystyrene matrixes.

Synthesis of Kawaguchipeptin B on the Solid Support. Kawaguchipeptin B (**7**) was synthesized on the range of aminomethyl resins as shown in Scheme 2.

The dipeptide Fmoc-Asp-Gly-OAllyl[11] was attached to each PS solid support to give **5**, which allowed synthesis of a linear precursor of the peptide **6** by standard DIC/HOBt chemistry. Couplings were monitored by the ninhydrin test,[12] with a double coupling only required for the first tryptophan

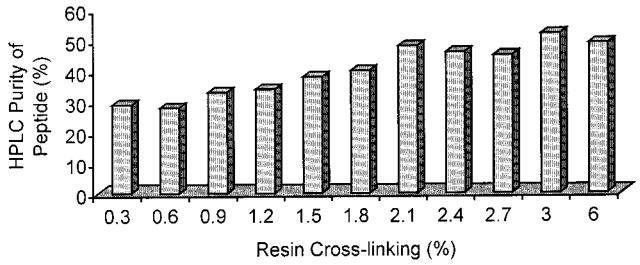


Figure 6. Purity of Kawaguchipeptin B synthesized on various cross-linked resins (HPLC analysis).

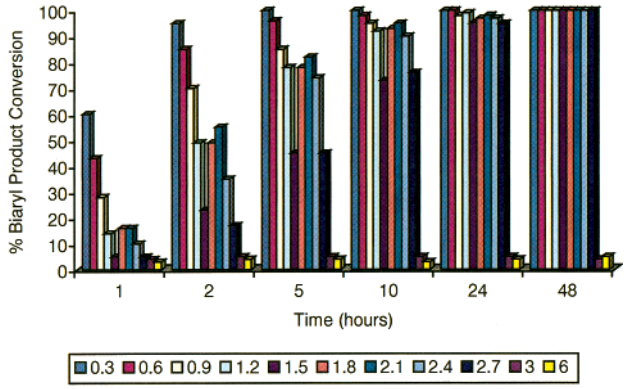


Figure 7. Suzuki reaction between phenyl boronic acid and the resin loaded 4-iodobenzoic acid.

residue. Palladium catalyzed deprotection[13] of the *C*-terminal glycine allyl protecting group and subsequent removal of the *N*-terminal Fmoc group was then effected on each resin. Finally a DIC/HOBt coupling was carried out to promote cyclization of the resin bound linear peptide to give Kawaguchipeptin B (**7**).[14]

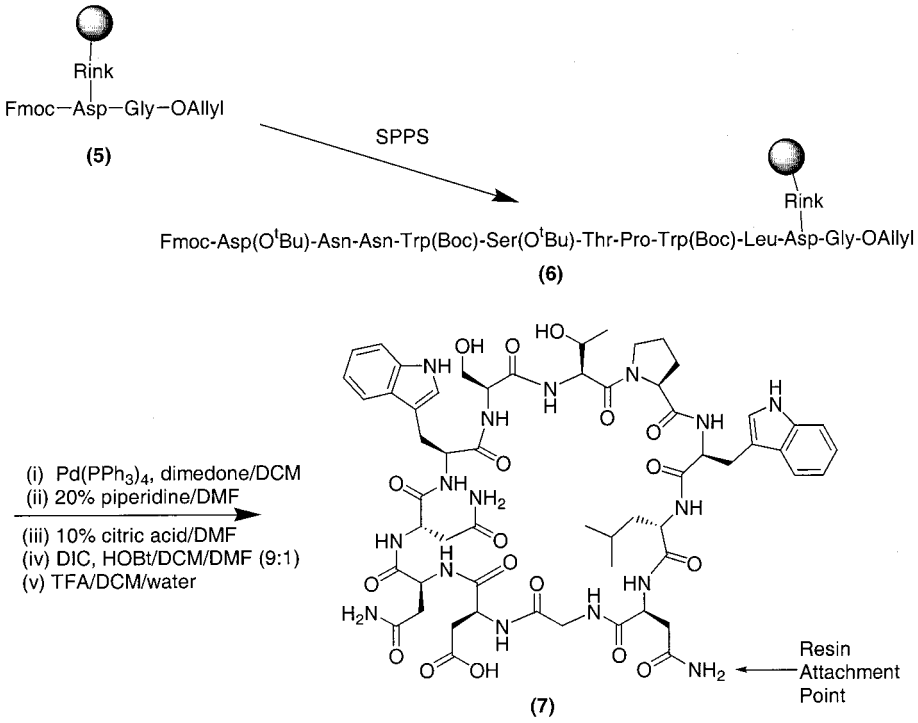
Cleavage from the resins was achieved with a solution of TFA/H_2O/DCM (95:2.5:2.5), and the peptide was purified by RP-HPLC and fully characterized by mass spectrometry (MS) and extensive NMR studies. The efficiency of the synthesis of the linear form of Kawaguchipeptin B showed a trend of increasing purity with increasing resin cross-linking. For the cyclization reaction, an improvement with increasing resin cross-linking was also observed, from 28% purity for the 0.3% resin to over 50% for the higher cross-linked materials (Figure 6). This may reflect the greater reactivity and accessibility of sites on the lower cross-linked PS resins, thereby allowing more side reactions to take place, or it might be a measure of increased site−site interactions, due to the increased site mobility.

