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Solvent Compatibility of Poly(dimethylsiloxane)-Based Microfluidic Devices

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This paper describes the compatibility of poly(dimethylsiloxane) (PDMS) with organic solvents; this compatibility is important in considering the potential of PDMS-based microfluidic devices in a number of applications, including that of microreactors for organic reactions. We considered three aspects of compatibility: the swelling of PDMS in a solvent, the partitioning of solutes between a solvent and PDMS, and the dissolution of PDMS oligomers in a solvent. Of these three parameters that determine the compatibility of PDMS with a solvent, the swelling of PDMS had the greatest influence. Experimental measurements of swelling were correlated with the solubility parameter, δ (cal$^{1/2}$ cm$^{-3/2}$), which is based on the cohesive energy densities, c (cal/cm^3), of the materials. Solvents that swelled PDMS the least included water, nitromethane, dimethyl sulfoxide, ethylene glycol, perfluorotributylamine, perfluorodecalin, acetonitrile, and propylene carbonate; solvents that swelled PDMS the most were diisopropylamine, triethylamine, pentane, and xylenes. Highly swelling solvents were useful for extracting contaminants from bulk PDMS and for changing the surface properties of PDMS. The feasibility of performing organic reactions in PDMS was demonstrated by performing a Diels−Alder reaction in a microchannel.

Several characteristics make poly(dimethylsiloxane) (PDMS) useful in fabricating microfluidic devices intended for bioanalysis: ease of fabrication (rapid prototyping, sealing, interfacing with the user), transparency in the UV−visible regions, chemical inertness, low polarity, low electrical conductivity, and elasticity.[1,2] PDMS does not swell in contact with water. The cost of fabrication in PDMS is low compared to that for many materials (e.g., glass or silicon) commonly used in microdevices and MEMs.[3]

There is a growing interest in using microfluidic systems for functions other than bioanalysis in water, including organic synthesis in organic solvents.[4−6] PDMS swells in contact with nonpolar solvents (e.g., hydrocarbons, toluene, and dichloromethane) and is not useful for manipulations requiring these solvents. The objective of this work was to define the solvent compatibility of PDMS as a first step in discerning what types of solvents (other than water) can be used in microfluidic systems fabricated in this material. It is clear that PDMS is not a universal material and that other classes of polymers (or perhaps even glass, despite the inconvenience of fabricating devices in rigid, brittle materials) will be required for non- and less-polar solvents. What are not clear are the characteristics of the solvents that are required for a solvent to be compatible with PDMS.

The problem of solvent compatibility has three aspects: (1) the solubility of a solvent in PDMS, since this solubility influences the swelling of the PDMS; (2) the solubility of solutes in PDMS (or more properly, the partition of solute between a solution and PDMS), since loss of solute from the solvent is a concern; and (3) the dissolution of PDMS oligomers in solvent, since these oligomers (present as contaminants in cross-linked PDMS) are potential contaminants in the products of reactions carried out in PDMS.

Background on Solubility. Many parameters have been used in calculating solubilities.[7,8] We have arbitrarily chosen to use cohesive energy density, c (cal/cm^3), the energy associated with the intermolecular attractive interactions within a unit volume of material.[8−10] The cohesive energy density can be expressed as $c = -U/V$, where U is the molar internal energy (cal/mol) and V is the molar volume (cm^3/mol). For two materials to be soluble, their cohesive energy densities must be similar, since this energy must be overcome to separate the molecules of the solute to allow the molecules of solvent to insert. For materials such as cross-linked polymers that do not dissolve, solubility is measured by the degree of swelling. The cohesive energy density is often expressed in terms of the solubility parameter, or Hildebrand value: $\delta = c^{1/2} = (-U/V)^{1/2}$ (cal$^{1/2}$ cm$^{-3/2}$).[8,11] The solubility parameter is useful for predicting the swelling behavior of a polymer in a solvent without knowing any other information about the solvent.

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(11) The units for δ can be expressed as the square root of the cohesive energy density (cal$^{1/2}$ cm$^{-3/2}$) or as the square root of a pressure (MPa$^{1/2}$), where 1 cal$^{1/2}$ cm$^{-3/2}$ = 0.488 88 MPa$^{1/2}$.

