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Improved reproducibility of chemical reactions on purified polystyrene resins monitored by ^{31}P MAS NMR

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Abstract—The use of polystyrene beads from different origins in solid-phase organic synthesis was investigated after a simple cleaning procedure of the starting material. The swelling and thermogravimetric properties and the reproducibility of a five-step reaction cascade were investigated. The resin loadings of polystyrene bound phosphines were quantitatively determined by ^{31}P MAS NMR via addition of triphenyl phosphate as reference compound and the loadings of intermediate products were evaluated by Fmoc cleavage.

The nature of size, shape, and functional groups of resin beads can have significant effects on the reproducibility and yield of solid-phase organic reactions. These properties vary considerably within and among batches of commercially available resins and also depend on their production conditions.[1] Here we report on improved reproducibility of reactions carried out on polystyrene (PS) beads **1a**–**j** from various origins and of different bead sizes and degrees of cross-linking (Table 1). Resins of the suppliers Avecia (Manchester, UK), Biosearch Technologies (Novato, Cal), Health Biotech (China), Houzen (San Mateo, Cal), Nankai University (Tianjin, China), Penta Biotech (Foster City, Cal) and Polymer Laboratories (Church Stretton, UK) were investigated. Some of the resins (e.g. **1e**) were slightly yellow and amounts of up to 2 w% of solvents (THF,

Table 1. Yield after Soxhlet extractions, bead size given by the manufacturer and determined in this study, median, swelling property and glass transition temperature of the purified PS resins **1a**–**j**

Comp.	Yield after Soxhlet extractions [%]	Bead distribution supplier [mesh]	Bead distribution this study[a] [mesh]	Median[b] [μm]	Swelling in DCM [ml/g]	T_g [°C]
1a	93	70–90	60–90	197	5.2	110.6
1b	98	70–90	50–80	237	5.2	111.2
1c	94	50–100	50–90	212	6.2	109.6
1d	99	50–100	50–80	223	6.8	109.4
1e	94	100–200	70–170	139	6.3	109.4
1f	97	100–200	100–200	106	5.7	109.6
1g	97	100–200	100–200	107	5.8	109.7
1h	94	200–400	170–400	56	6.6	109.6
1i	93	200–400	150–325	75	6.1	109.4
1j[c]	99	100–200	110–230	99	4.0	111.7

[a] 86–94% of the PS beads comprised in this range.
[b] Diameter where 50% by volume of the beads is reached.
[c] 2% DVB, all other resins cross-linked with 1% DVB.

Keywords: NMR; MAS; quantitative; ^{31}P; phosphines; resin; loading; polystyrene.

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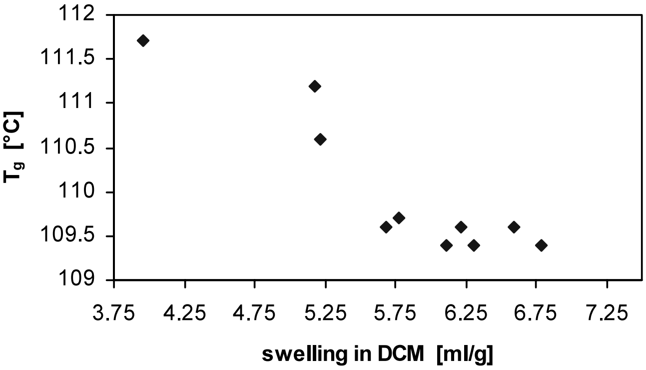
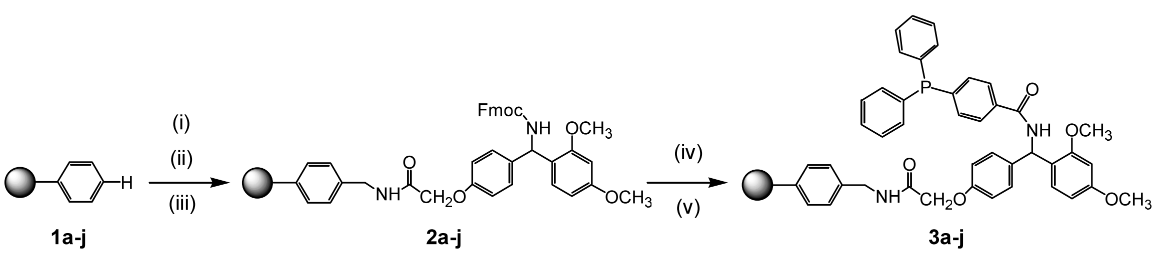


Figure 1. Graph of glass transitions (T_g) versus swelling properties of polystyrene resins in dichloromethane (DCM).

acetone) and traces of wetting agents from the suspension polymerization process (e.g. Triton X-100™) were detected in the ^{13}C MAS NMR spectra. All PS resins were purified by Soxhlet extraction using THF ($\approx$150 ml THF, 10 g PS beads, 5 h, approximately 30 distillation cycles). After removal of the solvent and washing twice with 30 ml of methanol, the shrunken PS beads were dried under vacuum overnight. The residual THF was removed by a second Soxhlet extraction step using methanol and the PS resins were dried under high vacuum to constant weight. The effectiveness of the cleaning steps was monitored by ^{1}H and ^{13}C MAS NMR. In addition to the monomer styrene and traces of wetting agents, considerable amounts of PS oligomers were observed in the ^{1}H NMR spectra of THF Soxhlet extracts after evaporation of the solvent. Gel permeation chromatographic analysis showed a surprisingly narrow molecular weight distribution of these oligomers. For example, $M_n = 15000$ g/mol, $M_w = 20800$ g/mol was found for **1i**, which corresponds to chain lengths of approximately 140–190 PS units. The yields after the cleaning steps are summarized in Table 1 together with physical data as bead size, swelling property and glass transition temperature.