Suzuki Reaction on the Resins. Each of the cross-linked resins were loaded with the Fmoc-Rink amide linker and then Fmoc deprotected. 4-Iodobenzoic acid was coupled to each resin by DIC/HOBt mediated coupling to give **8**, and a Suzuki[15] reaction with phenyl boronic acid (Scheme 3) generated the resin bound biaryl species (**9**).

An aliquot of each resin (10 mg) was removed from the reaction mixture at various times and cleaved with a solution of TFA:H_2O:DCM (95:2.5:2.5). The amount of product (**10**) formed with time was determined (Figure 7) by RP-HPLC analysis.

The initial rates of reaction on the cross-linked resins demonstrated a trend of decreasing initial rate with increasing

Scheme 2. Synthesis of Kawaguchipeptin B



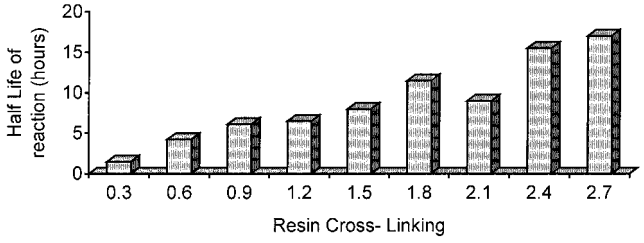
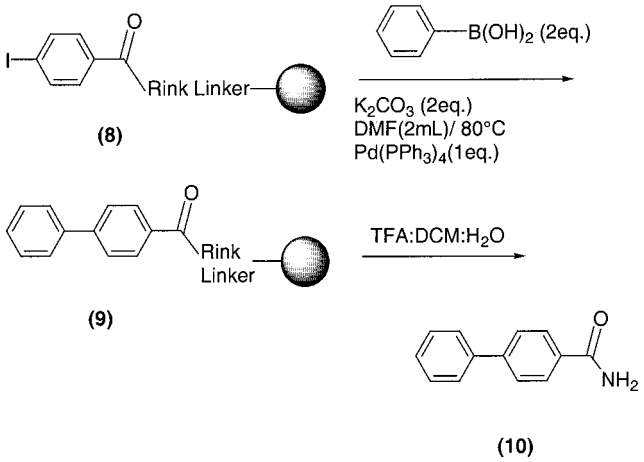


Figure 8. Half-life of Suzuki reaction of phenyl boronic acid and Rink loaded 4-iodobenzoic acid on the nine cross-linked resins.

Scheme 3. Suzuki Reaction of Each of the Different Cross-linked Resins



resin cross-linking. The initial rate of biaryl coupling with the 0.3% cross-linked resin was 47 times that of the 6.0% cross-linked resin, representing the accessibility of reactants to the polymeric matrix in a manner that parallels the Methyl Red cleavage.

The half-lives for the Suzuki reactions on the resins were calculated (Figure 8). In the extreme case, the reaction using the 0.3% resin was 50% complete after the first hour of reaction at 80 °C. The corresponding reaction with the 2.7% resin showed only a 6% conversion to product after 1 h. Complete conversion to product (**10**) was demonstrated in almost all the resins (0.3−2.7%) after 48 h.