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Table 1. Solubility Parameters, Swelling Ratios, and Dipole Moments of Various Solvents Used in Organic Synthesis

solvent	δ[a]	S[b]	μ (D)	ref[c]	rank[d]
perfluorotributylamine	5.6	1.00	0.0	10	32
perfluorodecalin	6.6	1.00	0.0	10	33
pentane	7.1	1.44	0.0	10	3
poly(dimethylsiloxane)	7.3	∞	0.6−0.9	8, 14	
diisopropylamine	7.3	2.13	1.2	10	1
hexanes	7.3	1.35	0.0	10	8
n-heptane	7.4	1.34	0.0	10	10
triethylamine	7.5	1.58	0.7	8,10	2
ether	7.5	1.38	1.1	10	6
cyclohexane	8.2	1.33	0.0	10	11
trichloroethylene	9.2	1.34	0.9	10	9
dimethoxyethane (DME)	8.8	1.32	1.6	10	12
xylenes	8.9	1.41	0.3	10	4
toluene	8.9	1.31	0.4	10	13
ethyl acetate	9.0	1.18	1.8	8,10	19
benzene	9.2	1.28	0.0	10	14
chloroform	9.2	1.39	1.0	10	5
2-butanone	9.3	1.21	2.8	10	18
tetrahydrofuran (THF)	9.3	1.38	1.7	10	7
dimethyl carbonate	9.5	1.03	0.9	8,10	25
chlorobenzene	9.5	1.22	1.7	10	15
methylene chloride	9.9	1.22	1.6	10	16
acetone	9.9	1.06	2.9	8,12	22
dioxane	10.0	1.16	0.5	10	20
pyridine	10.6	1.06	2.2	10	23
N-methylpyrrolidone (NMP)	11.1	1.03	3.8	10	26
tert-butyl alcohol	10.6	1.21	1.6	8,12	17
acetonitrile	11.9	1.01	4.0	10	31
1-propanol	11.9	1.09	1.6	8,10	21
phenol	12.0	1.01	1.2	8,12	29
dimethylformamide (DMF)	12.1	1.02	3.8	8,10	27
nitromethane	12.6	1.00	3.5	10	34
ethyl alcohol	12.7	1.04	1.7	8,12	24
dimethyl sulfoxide (DMSO)	13.0	1.00	4.0	10	35
propylene carbonate	13.3	1.01	4.8	10	30
methanol	14.5	1.02	1.7	8,12	28
ethylene glycol	14.6	1.00	2.3	8,12	36
glycerol	21.1	1.00	2.6	13,15	37
water	23.4	1.00	1.9	8,12	38

[a] δ in units of cal$^{1/2}$ cm$^{-3/2}$. [b] S denotes the swelling ratio that was measured experimentally; $S = D/D_0$, where D is the length of PDMS in the solvent and D_0 is the length of the dry PDMS. [c] References refer to literature values of δ and μ. [d] Rank refers to the order of the solvent in decreasing swelling ability (see Figure 1).

For a binary system, the Hildebrand−Scatchard equation relates the solubility parameters of nonpolar liquids to the enthalpy change on mixing them: $\Delta H_m = V_m(\delta_1 - \delta_2)^2\varphi_1\varphi_2$, where V_m is the volume of the mixture, δ_i is the solubility parameter of the component i, and φ_i is the volume fraction of i in the mixture.[8] For two components to be soluble in one another (i.e., for swelling to occur in a polymer−solvent system), the free energy of mixing must be favorable, that is, $\Delta G_m < 0$. Since $\Delta G_m = \Delta H_m - T\Delta S_m$, and $\Delta H_m \propto (\delta_p - \delta_s)^2$, swelling is maximal when $(\delta_p - \delta_s)^2$ is 0, where δ_p and δ_s are the solubility parameters of the polymer and solvent.[8]

Table 1 shows values of δ for a range of solvents often used in organic synthesis.[8,10,12] Although the Hildebrand−Scatchard equation suggests that solvents with δ similar to that of PDMS (δ = 7.3 cal$^{1/2}$ cm$^{-3/2}$) will swell PDMS effectively, the relationship between δ and swelling is not linear and differs for each polymer−solvent system. We therefore wished to calibrate this ranking experimentally. Many research groups have used gravimetric methods to determine the degree of swelling of a polymer by a solvent.[13−17] The degree of swelling is measured by the ratio of the mass of the swollen network and solvent combined to the mass of the dry extracted solid. This method has two major disadvantages. First, the mass of the combined swollen network and solvent must be measured while in equilibrium with the solvent in the vapor phase, so that evaporation of the solvent does not effect the measurement. Second, the gravimetric technique requires extra steps in its protocol compared to length measurements (described below), because the unpolymerized PDMS oligomers must first be extracted before measurement. In this research, we measured swelling by placing a solid piece of PDMS in a solvent for 24 h and then measuring the change in dimensions (e.g., length) of the solid while the PDMS was still submersed in the solvent in the liquid phase. The amount of un-cross-linked oligomers in solid PDMS is small (∼0−5%, w/w; see later discussion) compared to the cross-linked network, and the oligomers do not significantly affect the shape or length of the cross-linked PDMS. We, therefore, did not need to extract the oligomers from the PDMS before measuring the swollen length. The degree of swelling is expressed by the swelling ratio:[9,18] $S = D/D_0$, where D is the length of the solid PDMS in the solvent and D_0 is the length of the dry, solid PDMS.[19]

