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Polymer Discs – An Alternative Support Format For Solid Phase Synthesis

Nick Hird,[1] Ian Hughes[1] David Hunter,[1] Michael G.J.T. Morrison,[2] David C. Sherrington[2,*] and Lorna Stevenson[2]

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Abstract

Monolithic crosslinked polymer rods (~10 mm x 50 mm) have been prepared by polymerisation of styrene with divinylbenzene, poly(ethylene glycol) (PEG)400 diacrylate or PEG1000 diacrylate as crosslinker dissolved in a suitable solvent. Adjustment of the reaction composition allows soft but mechanically strong rods to be produced which can be readily cut into discs of 1-2.5 mm thickness. Discs with good swelling characteristics in toluene, DCM, MeOH and water, and which resist osmotic shock, have been prepared. Analogous vinylbenzyl chloride-based discs crosslinked either with divinylbenzene or with PEG1000 di-4-vinylbenzyl ether have also been produced. These have been chemically modified by reaction with NMe_3, and also used in a two stage solid phase synthesis. Discs of individual mass up to 0.25g capable of yielding up to 0.5 mmole of a single compound in a solid phase synthesis have been used and demonstrated to be viable supports. This almost certainly does not represent the upper limit.

Keywords: polymer supports; solid-phase synthesis

Introduction

Polymer supports in the form of suspension polymerised styrene-divinylbenzene beads have been the centre-piece of solid phase peptide synthesis ever since they were introduced by Merrifield in 1963. [1, 2] Not surprisingly they have also become a key component in the more recent developments involving solid phase combinatorial and parallel synthesis [3-5] and despite numerous ingenious, indeed fanciful alternatives, they remain overwhelmingly the polymer support of choice. These spherical particulate polymers have allowed a considerable degree of automation of organic synthesis to be achieved. In addition, they are also now starting to play a pivotal role in solution phase (combinatorial) synthesis where reagents and catalysts etc. are heterogenised on a polymer support [6-8] or a functional resin is used as a scavenger or an extractant to facilitate product work-up, purification and isolation [9-11].

[1] SmithKline Beecham, New Frontier Science Park, Harlow, Essex CM19 5AW, UK
[2] Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, UK
* Corresponding author. E-mail: M.P.A.Smith@strath.ac.uk

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Developments in automation have now reached such an advanced state that the weighing out and dosing of resin beads into columns, small batch reactors, well plates, or "tea bags" etc. [12] has become tedious and to some extent rate limiting. As a result of this resin suppliers are starting to make pre-weighed capsules of resin available[a] and rather sophisticated support formats such as microtubes™ [13] are starting to be developed. Concurrently with this there is also a trend in solid phase synthesis away from genuine combinatorial chemistry, to single compound parallel synthesis on supports. To optimise the advantages of automation it would be convenient to have a single polymer particulate or monolith of a convenient size for automated mechanical handling, and of such a chemical capacity as to provide enough of an individual compound from a synthesis for comprehensive structural characterisation, and indeed for initial biological screening in the case of both pharmaceutical and agrochemical species. It would also be additionally advantageous if such a support were to be cheap, easily prepared and could be utilised in current automated systems for use with established reactions. In principle a single large bead might fulfil this requirement but unfortunately the maximum size of particle available conveniently from suspension polymerisation methodology is ~1-2 mm, and methods of growing on particles to larger size are not convenient and potentially very costly.

With this background we thought it might be more practical to produce a small monolith of an appropriate size in a disc format and the latter might be made conveniently and cheaply as a slice from a monolithic rod or cylinder. This paper describes the development and use of such discs.

Results and discussion

1. Styrene-based discs

Monolithic polymer rods or cylinders (diameter 8-10 mm, length 50 mm) were produced by polymerising appropriate co-monomer mixtures in pyrex glass test tubes. The rods were retrieved by carefully breaking the tubes, and discs of appropriate thickness, ~1-2 mm (125-250 mg), cut from each rod using a sharp laboratory razor blade. Styrene-based polymers were examined initially as model networks (Tables 1 and 2). A number of criteria had to be met to produce useful rods and discs. First it was essential that rods were produced as defect-free as possible since defects proved to be sites of mechanical weakness when discs were cut. Azobisisobutyronitrile used at 80°C as the free-radical initiator tended to generate bubbles in the rods (R1-R4), whereas 2,2'-azobis(2,4-dimethylvaleronitrile) used at 60°C produced defect-free monoliths (R5-16). To achieve high conversion the reaction time was increased simultaneously from 5 to 24 or 36 h.