The 3.0% and 6.0% resins displayed unusual behavior (Figure 7). The reaction yield for these resins was between 3 and 5%. No other products were observed, and the starting materials were still present after 48 h. The 3−5% yields obtained by the higher cross-linked resins could be attributed to reaction almost solely at the surface of the bead. With the beads used in the synthesis, this would correspond to reaction to a depth of 1.25 μm. This effect is believed to be due to restricted site accessibility to Pd(PPh$_3$)$_4$ in these relatively highly cross-linked resins in the solvent used for the Suzuki reaction since the same catalyst penetrated the resins successfully during the allyl deprotection step of the Kawaguchipeptin B synthesis (Scheme 2) in DCM:THF (1:1) to effect complete deprotection of the allyl group, although little is known about the exact nature of the active transition states in the catalytic cycle of the Pd(PPh$_3$)$_4$ catalyst in the Suzuki reaction.[16] Thus, the Suzuki reactions (for 48 h at 40 °C) were repeated on the higher cross-linked resins in the original solvent (DMF) as well as DCM:THF (1:1), dioxane, and MeOH to highlight the importance of resin swelling in this reaction. The reaction was observed to proceed to completion in the case of the DCM:THF and dioxane solvents. The reaction proceeded to 5% in the case of the DMF and only 1.6% in the case of the MeOH solvent system. Clearly solvent choice is dramatic, with a huge change in going from DMF to DCM:THF, in terms of resin accessibility, although both of these solvents tend to be used interchangeably in solid-phase synthesis.

Conclusions

In conclusion, we have synthesized a range of DVB cross-linked PS beads and investigated their physical and chemical properties in a number of reactions. We have shown that the choice of optimal resin for chemical synthesis depends greatly upon the chemistries that are to be carried out on them. Surprisingly, we found that during peptide synthesis a higher cross-linked resin gave higher yields and fewer byproducts. As expected, kinetic studies showed that diffusion into the polymeric matrix can become rate limiting with the higher cross-linked materials, with appreciably lower rates of cleavage demonstrated for the 3.0% and 6.0% resins compared with the chemically more accessible 0.3% resin, although solvent choice was also very important. The Pd-$(PPh_3)_4$ catalyzed Suzuki reaction in DMF showed that increasing resin cross-linking caused the rate of reaction to fall until a critical point was reached. After this point the only reaction that occurred seemed to correspond to reaction at the surface of the beads. However these studies also showed the crucial effect of solvent variation. Thus although the Suzuki reaction failed in DMF with the more highly cross-linked resins, in DCM/THF all the resins studied gave complete conversion. Considering the widespread manner in which these solvents are used in solid-phase synthesis, this is an important observation to bear in mind when carrying out synthesis. These studies also demonstrate the dramatic differences in kinetics between the 0.9% and the 2.1% resins. Since 1% and 2% cross-linked resins are the most widely used materials in solid-phase organic synthesis, it suggests that care should always be taken when choosing a specific resin for synthesis.

Experimental Section

General. Analysis was carried out on a HP Chem Station 1100, with a 150 mm × 3 mm reverse-phase C_{18} column. Polymeric beads were sieved using a Reutsch Sieving Unit, with Endcotte Stainless Steel Sieves, sizes 500−355 μm, 355−250 μm, 250−125 μm, 125−45 μm, and <45 μm. An anchor shaped stirrer was used during the suspension polymerizations, inserted 2.5 cm below the surface of the aqueous phase. All Fmoc amino acids used in this study were purchased from Calbiochem-Novabiochem UK. Ltd. and were used as supplied. Styrene, divinylbenzene (DVB), benzoyl peroxide (BPO), PVA, 4-iodobenzoic acid, phenyl boronic acid, and Methyl Red dye were purchased from Aldrich Chemical Co. DVB was purified by distillation before use.