RESULTS AND DISCUSSION

Swelling of PDMS in Organic Solvents. Prediction of swelling of PDMS by a solvent is important when considering which solvents to use in performing organic syntheses in microfluidic devices made in PDMS, which cosolvents to use in separations, or which nonpolar components to expect to lose from aqueous solution by contact with PDMS. Swelling of microchannels has many implications. Swelling changes the cross-sectional area of the channel and, therefore, the rate and profile of flow. Changes in channel dimensions due to swelling can effect integration of the channel with components such as membranes, detectors, mixers, or electrodes. Swelling also changes surface properties and may cause the microfluidic device to deseal if the PDMS is bonded to a glass substrate.

Here, we calibrate the relation of the solubility parameter, δ, of each solvent listed in Table 1 to the extent of swelling of PDMS. The degree of swelling is measured by the swelling ratio, S; Table 1 also reports the values of these ratios. Figure 1 plots the swelling ratio observed for each solvent against its solubility parameter. The inset lists the solvents in descending order of solubility in PDMS.[20] As expected, solvents that have a solubility parameter similar to that of PDMS (δ = 7.3 cal$^{1/2}$ cm$^{-3/2}$) generally swell PDMS more than solvents that have a solubility parameter

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(19) Swelling in terms of volume is calculated by $\Delta V = S^3$.

(20) In this paper, the number associated with the solvent, e.g., hexanes (8) indicates the rank of the solvent from Figure 1, in descending order of solvability in PDMS.

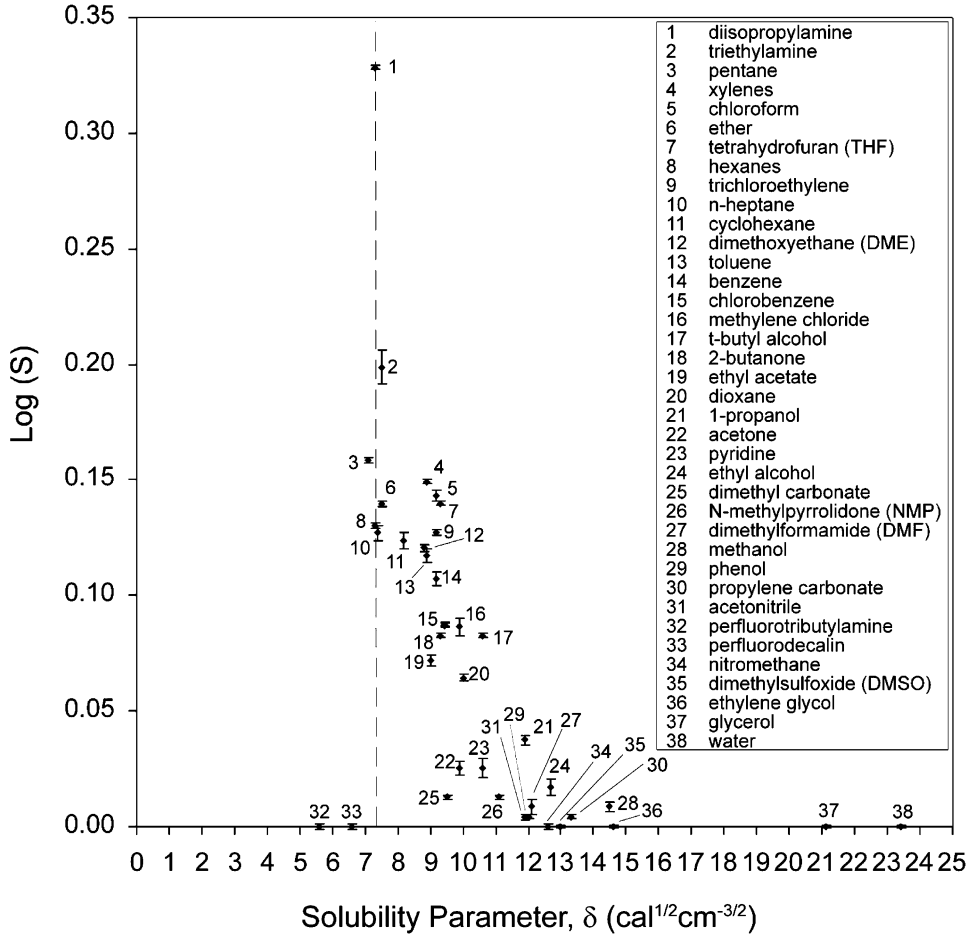

Figure 1. Relationship between swelling ratio (S) (shown as Log (S)) of PDMS in various solvents and the solubility parameter (δ) for these solvents. The solvents are numbered in order of decreasing swelling ability (e.g., "1" has the most swelling ability and "38" has the least swelling ability). The dashed line indicates the solubility parameter of PDMS ($\delta = 7.3$ cal$^{1/2}$ cm$^{-3/2}$). In general, a greater degree of swelling is observed with solvents that have a value of δ similar to that of PDMS.

