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A Measure of Solvent Effects on Swelling of Resins for Solid Phase Organic Synthesis

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Abstract: The swelling abilities of many solvents were examined volumetrically on Wang, Merrifield, TentaGel S RAM, MBHA, Trityl, and Rink amide resins. A tabular summary is presented as a synthetic tool to aid in solvent choice for solid phase organic synthesis methods development.

Keywords: resins; solvent and solvent effects; solid-phase synthesis.

Dedicated to Professor Alan R. Katritzky on the occasion of his 70th birthday.

Solid phase synthesis, which was originally extensively investigated for peptide and other oligomer synthesis,[1,2] has recently emerged as a powerful method for the construction of libraries of small organic compounds.[3-8] Many common reactions have been successfully transferred from their solution phase origins to various solid supports.[7] Among other factors, the solvation of the resin used in the reaction medium is crucial for rapid and complete transformation. When the resin beads are not well swollen in solvents, this can result in poor reaction site accessibility and diminished reaction rates. This was actually observed by Merrifield as early as the very beginning of the solid phase synthesis of peptides.[2] The swelling properties of resins for peptide synthesis and peptide-resins in a number of solvents have been documented over the years,[9-15] and the correlation of swelling abilities with solvent properties, such as polarities, solubility, and hydrogen bonding abilities, has been proposed.[9-12] However, most of these studies focused on peptide-resins, correlation with physical properties of the solvent, and amide-bond forming conditions. We believe that a semi-quantitative study examining the swelling abilities of a number of common solvents on resins frequently used in solid phase organic synthesis (SPOS) would help chemists to pick an appropriate solvent for their particular reactions. The solvent will then not only be suitable for the particular reaction, as in solution phase, but will also swell the selected solid support, allowing reagent access to the resin-bound reactive functionality.

We first examined three common resins (in four forms, Figure)[16] with thirty-six regular solvents and three mixed solvents. The swelling volume of these resins was determined in the following way: five hundred milligrams of an appropriate dry resin was added to a graduated 5-mL syringe, which was equipped with a thin, fine polypropylene filter. An appropriate solvent (5 mL) was added and the plunger was inserted. The mixture was vortexed for 30 seconds for maximum resin/solvent mixing, and let stand for 1 hour for thorough

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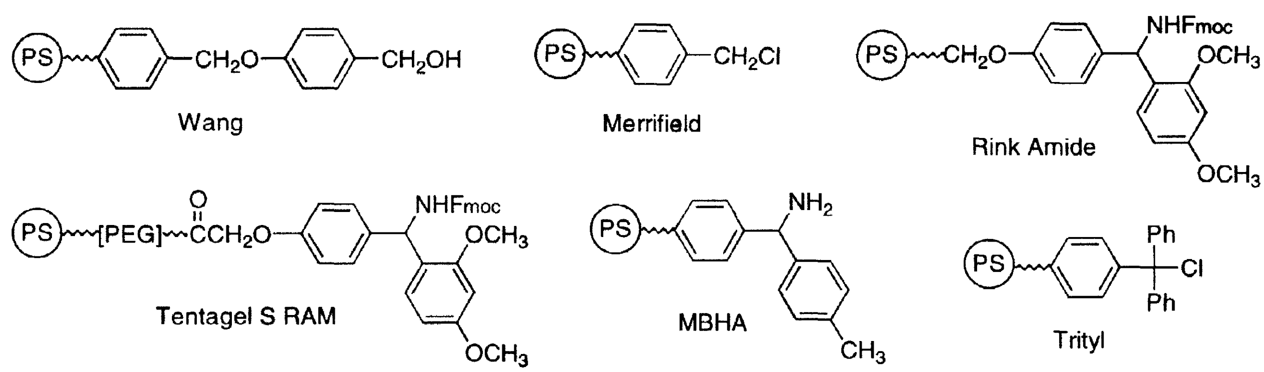
equilibration. After being vortexed again, extra solvent was removed by another syringe *via* a luer-lok connector, and the volume of the swollen beads was recorded. In their dry state, all of the resins generally account for 0.8-1.0 mL/g. Swelling for 24 h was tested but no significant difference was observed in any case.



These results are summarized in Table 1. The solvents were arranged according to their swelling ability for Wang resin. A few solvents [*e.g.* *N*-methylpyrrolidone (NMP), pyridine, THF, DMF, CH_2Cl_2] can swell all Wang, TentaGel and 4-methylbenzhydrylamine (MBHA) resins, but some of them (*e.g.* glyme, CH_3CN, THF/H_2O) have specific preferences. We noted that 2-methoxyethanol, ethylene glycol and dimethoxyethane can swell Wang resin nicely; acetonitrile is a good solvent for TentaGel resin; and both ethylene glycol and dimethoxyethane swell MBHA well. As expected, the trends observed for swelling of Tentagel were very different from those seen for the straight polystyrene resins, with the polar and protic solvents providing better relative swelling. While the ranges observed were less than for the plain polystyrene resins, the swelling of the Tentagel resin was clearly affected by solvent choice. Surprisingly, significant differences were seen for the swelling of neutralized MBHA versus its HCl salt, again with the more polar, protic solvents preferentially swelling the salt form.