Suspension Polymerization. Premixed organic phase (Table 1) was added to the aqueous phase (2.5 g of PVA (87−89% hydrolyzed, Mr 85−150 kDa), 1000 mL H_2O, 60 °C, N_2 degassed for 30 min) while stirring (in a 2.5 L "goldfish bowl"). The suspension was allowed to equilibrate for 25 min, and the temperature raised to 90 °C for 6 h. The heat was removed and the suspension poured into ice and stirred slowly in an open atmosphere for 16 h. The beaded resin product was filtered (polypropylene filter sheeting), washed (H_2O, 10 L, THF:H_2O, 3 L; THF, 1 L; Et_2O, 0.5 L; MeOH, 0.5 L; Et_2O, 0.5 L), and dried in vacuo. The beads were then sieved.

Table 1. Stoichiometry of the Premixed Organic Phase in the Suspension Polymerization Series

resin cross-linking	styrene (mmol)	divinyl benzene (mmol)	vinyl benzyl chloride (mmol)
0.3	128.6	0.4	17.1
0.6	128.1	0.9	17.1
0.9	127.7	1.3	17.1
1.2	127.3	1.8	17.1
1.5	126.8	2.2	17.1
1.8	126.4	2.6	17.1
2.1	126.0	3.1	17.1
2.4	125.5	3.5	17.1
2.7	125.0	4.0	17.1
3.0	124.6	4.8	17.1
6.0	120.3	8.8	17.1

Resin Swelling Experiments. Swelling experiments were conducted by the addition of solvent to 100 mg of resin in polypropylene tubes, mechanical agitation to remove trapped bubbles, solvent removal in vacuo, and reequilibration for 15 min with mechanical agitation. The solvent was removed by gravity with agitation of the tubes and also by compression of a syringe barrel until the resin posed a resistance to the compression. Both methods gave identical results at higher cross-linking, but the lowest cross-linked resins were found to be very compressible once swollen. The resin was then washed (DCM × 3 bed volumes, removed in vacuo; and Et_2O, removed in vacuo), followed by the addition of the new solvent.

Synthesis of Aminomethyl Resin Beads.[10] To each resin (1 g, 0.5 mmol) were added DMF (50 mL), dioxane (10 mL), and potassium phthalimide (1 g, 5 mmol), and the resulting suspension was heated at reflux for 8 h. The resins were washed (hot H_2O, 50 mL, hot DMF, 50 mL, DMF:H_2O (1:1), 50 mL, DCM, 30 mL) and dried in vacuo. The resin (1 g, 0.5 mmol) was added to EtOH (50 mL) and hydrazine hydrate ($N_2H_4 \cdot H_2O$) (1 mL), and the suspension was heated at reflux for 8 h. The resin was washed as described above and dried in vacuo.

Quantitative ninhydrin tests were carried out after coupling using DIC (2 equiv) and HOBt (catalytic, 5 mg) and *N*-deprotection of Fmoc-Gly-OH on each of the resins: 0.3% (0.47 mmol/g), 0.6% (0.50 mmol/g), 0.9% (0.52 mmol/g), 1.2% (0.51 mmol/g), 1.5% (0.47 mmol/g), 1.8% (0.46 mmol/g), 2.1% (0.52 mmol/g), 2.4% (0.51 mmol/g), 2.7% (0.47 mmol/g), 3.0% (0.48 mmol/g), and 6.0% (0.52 mmol/g).

Cleavage of Methyl Red. The aminomethyl resins (100 mg, 0.05 mmol) were swollen in DCM. Fmoc Rink linker (4-[(*R*,*S*)-α-[1-(9*H*-fluoren-9-yl)-methoxyformido]-2,4-dimethoxybenzyl]-phenoxyacetic acid) (53.6 mg, 0.1 mmol) was dissolved in DCM:DMF (9:1, 3 mL), and HOBt (5 mg) and DIC (12 mg, 0.1 mmol) were added. The solution was allowed to stand for 20 min, the aminomethyl resin slurry was added, and the reaction mixture was shaken for 4 h. The resin was washed (DCM, DMF, Et_2O) and dried in vacuo. The Fmoc Rink linker was deprotected by treatment of each resin with 20% piperidine/DMF solution (5 mL, 2 × 3 min treatments), and each of the resins was washed and dried as described above. Methyl Red ([2-[4-(dimethylamino)phenyl-azo]benzoic acid]) (10 equiv) was dissolved in DCM:DMF (9:1, 3 mL), and DIC (10 equiv) and HOBt (10