substantially different from that of PDMS. This relation between S and δ, however, deviates in small but important ways. For example, acetone and methylene chloride have indistinguishable solubility parameters ($\delta = 9.9$ cal$^{1/2}$ cm$^{-3/2}$), but methylene chloride swells PDMS much more than does acetone. This observation can be explained by the polarity of the solvent. The solubility parameter can be expressed by a sum of the dispersion forces, polar forces, and hydrogen-bonding forces within the material (Hansen's total solubility parameter);[8] that is, $\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$. While two solvents may have a similar total solubility parameter, the contributions that make up this value may be different. Two solvents with the same value of δ but a different proportioning of these values among δ_d, δ_p, and δ_h may show substantial differences in swelling on exposure to PDMS. The partitioning of δ that is most similar to that of PDMS will result in the greatest swelling. Unfortunately, values of δ_d, δ_p, and δ_h are not readily available for PDMS or for many organic solvents.[21] In this paper, we consider the dipole moment of the solvent, μ (D) (representing the polar contributions), to help explain trends in solubility, since μ is readily available for most materials (Table 1). For example, in the case of acetone ($\mu = 2.88$ D) and methylene chloride ($\mu = 1.60$ D), methylene chloride has smaller polar contributions to δ than does acetone. PDMS has a δ made up of primarily dispersion forces; PDMS also has low polar contributions ($\mu = \sim 0.6-0.9$ D),[22] so it is not surprising that methylene chloride is more soluble in PDMS than is acetone.

We grouped the solvents in Figure 1 into four classifications, depending on their solubility effect on PDMS: solvents that have low solubility ($1.00 < S < 1.10$), moderate solubility ($1.10 < S < 1.22$), high solubility ($1.28 < S < 1.58$), and extreme solubility ($1.58 < S < 2.13$). Some solvents in which solubility parameters were not available are listed in Tables 2[23] and 3[24,25] and are also included in this analysis.

General Observations. *Low Solubility.* Low-solubility solvents generally have $\delta \geq 9.9$ cal$^{1/2}$ cm$^{-3/2}$. These solvents range from water (38) to 1-propanol (21) and include most alcohols (1-propanol, ethanol, methanol, phenol, ethylene glycol, glycerol), nitriles (acetonitrile), disubstituted amides (NMP, DMF), and tetrasubstituted ureas (1,1,3,3-tetramethylurea), sulfoxides (DMSO,

(21) Literature values of δ_d, δ_p, and δ_h for a limited number of polymers and solvents are available in: Du, Y.; Xue, Y.; Frisch, H. L. *Physical Properties of Polymers Handbook*; AIP Press: Woodbury, NY, 1996.

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Table 2. Swelling Ratios of PDMS in Solvents with an Undefined Solubility Parameter

solvent	S	μ (D)	ref
acetic anhydride	1.02 ± 0.01	2.80	10, 12
tetramethylene sulfone	1.00 ± 0.01	4.68	10
trifluoroethanol	1.01 ± 0.01	2.46	25
1,1,3,3-tetramethylurea	1.02 ± 0.01	3.47	10

Table 3. Equilibrium Swelling Ratios of PDMS in Amines

solvent	S	μ (D)	ref
dipropylamine[a]	∞	1.07	26
tetramethylethylenediamine	1.50		
diisopropylethylamine	1.40		
tributylamine	1.34	0.76	10
dimethyldodecylamine	1.25		
ethylenediamine	1.00	1.94	27
analine	1.00	1.51	10
pentaethylenehexamine	1.00		

[a] Dipropylamine swelled PDMS to $S = 2.61$ after the polymer was immersed in the solvent for 19 days. The PDMS dissolved completely after 39 days.

tetramethylene sulfone), pyridines, and nitro compounds (nitromethane). These solvents generally have moderate to high polar contributions ($\mu > 1.4$ D). Fluorocarbons (perfluorodecalin, trifluoroethanol, perfluorotributylamine) also do not swell PDMS,[26] although they may have a small dipole moment and a solubility parameter similar to PDMS (for example, $\mu = 0$ D and $\delta = 6.6$ cal$^{1/2}$ cm$^{-3/2}$ for perfluorodecalin). Low-solubility solvents can be used with PDMS without swelling and are, therefore, compatible with microfluidic systems fabricated in PDMS. In principle, it should be possible to consider carrying out synthetic reactions in these solvents in PDMS microreactor systems.