The second requirement was for rods to be soft enough to cut, and it was found necessary to have a swelling solvent present during polymerisation to allow this. For styrene/divinylbenzene mixtures (R1-7) toluene was found to be very suitable. Absence of any solvent

[a] *e.g.* Argonaut Technologies Inc., San Carlos, CA 94070, USA – Arco Caps®

Table 1 Synthesis of model rods and discs therefrom using styrene and various crosslinkers[a]

Rod	Crosslinker[b]			Styrene (g)	Solvent[c] (g) (% organic phase)	Reaction time[d] (h)
	Type	Mass (g)	Wt%			
R1	DVB(tech 80%)	0.16	5.1	2.34	2.50 (50)	5[e]
R2	DVB(tech 80%)	0.32	5.1	4.68	0	3[e]
R3	DVB(tech 80%)	0.20	5.1	3.13	1.67 (33)	5[e]
R4	DVB(tech 80%)	0.25	5.1	3.75	1.00 (20)	5[e]
R5	DVB(tech 80%)	0.24	5.1	3.51	1.25 (25)	10
R6	DVB(tech 80%)	0.14	3.0	3.61	1.25 (25)	12
R7	DVB(tech 80%)	0.02	0.4	3.73	1.25 (25)	18
R8	PEG(400)diac	0.72	24	2.32	1.50 (33)	36
R9	PEG(400)diac	0.30	10	2.70	1.50 (33)	36
R10	PEG(400)diac	1.50	50	1.50	1.50 (33)	36
R11	PEG(1000)diac	1.11	35	2.06	1.50 (32)	24
R12	PEG(1000)diac	0.74	26	2.06	1.50[f] (35)	24
R13	PEG(1000)diac	1.11	35	2.06	1.50[f] (32)	24
R14	PEG(1000)diac	2.20	52	2.06	3.00[g] (41)	36
R15	PEG(1000)diac	2.20	52	2.06	1.50[g] (26)	36
R16	PEG(1000)diac	0.30	10	2.70	1.50[g] (33)	36

[a] See Experimental for more details
[b] DVB = technical divinylbenzene (80%, balance is ethylstyrene); PEG(400)diac = PEG400 diacrylate ester; PEG(1000)diac = PEG1000 diacrylate ester
[c] Toluene
[d] 2,2'-Azobis(2,4-dimethyl valeronitrile) (ADMVN) at 60°C
[e] Azobisisobutyronitrile (AIBN) at 80°C
[f] THF
[g] DMF

led to hard glassy rods which shattered easily. Likewise use of a precipitating porogen (*e.g.* alcohols) similar to the methodology described by Svec *et al* [14] for producing monolithic column packings led to macroporous rods which were very friable when attempts were made to cut them, although others have reported success in machining these in a lathe [15]. When PEG400 diacrylate was used in place of divinylbenzene (R8-10) toluene was also a suitable solvent; however with PEG1000 diacrylate as the crosslinker (R11-16) this solvent induced polymer network phase separation, as indeed did tetrahydrofuran. Dimethylformamide proved suitable in this case.

The third requirement was to balance the weight% of crosslinker and volume% of solvent used, again so that rods were soft enough to cut, but not too fragile such that they disintegrated on cutting. Rod R6 employing divinylbenzene and R15 using PEG1000 diacrylate as the crosslinker proved to be the most suitable systems.