Table 2. Effect of Time on Percent Cleavage of Methyl Red Carboxamide from the Different Cross-Linked Resins

	resin cross-linking										
time (min)	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3.0	6.0
0	0	0	0	0	0	0	0	0	0	0	0
0.25	10.1	8.0	3.3	3.0	0	1.5	1.2	0	1.9	2.8	2.1
0.5	16.5	14.2	12.7	7.4	10.4	2.4	2.9	2.0	5.7	6.1	5.8
1.0	38.9	34.6	28.1	18.4	19.5	25.2	5.2	24.3	6.6	6.9	7.3
2.0	56.8	53.5	36.1	28.2	34.5	27.8	33.5	20.4	25	15.7	22.8
5.0	79.4	70.0	61.0	24.5	39.1	31.7	40.0	32.3	25.7	22.5	24.6
60	98.7	100	90.3	86.1	100.0	97.5	100	100	100	94.9	93.5
90	100	100	100	100	100.0	100	100	100	100	100	100

mg) were added. The solution was allowed to stand for 20 min, and then the swollen aminomethyl resins were added to each solution. The reaction was shaken for 16 h, and the resin was filtered, washed, and dried as described above. Methyl Red-Rink loaded resin (10 mg, 3.7 mmol) was treated with TFA/H_2O/DCM (95:2.5:2.5, 1 mL) with agitation. At 15 s, 30 s, 1 min, 2 min, 5 min, 15 min, 30 min, 60 min, and 210 min, 2 μL aliquots (accurate Gilson pipet P20) were withdrawn from each experiment and diluted to 1 mL with DCM. The absorbance of each aliquot (λ = 530 nm) was measured (normalized in Table 2). UV γ_{max}: 530 nm. TLC (EtOAc) R_f 0.37. ES-MS: 269.3 ($(M + H^+)^+$), 559.4 ($(2M + H^+)^+$). ^{1}H NMR (MeOH-d_4): δ 3.00 (s, 6H), 6.8 (d, J = 9.0 Hz, 2H), 7.3 (td, J = 7.5 Hz, 1.0 Hz, 1H), 7.4 (td, J = 7.5, 1.0, 1H), 7.7 (dd, J = 8 Hz, 1.5 Hz, 1H), 7.7 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.8 (d, J = 9.0 Hz, 2H). ^{13}C NMR (MeOH-d_4): δ 40.6, 110.5, 114.6, 124.2, 128.0, 128.3, 129.6, 132.2, 141.7, 148.3, 151.8, 167.1.

Kawaguchipeptin B Synthesis.[14] To 1 g (0.5 mmol) of each cross-linked aminomethyl resin was added a premixed suspension of DCM:DMF (9:1, 10 mL) and Fmoc-Rink linker (4-[(*R*,*S*)-α-[1-(9*H*-fluoren-9-yl)-methoxyformido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (540 mg, 1 mmol), DIC (1,3-di-isopropylcarbodiimide) (126 mg, 1 mmol), and HOBt (1-hydroxybenzotriazole) (20 mg). The resulting resin suspension was shaken for 3 h. Coupling completion was monitored by the classical ninhydrin test. The resins were each deprotected with 20% piperidine/DMF, 5 mL for 3 min and then again for 1 min, and washed with DCM (10 bed volumes), DMF (3 bed volumes), DCM (10 bed volumes), and dried in vacuo.

Fmoc Asp(O^{t}Bu)-Gly-Allyl (509 mg, 1 mmol) was added to DCM:DMF (9:1) (10 mL), DIC (126 mg, 1 mmol), and HOBt (20 mg) and allowed to stand for 20 min. The resulting suspension was added to each resin and shaken for 3 h until the resin was negative by the ninhydrin test.