Moderate Solubility. We classify solvents ranging from dioxane (20) to chlorobenzene (15) as moderately soluble solvents in PDMS. These solvents have a range of solubility parameters ($9.1 < \delta < 11.3$) and dipole moments ($0.46 < \mu < 2.78$) that overlap with either the high- or low-solubility groups. These observations reemphasize the fact that the proportioning of dispersion, polar, and hydrogen forces for a particular solvent greatly influences its ability to swell PDMS. For instance, PDMS is generally swollen by ethers, but the swelling ratio in dioxane is moderately low ($S = 1.16$), perhaps because dioxane has a lower proportion of dispersion forces than the high-swelling ethers. On the other hand, PDMS is generally not soluble in alcohols, but *tert*-butyl alcohol swells PDMS moderately ($S = 1.21$); *tert*-butyl alcohol has a larger contribution of dispersion forces to δ than do the other alcohols tested.

High Solubility. High-solubility solvents generally have a solubility parameter in the range 7.3−9.5 cal$^{1/2}$ cm$^{-3/2}$. In Figure 1, these solvents range from benzene (14) to pentane (3) and include acyclic and cyclic hydrocarbons (pentanes, hexanes, heptane, cyclohexane), aromatic hydrocarbons (xylenes, toluene, benzene), halogenated compounds (chloroform, trichloroethylene), and ethers (diethyl ether, dimethoxyethane, tetrahydrofuran). These solvents tend to be nonpolar or only slightly polar, having $\mu \leq 1$ D, with the exception of ethers ($\mu = 1.69$ D for tetrahydrofuran). The main contribution to δ is from dispersion forces.

High-solubility solvents alone are generally not compatible with PDMS microfluidic devices because of high swelling; PDMS will absorb these solvents from a microchannel, and the polymer will saturate with the solvent over time. A high-solubility solvent may be mixed with another, low-solubility solvent to produce a mixture that does not swell PDMS[27] (or at least reduces the swelling relative to the highly swelling solvent).[28]

High-solubility solvents are also useful for other types of applications requiring PDMS that is free from contaminants, since high-solubility solvents can be used to extract un-cross-linked PDMS from the bulk polymer (see section on Dissolution of PDMS Oligomers in Organic Solvents). For example, Graham et al. used hexane for extracting oligomers from PDMS to avoid transferring contaminants onto a self-assembled monolayer surface during microcontact printing.[29] Figure 1 lists other high-solubility solvents that could be useful for this purpose.

Extreme Solubility. The extremely soluble solvents are certain secondary and tertiary amines that swell PDMS to the greatest extent: diisopropylamine, dipropylamine, and triethylamine. (See section on Reactive Solvents for the swelling of PDMS in dipropylamine.) The swelling of PDMS in diisopropylamine and triethylamine is not surprising, as the solubility parameters of both solvents ($\delta = 7.3$ and 7.5 cal$^{1/2}$ cm$^{-3/2}$, respectively) are similar to that of PDMS. The extent of swelling of PDMS in amines, however, is surprising. Table 3 lists others amines that we tested with PDMS.

Changing the Surface Properties of PDMS. PDMS has repeating units of −OSi(CH$_3$)$_2$− groups. This chemical structure leads to a hydrophobic surface ($\theta_a^{H_2O} = 108°$).[30] Exposing this surface to an air or oxygen plasma introduces silanol (Si−OH) groups, destroys methyl groups (Si−CH$_3$), and makes the surface hydrophilic.[30−32] PDMS that has been treated with plasma can be kept hydrophilic indefinitely by keeping the surfaces in contact with water or polar organic solvents; otherwise, if the surface is left in contact with air, surface rearrangements occur that bring new hydrophobic groups to the surface to lower the surface free energy.[1,2]

Extracting un-cross-linked PDMS contaminants from the bulk polymer using organic solvents decreases the rate of regeneration of the hydrophobic surface. Figure 2 shows a comparison of contact angles (of water) between samples of extracted and nonextracted PDMS that were oxidized (i.e., treated with plasma) and not oxidized. These surfaces were left in contact with air after initially being treated with an air plasma for 60 s.

We used an extremely soluble solvent, diisopropylamine, to extract the soluble components from cross-linked PDMS (1.5 cm

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(27) High-solubility solvents are not completely incompatible with PDMS. Generally, a mixture of solvents may or may not be soluble depending on the proportioning of δ_d, δ_p, and δ_h. The problem of determining these mixtures for PDMS is that it would require knowing δ_d, δ_p, and δ_h for each solvent, but these data are not available for many solvents.