Table 2 Physical characterisation of rods and discs prepared from styrene and various crosslinkers

Rod	Physical properties of rod	Swelling of discs			
		DCM	Toluene	CH_3OH	H_2O
R1	fragile – gas bubbles	-	-	-	-
R2	hard – gas bubbles	-	-	-	-
R3	fragile – gas bubbles	-	-	-	-
R4	slightly hard – gas bubbles	-	-	-	-
R5	soft, not fragile	1.0	2.0	~0	~0
R6	soft, not fragile	3.6	4.5	~0	~0
R7	soft, not fragile	-	5.2	~0	~0
R8	fragile	1.8	2.1	~0	~0
R9	soft, not fragile	3.2	2.4	~0	~0
R10	fragile	1.8	0.8	0.2	0.2
R11	phase separated	-	-	-	-
R12	phase separated	-	-	-	-
R13	soft – not fragile	12.1	5.8	0.2	0.2
R14	fragile	6.9	2.7	1.2	0.6
R15	soft – not fragile	9.2	3.7	1.3	0.3
R16	soft – not fragile	[c]	[c]	~0	~0

[a] See Experimental for more details

[b] [V(swollen) – V(initial)]/V(swollen); V measured from diameter and thickness using micrometer screwgauge; no entry means not recorded

[c] Sample disc disintegrated

The fourth important requirement was that discs cut from rods should swell adequately in a range of solvents and should be able to be cycled through a number of swelling/deswelling cycles without undergoing disintegration through osmotic shock [16]. The swelling data in Table 2 shows that while the divinylbenzene crosslinked species (R5-7) swell adequately in non-polar organic solvents they are non-swellable in water and other protic solvents. PEG400 diacrylate (R8-10) as the crosslinker did not improve the water compatibility significantly but rods made from PEG1000 diacrylate (R13-15) showed reasonable levels of up-take of water and methanol providing the PEG content was not too low (R16). Susceptibility to osmotic shock proved to be a problem, even with the divinylbenzene crosslinked discs (R6-7) which otherwise showed good properties. However, the discs prepared with the PEG1000 diacrylate showed very robust behaviour on swelling and de-swelling and these were felt to be the most favourable candidates for use as macroscopic supports.

2. Vinylbenzyl chloride-based discs

Rods and discs therefrom based on formulations close to R6 and R15 were selected for further investigation with styrene replaced by vinylbenzyl chloride as a functional comonomer. The data in Table 3 shows the five rods prepared. R21 was prepared with PEG1000 di-4-vinylbenzyl ether [17, 18] (synthesised in-house [19]) as the crosslinker to mimic the solvation behaviour offered by PEG1000 diacrylate but to eliminate the ester group as a

possible site for side-reactions during chemical synthesis on the disc. Two levels of vinylbenzyl chloride (10 and 50wt%) were also investigated. The preparation of the rods and cutting of the discs went as planned and then each disc was exhaustively extracted with acetone in a Soxhlet apparatus then vacuum dried at 50°C. The elemental microanalytical data and corresponding loading of chloromethyl groups on each disc are shown in Table 3 and there is reasonably good correlation with the level of vinylbenzyl chloride used in each polymerisation. The discs also showed good mechanical stability and response to solvent as predicted from the styrene-based model studies.

Table 3 Synthesis of rods and discs therefrom using styrene, vinylbenzyl chloride (VBC) and various crosslinkers[a]

Rod	Crosslinker[b]			Styrene (g)	VBC (g) (wt%)	Solvent (g) (% organic phase)	Microanalytical data for discs (%)			Loading $-CH_2Cl$ (mmol g^{-1})
	Type	mass (g)	wt %				C	H	Cl	
R17	DVB(tech 80%)	0.10	2.4	1.65	1.75 (50)	1.3[c] (27)	79.5	6.4	15.3	4.32
R18	DVB(tech 80%)	0.10	2.4	3.05	0.35 (10)	1.3[c] (27)	88.5	7.4	2.45	0.69
R19	PEG(1000)diac	2.20	50	0	2.20 (50)	1.5[d] (25)	65.1	6.65	12.6	3.55
R20	PEG(1000)diac	2.20	50	1.76	0.44 (10)	1.5[d] (25)	76.1	7.4	3.1	0.87
R21	PEG(1000)dst[e]	1.00	50	0	1.00 (50)	0.75[d](27)	65.4	6.8	13.9	3.91