Based on these results, we selected seven solvents as models to test other resins, including Merrifield, Trityl and Rink amide resins (Figure),[16] as well as Wang resins with high loading (HL, 1.16 mmol/g) and 2% DVB cross-linking. These results are collected in Table 2. While the trends are the same, the observed swelling volume is usually equal or lower for higher loading resin or resin with higher DVB cross-linking.[13]

In conclusion, we surveyed the resin swelling properties of a number of solvents. Actually, this survey helped us to pick suitable solvents for our internal library development effort. Hopefully it will also assist others to select potential reaction media for their reactions in solid phase organic synthesis. As a rough guideline, we believe that swelling of greater than 4.0 mL/g is indicative of a good solvent, between 2.0-4.0 mL/g a moderate solvent and less than 2.0 mL/g a poor solvent, which should be avoided. It should be pointed out that this study was intended to provide an easy-to-follow table for choosing solvents for SPOS reactions. A careful explanation or correlation between the swelling abilities of these solvents and their physical properties is beyond the scope of this report; related studies of this type can be found in the literature for a limited solvent range.[9-12]

Table 1. Swelling Properties of Four Resins in Thirty-nine Solvents (volume in mL/g).

Solvent	Wang Resin (low loading)	TentaGel S RAM	MBHA Neutralized	MBHA HCl Salt
NMP	6.4	4.4	7.2	8.6
Pyridine	6.0	4.6	7.0	4.8
THF	6.0	4.0	7.2	6.0
N,N'-Dimethylacetamide	5.8	4.0	5.8	7.5
$CHCl_3$	5.6	5.6	8.0	5.0
Dioxane	5.6	4.2	6.4	3.5
CH_2Cl_2	5.4	5.6	7.6	6.0
DMF	5.2	4.4	5.6	6.5
1,2-Dichlorobenzene	4.8	5.2	5.6	2.1
$HOCH_2CH_2OH$	4.8	2.0	5.6	6.0
$MeOCH_2CH_2OMe$	4.8	2.0	5.8	5.5
2-Butanone	4.4	2.0	4.8	3.5
Benzene	4.4	4.4	6.8	4.5
$ClCH_2CH_2Cl$	4.4	5.4	6.8	5.5
DMSO	4.2	3.8	2.2	8.3
EtOAc	4.2	2.0	3.6	3.2
2-$MeOCH_2CH_2OH$	4.0	2.4	2.8	5.5
Toluene	4.0	3.6	6.4	5.5
2-$EtOCH_2CH_2OH$	3.6	2.0	2.8	5.0
CH_3COCH_3	3.6	2.8	3.6	3.0
Xylene	3.0	2.0	5.6	3.0
THF/H_2O (1:1)	2.8	5.2	4.4	6.4
AcOH	2.8	5.2	4.0	4.5
Et_2O	2.8	2.0	3.4	2.0
CCl_4	2.4	2.8	5.6	2.1
t-BuOMe	2.4	1.6	3.8	2.0
CH_3CN/H_2O (1:1)	2.0	4.0	2.0	3.0
n-BuOH	2.0	2.0	2.0	2.1
n-PrOH	2.0	2.0	2.0	2.6
DMF/H_2O (1:1)	2.0	4.0	2.0	3.3
i-PrOH	2.0	2.0	2.0	2.1
CH_3CN	2.0	4.0	2.8	2.0
EtOH	2.0	1.8	2.0	3.0
CH_3NO_2	2.0	4.4	2.8	2.0
Trifluoroacetic acid	2.0	6.4	4.0	4.5
Heptane	1.6	1.6	1.6	2.0
MeOH	1.6	3.6	1.2	5.0
t-BuOH	1.6	1.6	2.0	1.9
H_2O	1.6	3.6	2.2	1.0

Table 2. Swelling Properties of Five Resins in Seven Solvents (volume in mL/g).

Solvent	Wang (HL)	Wang (2% DVB)	Merrifield	Trityl Resin	Rink Amide
THF	6.0	5.7	7.7	5.3	4.5
DMSO	4.0	2.6	1.8	1.9	1.8
$MeO(CH_2)_2OH$	3.7	3.3	1.8	1.8	1.6
THF/H_2O (1:1)	3.3	3.5	3.1	3.0	2.8
CH_3CN	2.6	2.6	1.8	1.8	2.0
Bu^tOMe	1.8	3.3	3.3	1.8	1.4
MeOH	1.8	1.8	1.8	1.6	1.8

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16. All of the resins used are bought from NovaBiochem except TentaGel S Ram which supplied by RAPP Polomere; they are in 100-200 mesh particle size, except Trityl resin which is 200-400 mesh and contain 1% DVB cross-linking except one of the Wang resin and MBHA containing 2% DVB. Neutral MBHA were obtained by washing the MBHA HCl resin with DCM (1x), 5% DIEA/DCM (2x, 1 h each), DCM (2x), and MeOH (2x), and drying under vacuum. Loadings (mmol/g) for Wang (low loading) 0.60, Wang (HL) 1.16, Wang (2% DVB) 0.75, TentaGel S Ram 0.30, MBHA 0.80, Merrifield 0.95, Trityl 0.84, Rink amide 0.57.