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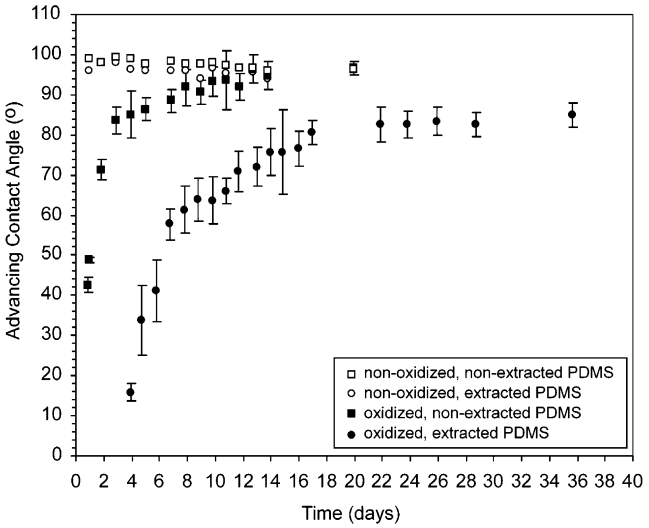

Figure 2. Advancing contact angle measurements of water on PDMS surfaces that were extracted or nonextracted and oxidized or nonoxidized. Surfaces that were extracted and oxidized remained hydrophilic in air for days; surfaces that were not extracted and oxidized regenerated the hydrophobic surface within hours. Error bars for the oxidized surfaces are shown and give an error of ±1 standard deviation (sample size $N = 30$). Surfaces that were not oxidized (either extracted or not extracted) remained hydrophobic. An average error of ±2° (1 standard deviation) was measured for these surfaces; error bars were omitted on the graph for clarity.

× 1.5 cm × 0.2 cm, *lwh*) for 1 day at 25 °C (see section on Dissolution of PDMS Oligomers in Organic Solvents). The diisopropylamine was removed from the cross-linked PDMS by immersing the samples in ethyl acetate (1 day) and acetone (2 days) and then drying in a 90 °C oven for 2 days.[33] PDMS surfaces that were extracted and then oxidized retained $\theta_a^{H_2O} < 30°$ in air for 4 days after plasma treatment. For PDMS that was oxidized but not extracted, un-cross-linked oligomers migrated to the surface within hours after plasma treatment. Extracted and nonextracted PDMS that were not oxidized gave average contact angles of $\theta_a^{H_2O} = 96° \pm 2°$ and $98° \pm 2°$, respectively.

We observed that extracted and oxidized PDMS sealed better with other similarly treated pieces of PDMS than nonextracted PDMS that had been similarly oxidized. This property is important for the assembly of microfluidic devices, because assembly often involves alignment and contact of PDMS layers after the layers have been oxidized.[34−36] When nonextracted PDMS layers are used, irreversible sealing typically requires contact of the layers within 1 min after plasma treatment.[1] Although this amount of time is sufficient to seal simple devices irreversibly (i.e., the assembly of channels in PDMS to a flat surface of PDMS), complicated and precise alignment of layers may take several minutes.[37] By oxidizing two pieces of extracted PDMS, we were able to seal two pieces irreversibly as long as 90 h after plasma treatment.[38]

There are several advantages to having hydrophilic surfaces of PDMS that are slow to regenerate into the hydrophobic surface. Hydrophilic surfaces are useful in filling and working with microfluidic devices using water as a fluid; hydrophobic microchannels nucleate air bubbles easily and make it difficult to get rid of air bubbles in the channels.[39] The slow surface rearrangements of extracted PDMS that has been oxidized may make it a better substrate for surface modification (i.e., by treating the surfaces with silanes[40−42] or polyelectrolyte multilayers[43−45]) than nonextracted PDMS.

Deswelling PDMS. PDMS that is extracted with either the high- or extreme-solubility solvents can deswell back to its original shape after removal of the solvent. If the PDMS is not dried evenly, however, it tends to buckle, since uneven evaporation creates a stress in the polymer. For instance, if the PDMS is removed from a highly swelling solvent and left on a surface to be dried in air, the solvent evaporates faster on the side of the polymer exposed to air, and that side will shrink faster than the side touching the surface, where evaporation is slow. To avoid cracking of PDMS during deswelling, we placed the swollen polymer into decreasingly soluble solvents that were miscible with the high-solubility solvent. We deswelled PDMS by removing it from diisopropylamine, placing the swollen polymer in toluene, ethyl acetate, and then acetone (each solvent for 1 day, changing the solvent once), drying the polymer in air, and then placing the polymer in an oven (90 °C) for 2 days. Swelling and deswelling of PDMS did not influence the ability of the polymer to make conformal (van der Waals) contact with other smooth surfaces.