[a] ADMVN initiator, 60°C, 24 h, See Experimental for more details
[b] See note b) Table 1
[c] Toluene
[d] DMF
[e] PEG(1000)dst = PEG1000 di-4-vinylbenzyl ether

3. Chemical reactions on discs

As an initial probe reaction, discs D19 and D20 cut from the corresponding rods were quaternised with three mole equivalents of NMe_3 (Table 4). These discs were crosslinked with the PEG1000 diacrylate species and the loadings of $-CH_2Cl$ groups were 50 and 10% respectively. Disc 19a, for example, weighed 234.2 mg initially and contained 0.77 mmol CH_2Cl, whereas disc 2a weighed 126.4 mg and contained 0.11 mmol CH_2Cl. Duplicate experiments were performed with one reaction run for 24 and the other for 48 hours. Each disc proved mechanically robust and quantitative recovery was facile using a pair of tweezers. No

Table 4 Reaction of VBC-based discs with trimethylamine to form benzyl ammonium residues[a]

DISC	Initial form of disc					Reaction time (h)	Product form of disc						
	Mass (mg)	Disc composition (wt%)			$-CH_2Cl$ (mmol)		Mass (mg)	Elemental microanalytical data (%)				$+$ $-CHNMe_3$ Cl^- (mmol)	Conversion of $-CH_2Cl$ groups (%)
		PEG (1000) da	VBC	St				C	H	Cl	N		
D19a	234.2	50	50	0	0.77	24	279.6	60.6	7.75	11.8	2.35	0.46	60
D19b	235.8	50	50	0	0.84	48	294.6	61.5	7.45	12.65	2.35	0.49	59
D20a	126.4	50	10	40	0.11	24	135.9	73.0	7.55	2.65	1.15	0.11	~100
D20b	133.3	50	10	40	0.12	48	145.2	71.9	8.05	2.50	1.05	0.11	92

[a] See Experimental for more details

difference was found between reactions run for 24 and 48 hours. The lightly loaded discs D20a,b were converted essentially quantitatively to their quaternised derivatives whereas the conversion of the more heavily loaded discs D19a,b levelled at ~60%. It is worth noting that the compositions of all discs with respect to PEG content and crosslink ratio are the same (*i.e.* ~50wt% and ~1 crosslink per 5 VBC units). Thus the levelling of the conversion in the case of the more highly loaded discs is probably associated with collapse or desolvation of the resin matrix in the solvent tetrahydrofuran, as the benzyltrimethylammonium salt content rises with conversion. Appropriate manipulation of the reaction solvent character would be expected to remedy this.

As a more exacting test of the discs we have employed a multi-step synthesis of 2-hydroxy-7-methylbiphenylcarboxylic acid methyl ester (Figure 1) which we have previously used on both conventional and developmental resins [19]. The reaction conditions are more demanding and in particular it is known that the Suzuki coupling second step can be problematical on resins. To avoid possible side-reactions discs prepared with divinylbenzene and the PEG1000 di-4-vinylbenzyl ether crosslinkers were employed. The results of the first reaction attachment) step are summarised in Table 5. Two discs were used in each reaction and all were recovered intact. Clearly attachment of the 5-bromosalicylic acid methyl ester to disc occurs with good conversion, less so with disc D18, and rather poorly with disc D17. D21 is 50% loaded with $-CH_2Cl$ groups and the long PEG1000 based crosslinker seems to facilitate this reaction. The results with D18 which is only 10% loading with $-CH_2Cl$ are much better than with D17 which is 50% loaded, although both discs have the same DVB content and were prepared with the same level of toluene solvent. Clearly the higher loading of D17 leads to poorer conversion. This disc was ~2.5 mm thick and on inspecting a cleaved cross-section a clear "sandwich" morphology was apparent, the disc having apparently reacted to a depth of