The bead sizes were determined by the dynamic light scattering method on a Mastersizer X, Malvern Instruments, Worcestershire, UK. The PS beads (90–120 mg) were completely suspended in 150 ml water by addition of traces of the wetting agent Triton X-100™. The PS bead distributions evaluated in this study agree with the data given by the manufacturers, with some of the resins showing a trend to slightly increased bead sizes (Table 1). The uniformity of the bead size distribution of each sample was examined by comparison of the median diameter (value at which 50% by volume of the sample is reached) with the mean diameter at which 50% of the number of PS beads is taken into account. All ratios were between 0.98 and 1.02, confirming regular bead distributions. Reproducible data of swelling properties were obtained by using graduated glass columns and applying the following procedure: the dry volumes of the PS beads (1–2 g) were first determined in a column of 5.0 mm inner diameter, the beads were then transferred to a column of 10.0 mm inner diameter and the increase in volumes of the PS beads swollen in dichloromethane were determined after 1 h of equilibration time. No differences of swelling properties between untreated and Soxhlet extracted resins were observed. The glass transition temperatures of the dry PS beads were determined by temperature modulated differential scanning calorimetry (DSC) using a Du Pont-TA DSC 2910 equipment. The T_gs given in Table 1 are mean values of 2–5 measurements (with standard deviations of ±0.2°C). Linear PS samples without cross-linking (Mws of 2.57×10^6 and 0.98×10^6 g/mol) showed T_gs of 107.2 and 106.5°C. For **1j**, a resin cross-linked with 2% DVB (all other resins 1% DVB), an increased T_g was found (111.7°C) in accordance with Ref. 2. In Figure 1 a graph of the T_gs versus the swelling properties of the purified resins is shown. The data indicate a cross-linking >1% for **1a** and **1b**. Generally, the glass transitions for cleaned and dry PS beads were 1–2°C higher than for the starting materials contaminated with solvents.[2]

The purified polystyrenes **1a**–**j** were converted to the Fmoc-Rink amide AM resins **2a**–**j**,[3] followed by derivatization to the carboxy triphenylphosphines, as indicated in Scheme 1. The amount of *N*-(chloromethyl)-phthalimide used for the initial reaction step (i) allowed a maximal loading of 0.90 mmol/g for the Fmoc-Rink amide AM resins **2a**–**j**. The actual loadings of these derivatives were determined by Fmoc cleavage followed by quantitative UV detection. The mean value of 0.85±0.04 mmol/g observed for all purified resins (see Table 2) demonstrate the excellent reproducibility of the first reaction steps with overall yields of 90–98%. The use of not purified PS resins showed considerably decreased reactivity, e.g. for **1e** the isolated intermediate product after the conversion to the AM resin (steps i and ii, Scheme 1) still was light yellow with beads sticking together after the washing procedure. For **1e** and **1i**, both PS starting materials



Scheme 1. *Reagents*: (i) *N*-(chloromethyl)phthalimide, $FeCl_3$, DCM; (ii) N_2H_4, ethoxyethanol; (iii) Fmoc-Rink linker,[3] PyBOP®, HOBt, DIPEA, DMF; (iv) piperidine, DMF; (v) carboxy triphenylphosphine, PyBOP®, DIPEA, DMF.

Table 2. Loadings and reaction yields of intermediate Fmoc-Rink amide AM resins **2a–j** determined by Fmoc cleavage followed by UV quantification, and loadings and purity of the carboxy triphenylphosphines **3a–j** determined by ^{31}P MAS NMR and by phosphorus elemental analysis

Comp.	Loading Fmoc [mmol/g]	Yield[a] [%]	Comp.	Purity[b] [mol%]	Loading[c] ^{31}P NMR [mmol/g]	Loading P elemental anal. [mmol/g]
2a	0.84	93	**3a**	97	0.74	0.73
2b	0.81	90	**3b**	97	0.69	
2c	0.82	90	**3c**	90	0.67	0.69
2d	0.82	91	**3d**	91	0.71	0.72
2e	0.88	97	**3e**	95	0.71	0.73
2f	0.82	91	**3f**	97	0.72	0.71
2g	0.88	97	**3g**	97	0.71	
2h	0.88	98	**3h**	97	0.72	
2i	0.86	95	**3i**	96	0.73	0.75
2j	0.85	94	**3j**	97	0.70	
2a[d]	0.75	83	**3a**	95	0.66	0.69
2d[d]	0.76	84	**3d**	94	0.71	0.71
2e[d]	0.71	79	**3e**	93	0.69	0.73
2I[d]	0.66	73	**3i**	93	0.59	0.63

[a] Yields after reaction steps i–iii (Scheme 1).