Influence of Swelling on PDMS Bonded to Glass. Glass is sometimes used as a substrate for mounting microfluidic devices made in PDMS.[1,2,39] PDMS bonds irreversibly to glass when the surfaces of the two are oxidized in an air plasma and then brought together. To test the influence of swelling on the desealing of a piece of PDMS that is chemically bonded to a glass substrate, we placed the bonded pieces into different solvents from each solvent category for 24 h. The low-solubility solvents (solvents 21−38 in Figure 1) are the most compatible with PDMS and glass; these solvents do not release (i.e., deseal) the pieces. The moderately

(33) We did not test the extracted PDMS (1.5 cm × 1.5 cm × 0.2 cm, *lwh*) directly for the presenece of residual diisopropylamine. We infer that diisopropylamine was removed from the bulk of the PDMS, since an extraction procedure similar to the one described here was used for the extraction of microchannels in PDMS (6.5 cm × 1.5 cm × 0.5 cm, *lwh*)—a ^{1}H NMR spectrum of a solution that was allowed to flow through these channels for 24 h showed the absense of diisopropylamine.

(34) Chiu, D. T.; Pezzoli, E.; Wu, H.; Stroock, A. D.; Whitesides, G. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 2961−2966.

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(37) By placing nonextracted pieces of PDMS in a 90 °C oven for ∼10 min after contact, we obtained irreversible sealing as long as 1 h after plasma treatment. We found that this procedure was not always reproducible, however.

(38) To prepare the oxidized surfaces, pieces of PDMS were oxidized in a plasma, allowed to stand in contact with ambient air for 1 min at room temperature, contacted, and immediately placed in a 90 °C oven for 10−20 min.

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Table 4. Swelling and Reactivity of Various Acids, Bases, and Solvents Commonly Used in Organic Synthesis

solvent	weight %[a]	molarity[b]	S
acetic acid	100	17.0	1.00 ± 0.01
ammonium hydroxide	29	7.5	1.02 ± 0.01
chloroacetic acid	6	1.0	1.02 ± 0.01
dipropylamine	100	7.3	dissolves
hydrochloric acid	37	12.0	1.02 ± 0.01
nitric acid	70	16.0	1.01 ± 0.01
phosphoric acid	86	15.0	1.01 ± 0.01
potassium hydroxide	28	10.0	1.00 ± 0.01
sodium hydroxide	19	10.0	1.01 ± 0.01
sulfuric acid	5	1.0	1.01 ± 0.01
sulfuric acid	96	18.0	dissolves
trifluoroacetic acid	2	0.3	1.00 ± 0.01
trifluoroacetic acid	100	13.4	dissolves

[a] Denotes weight percent in H_2O. [b] Molarity in units of mol/L.

and highly soluble solvents do deseal PDMS from glass. Under these conditions, the glass inhibits the PDMS from reaching equilibrium swelling, since glass itself does not expand or swell in the presence of these solvents. The PDMS is therefore under stress; stress is relieved when the polymer deseals from glass, at times even breaking the glass or tearing the PDMS.

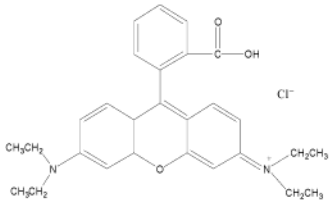
Swelling of PDMS in Acids and Bases. Swelling of a polymer in an acid or a base cannot be predicted by considering solubility parameters, as the solubility parameter does not account for ionic interactions and chemical reactions. We therefore tested the swelling of PDMS in common acids and bases used in organic synthesis. Table 4 lists these acids and bases, as well as the measured swelling ratios of PDMS in these solutions after 24 h. PDMS did not swell considerably in any of the acids and bases in the concentrations listed; PDMS is therefore compatible with these solutions (except for the ones in which the PDMS dissolved, see below) for organic synthesis.

Reactive Solvents. We define reactive solvents as ones that react with PDMS to break the polymer down into smaller subunits (Table 4). The first group of solvents that reacted with PDMS are certain acids: concentrated sulfuric acid and trifluoroacetic acid. Both of these acids dissolved PDMS and left a white precipitate after being immersed for 24 h. The products of the reactions consisted of oligomers with different numbers of dimethylsiloxane subunits, $-(CH_3)_2SiO-$, determined by mass spectrometry and IR.