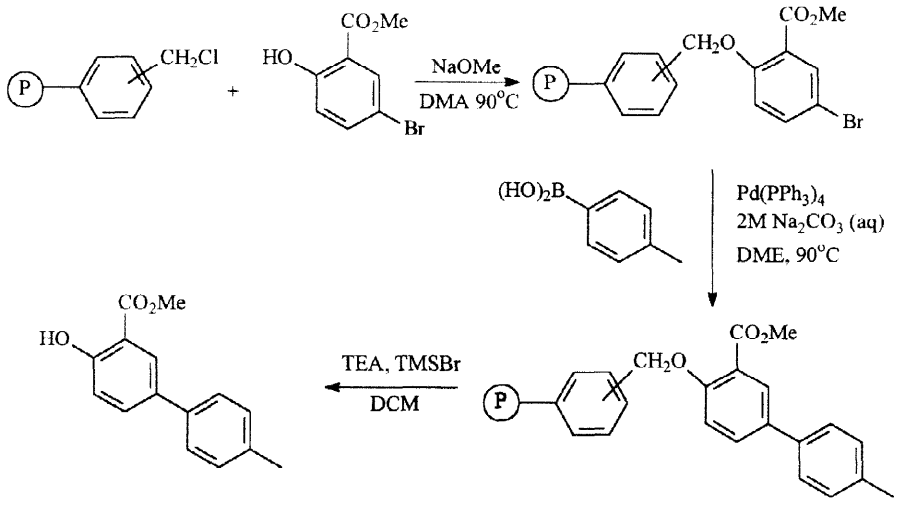

Figure 1 Solid phase synthesis of 2-hydroxy-7-methylbiphenylcarboxylic acid methyl ester on a polymer disc

Table 5 Attachment of 5-bromosalicylic acid methyl ester to VBC-based discs[a] (Figure 1)

DISC	Initial form of disc					Product form of disc						Conversion of -CH_2Cl groups (%)
	Mass[b] (mg)	Disc composition (wt%)			-CH_2Cl (mmol)	Mass (mg)	Elemental microanalytical data (%)				Br content (mmol)	
		DVB	VBC	St			C	H	Cl	Br		
D17	430.5	2.4	50	47.6	1.86	724.4	63.75	5.8	6.05	10.3	0.93	29
D18	553.5	2.4	10	87.6	0.38	672.9	79.8	7.45	1.76	2.75	0.23	60
D21	216.1	50[c]	50	-	0.84	388.9	52.8	4.65	4.60	15.0	0.73	87

[a] See Experimental for more details

[b] Note: 2 discs were used each time so that one could be retained and the second used in step 2 (Table 6)

[c] Crosslinker PEG1000 di-4-vinyl benzyl ether

only ~0.8 mm (Note: unreacted disc is clear, reacted disc is cream coloured). Elemental microanalysis of samples of the disc taken from the outer and inner layers yielded (%): exterior, C, 65.6; H, 5.1; Cl, 6.2; Br, 10.6, interior, C, 66.1; H, 5.1; Cl 8.2; Br, 6.2, corresponding to a Br content of 1.33 and 0.77 mmol g^{-1} for the exterior and interior portions respectively. This effect is very similar to the shrinking core phenomenon [20] seen with some

reactions on gel-type beads and confirms a major solvent/reagent diffusion limitation which is essentially absent in the case of the lightly loaded disc analogue D18. Thus with the heavily loaded disc D17 it is clear that deterioration in the solvent compatibility of the disc as it becomes loaded with the salicylic acid derivative causes contraction of the disc network, and hence gives rise to lower conversion in the attachment reaction.

The results of the Suzuki coupling second step of the synthesis are shown in Table 6. In this step only one disc was employed in each reaction and some minor chipping damage to the edge of each disc was incurred. This did not, however, inhibit facile recovery of the polymer. The analysis was performed by cleaving the products from the disc and performing LC-MS to both characterise and quantify the products. The conversion data for the Suzuki coupling and the overall conversion data therefore include the cleavage efficiencies. While overall the data are rather poor they do demonstrate that the proposed synthesis on the discs is viable. The Suzuki coupling reaction is known to proceed with considerable variability depending on the substitution pattern etc of the components, and a number of experimental variants have been described to improve its general applicability [21]. In our hands the reaction of interest here has given only modest results when used with a conventional resin bead format [19], and is clearly the limiting one with discs as well.