General Procedure for Peptide Synthesis. To each resin (1 g, 0.5 mmol) was added a solution of Fmoc-AA-OH (side chain protected as shown below), DCM:DMF (9:1, 10 mL), DIC (126 mg, 1 mmol), and HOBt (20 mg), and the solution was shaken for 3 h and monitored for a negative ninhydrin test.[12] The coupling was repeated in only one case, the first Fmoc-Trp(Boc)-OH residue. After successful coupling, the resin was washed and Fmoc deprotected as described above. (Amino acids used: Fmoc-Leu-OH, Fmoc-Trp(Boc)-OH, Fmoc-Pro-OH, Fmoc-Thr(O^{t}Bu)-OH, Fmoc-Ser(O^{t}Bu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Asn-OH, Fmoc-Asn-OH, Fmoc-Asp(O^{t}Bu)-OH.) The C-terminal glycine allyl group was deprotected by treatment of the resin (1 g, 0.5 mmol) with DCM (5 mL), THF (5 mL), dimedone (70 mg, 0.5 mmol), and $Pd(PPh_3)_4$ (614 mg, 0.5 mmol) under N_2 for 16 h. The N-terminal Fmoc group was removed as described above, and the resins were washed with 10% citric acid. DIC/HOBt cyclization was then effected as described above, and the cyclized peptide was deprotected and cleaved from the resin with TFA:H_2O:DCM (95:2.5:2.5) before analysis by HPLC, ES-MS, and NMR.

^{1}H NMR assignment verified by TOCSY and NOESY, recorded on a 500 MHz spectrometer at 298 K in DMSO-d_6 (NH, CH_α, CH_β, other): Trp(I) 7.407, 4.415, 3.157; 2.914, 10.827 (indole NH), 7.556, 6.976, 7.304, 7.049 (Ar-H). Leu 7.798, 4.262; 4.262, 0.845, 1.545; 1.484; 1.425. Asn(I) 8.266, 4.627, 2.559; 2.455, 7.465; 7.28 ($CONH_2$). Gly 8.285, 3.817; 3.67. Asp 8.816, 4.555, 2.779; 2.481. Asn(II) 7.908, 4.293, 2.851; 2.401, 7.495; 7.122 ($CONH_2$). Asn(III) 7.897, 4.494, 2.638; 1.847, 7.579; 7.112 ($CONH_2$). Trp(II) 8.538, 4.318, 3.307; 2.925, 7.485 (CH_γ), 10.597 (indole NH), 7.099; 6.965; 7.304; 7.051 (Ar-H). Ser 8.091, 4.338, 3.7. Thr 7.331, 4.603, 3.938, 0.971 (CH_γ). Pro 4.294, 3.517 (CH_δ), 1.352; 1.628; 1.866; 1.523. ES-MS: 1284.7 ($(M + H)^+$), 1306.6 ($(M + Na)^+$), 1322.6 ($(M + K)^+$). HPLC gradient 0−50% MeCN over 70 min, R_T 58.2 min.

Suzuki Reaction on the Different Cross-Linked Resins. Each resin (0.3%, 0.6%, 0.9%, 1.2%, 1.5%, 1.8%, 2.1%, 2.4%, 2.7%, 3.0%, and 6.0%, 100 mg, 0.05 mmol $-NH_2$) was suspended in DMF (1.5 mL) and treated with K_2CO_3 (0.1 mmol, 13.8 mg), $PhB(OH)_2$ (phenyl boronic acid) (0.1 mmol, 12.1 mg), and $Pd(PPh_3)_4$ (0.05 mmol, 61.2 mg) (added by way of one 0.5 mL aliquot of stock solution of 1.34 g of catalyst in 11 mL of DMF per tube). The resulting suspension was heated at 80 °C, and 5 mg aliquots of resin was removed from the suspension at various time intervals. The resin was then cleaved with TFA/H_2O/DCM (95:2.5:2.5) and analyzed by HPLC and ES-MS. HPLC gradient 20−100% MeCN in 9 min, 4-iodobenzoic acid (7.4 min), 4-phenylbenzoic carboxamide (8.6 min). ^{1}H NMR (MeOH-d_4) δ 7.26 (t, J = 7.0 Hz, 1H), 7.34 (t, J = 7.0 Hz, 2H), 7.54 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 7.0 Hz, 2H). ^{13}C NMR (MeOH-d_4) δ 128.4, 128.5, 129.4, 129.6, 130.3, 142.5, 146.4, 169.5. TLC (EtOAc): R_f 0.36.

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