[b] Relative amounts of phosphines, as by-products the corresponding phosphine oxides were observed.

[c] Total loading with phosphine oxides included.

[d] Data from not purified resins.

where soluble PS oligomers were extractable, markedly decreased reaction yields of 79 and 73% were obtained (steps i–iii). Most likely the purification of PS resins lead to improved yields of the aminomethylation reaction (step i, Scheme 1).

After the conversion of **2a–j** to the corresponding carboxy triphenylphosphine derivatives **3a–j**, the loadings were determined by ^{31}P MAS NMR in analogy to the method developed for ^{13}C MAS NMR.[4] The resins (m_{Resin}, 12–30 mg, depending on the swelling property) and the reference compound O=P(OPh)$_3$ (m_{ref}) were weighed directly into Zirconia rotors followed by addition of chloroform doped with 0.1 M chromium(III) acetylacetonate as relaxation reagent. The loading l_i was determined according to the equation

$$l_i = \frac{1000}{MG_{ref}} \frac{I_i}{I_{ref}} \frac{m_{ref}}{m_{\mathrm{Resin}}} [\mathrm{mmol/g}],$$

where MG_{ref} is the molecular weight of triphenyl phosphate. The relative intensities of the reference signal I_{ref} as well as I_i of the polymer-bound component were determined from the ^{31}P{^{1}H} MAS NMR spectra, recorded on a Bruker ASX-400 NMR spectrometer. The experiments were performed at ambient temperature using a 4 mm CP/MAS broadband probe at a MAS rotation rate of 2000 Hz. In Figure 2(a) the ^{31}P spectrum of **3g** is shown. The spectrum is referenced relative to the signal of triphenyl phosphate at −18.0 ppm and the signals at −5.9 and 28.5 ppm originate from the expected phosphine and from the phosphine oxide by-product. For **3a–j**, relative amounts of 90–97 mol% of resin-bound carboxy triphenylphosphine were detected, with the phosphine oxides as the only by-products. The ^{31}P NMR spectra of samples doped with 3–23 mol% of the free phosphine ligand (δ^{31}P = −5.0 ppm, CDCl$_3$ solution in absence of PS beads) showed two additional signals at −5.2 (broad) and −5.4 ppm (narrow), clearly distinguishable from the resin-bound species. The presence of two resonances may be explained by the same effect found for the doubling of all carbon NMR signals of toluene interacting with polystyrene resins.[5] The ^{31}P NMR signals of the free ligand were not detectable in any of the investigated

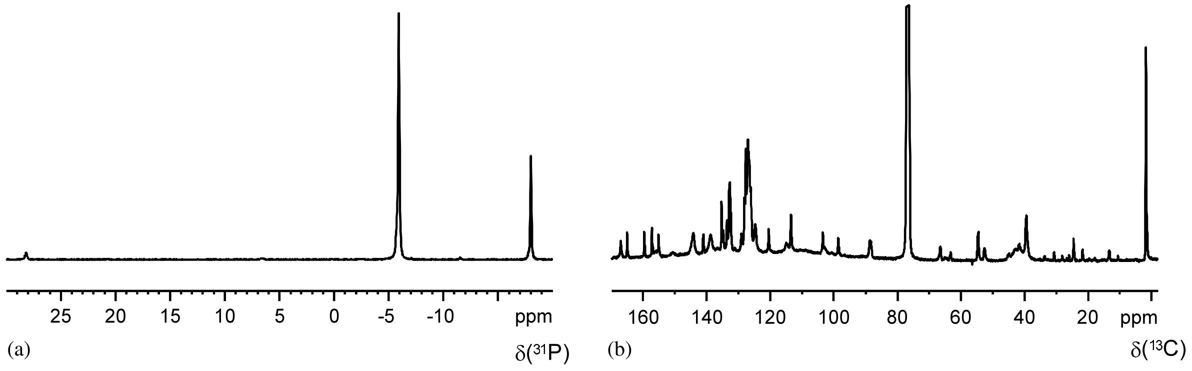


Figure 2. ^{31}P{^{1}H} and ^{13}C{^{1}H} MAS NMR spectra of resin-bound carboxy triphenylphosphine **3g** swollen in CDCl$_3$.

resins **3a**–**j**. The total loadings obtained by the ^{31}P NMR method (with the phosphine oxides included) showed good agreement with the data obtained by phosphorus elemental analysis (Table 2). The ^{31}P NMR data of **3g** was cross-checked by the ^{13}C MAS NMR method from Ref. 4 [method A]. The five individual signals from 150–175 ppm visible in the spectrum (Fig. 2(b)) originate from two amide and three phenoxy groups of structures **3** (Scheme 1). With the relative intensities of the dominant signals of $CDCl_3$ at 77.0 ppm and tetrakis(trimethylsilyl)silane at 1.4 ppm, a loading of 0.70 mmol/g was obtained, confirming the data from ^{31}P MAS NMR.

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