Conclusion

It is anticipated therefore that with reaction schemes known to proceed efficiently on resin beads, the transfer to a disc format should be relatively straightforward. Furthermore, bearing in mind that we have shown a single disc monolith of up to ~0.25 g can be readily prepared and handled successfully, the synthesis of up to ~0.5 mmol of single compound per monolith seems readily achievable.

Table 6 Suzuki coupling reaction involving 5-bromosalicylic acid methyl ester residues on VBC-based discs[a]

DISC	Initial form of disc		Mass of recovered disc (mg)	Hplc yields of cleaved products (%)[b]				Second step conversion to cleaved Suzuki product (%)	Overall conversion to cleaved Suzuki product
	Mass[c] (mg)	Br content (mmol)		I	II	III	IV		
D17	244.7	0.32	157.8	41	11	33.5	12.5	12.5	4.0
D18	219.8	0.075	134.7	26	--	53	18	18.5	11.0
D21	96.7	0.18	94.8	14	3	67	12	12.5	10.5

[a] See Experimental for more details
[b] I = 5-bromosalicyclic acid; II = unknown; III = 5-bromosalicyclic acid methyl ester; IV = Suzuki coupled product
[c] Now refers to a single disc in each reaction carried forward from first step (Table 5)

Perhaps most importantly the synthesis of discs in the way we have described does not require knowledge of, and experience with, a specialised technique such as suspension polymerisation, used for the preparation of resin beads. Monoliths of this type could therefore be readily synthesised in-house by would-be users and we believe could make an important contribution in, for example, solid phase scavenging and recovery processes.

Experimental

1. Rod and disc synthesis

Polymerisation mixtures (co-monomers and solvent, Tables 1 and 3) typically ~5 ml were placed with 1 wt% free-radical initiator in a pyrex test tube (o.d. ~10 mm) and sealed with a rubber septum. The solution was degassed with N_2 for 10 minutes and then heated to induce polymerisation (Tables 1 and 3). Polymer rods were recovered by breaking the test-tube and discs of appropriate thickness cut using a razor blade. Each disc was exhaustively extracted with acetone in a Soxhlet before vacuum drying at 50°C.

2. Quaternisation of VBC-based discs

Each polymer disc was swollen in tetrahydrofuran (THF) (15 ml) and gently magnetically stirred. Trimethylamine (33% in MeOH, 1 ml, ~3 equiv.) was added and the reaction heated to reflux (see Table 4). The disc was removed from the reaction mixture using tweezers and was washed with THF, THF/H_2O (1:1), THF and DCM (all 3 x 10 ml) before being vacuum dried at 50°C.

3. Stepwise Synthesis on VBC-based discs

3.1 Step 1

Each disc, 5-bromosalicyclic acid methyl ester (3 equiv.) and sodium methoxide (3 equiv.) were gently magnetically stirred in DMF (dry, 15 ml) under N_2 and heated to 90°C for 48 h. The isolated disc was washed with THF, THF/H_2O (1:1), THF, DCM, MeOH and diethyl ether (all 2 x 10 ml) before being vacuum dried at 50°C.

3.2 Step 2

Each disc was gently magnetically stirred in N_2 degassed dimethoxyethane (15 ml). Tetrakis(triphenylphosphine)palladium (20 mg) was added and the reaction mixture was stirred under N_2 for 5 minutes. Aqueous Na_2CO_3 (2M, 6 equiv.) and 4-tolylboronic acid (3 equiv.) were added and the reaction mixture stirred rapidly and heated to 90°C for 17 hours. The disc was removed and washed and dried as in the first step.

3.3 Cleavage

A sample of disc (~50 mg) was placed in the cleavage solution (1 ml) consisting of trifluoroacetic acid (TFA)/trimethylsilyl bromide (TMSBr)/DCM (1:1:5) for 4 hours. The solution was filtered and the polymer was washed with DCM (2 ml). The filtrate was evaporated leaving an oil which was analysed and assayed by LC-MS (hplc: Zorbax SB-C18, 40°C, 3 ml min^{-1}, A (0.1% TFA/H_2O), B (0.1% TFA/MeCN) gradient 0-100% B; MS – Hewlett Packard Electrospray, API-ES).

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