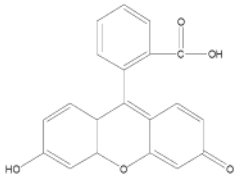
Certain organic reagents react with PDMS. A 1 M tetrabutylammonium fluoride (TBAF) solution in THF dissolves PDMS, most likely by breaking Si−O bonds and forming Si−F bonds, in a reaction similar to the etching of glass that occurs in hydrogen fluoride.[46] Dipropylamine also dissolves PDMS, although more slowly than TBAF. Dipropylamine first swells PDMS over a period of weeks before dissolving[47] the PDMS into dimethylsiloxane subunits, $-(CH_3)_2SiO-$ (determined by mass spectrometry); we have not determined the processes involved in this solublization. Reactive solvents can be used as etching agents for PDMS.

Partitioning of Solutes between a Solvent and PDMS. The solubility of solutes in PDMS is a factor to consider when organic reactions are performed in systems made in PDMS, since the loss of solute from the solvent is a concern. Whether a solute prefers to partition into the PDMS phase or the solvent phase depends on the relative interactions among these three components. For this ternary system, these interactions can be described by the Flory−Huggins interaction parameters: $\chi_{polymer-solute}$, $\chi_{polymer-solvent}$, and $\chi_{solute-solvent}$.[48] As with swelling, the Flory−Huggins interaction parameter depends on the solubility parameter, δ, of each component: $\chi = (\delta_1 - \delta_2)^2 V_1/RT$, where V_1 is the molar volume of component 1, R is the real gas constant, and T is the temperature.[8] Maximum mixing or interaction between components exists when χ is small, e.g., when $(\delta_1 - \delta_2)^2$ is 0. Although these relationships exist, it is difficult to predict the partitioning of solutes because solubility parameters for solutes are not readily available, and it is difficult to measure each of the parameters. We therefore wished to test the partitioning of a few solutes in different solvents experimentally.

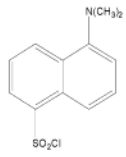
We tested the partitioning of a few UV-active compounds (rhodamine B chloride, fluorescein, and dansyl chloride) in different mixtures of PDMS prepolymer and solvent.



rhodamine B chloride



fluorescein



dansyl chloride

To form a mixture, and not a solution or a suspension with the PDMS prepolymer, the compounds to be tested were dissolved in a low-solubility solvent (e.g., a solvent that is immiscible with PDMS prepolymer). The ideal choice of low-solubility solvent (from Figure 1) had three characteristics: (1) the solvent solvated each of the compounds; (2) the solvent did not react with the solute, nor quench the fluorescence of the solute in the presence of PDMS prepolymer; and (3) the solvent did not cause the PDMS prepolymer to cross-link. Solvents that best fit these criteria were water, propylene carbonate, nitromethane, and acetonitrile.[49] Partitioning experiments were performed with solutions of rhodamine, fluorescein, and dansyl chloride using the concentration of solute in each solvent that gave an absorbance (A) value of ~0.8. Equal amounts of solvent and PDMS prepolymer were mixed with vigorous shaking for 2 min and then allowed to

(46) Arias, F.; Oliver, S. R. J.; Xu, B.; Holmlin, R. E.; Whitesides, G. M. *J. Micromechan. Syst.* **2001**, *10*, 107−112.

(47) Pieces of PDMS began losing their shape and became gellike after being immersed in dipropylamine for 36 days.

(48) Young, R. J. *Introduction to Polymers*; Chapman and Hall: New York, 1991.

(49) From the low-solubility solvents listed in Figure 1, pyridine, NMP, DMF, and DMSO cross-linked the PDMS prepolymer into a clumpy gel upon mixing.

Table 5. Partitioning of Organic Compounds in Solvent/PDMS Mixtures

	partition ratios ($A_{solvent}/A_{solvent} + A_{PDMS}$) (for given solvent)				
compound	water	propylene carbonate	nitromethane	ethanol	acetonitrile
rhodamine	0.4 ± 0.1	0.83 ± 0.07	0.83 ± 0.08	0.97 ± 0.03[c]	0.71 ± 0.02
fluorescein	1.00 ± 0.04	*a*	*a*	*b*	*a*
dansyl chloride	*a*	1.00 ± 0.01	1.00 ± 0.01	*b*	1.00 ± 0.01[c]

[a] Compound did not dissolve in solvent. [b] Fluorescence of compound was quenched in the solvent/PDMS mixture. [c] Only the solvent phase was tested, since the PDMS phase was turbid after mixing with solvent.

partition in the dark for 24 h. The absorbencies of the solute in the solvent and PDMS phases were measured; here, we present the degree of partitioning of the solute in each of the phases as a ratio of absorbencies, $A_{solvent}/(A_{solvent} + A_{PDMS}) \leq 1$ (Table 5).

In these experiments, $\chi_{solute-solvent}$ is small, since we chose solvents in which the solute dissolved and made a clear solution. We thus assume that $\chi_{solute-solvent}$ is similar for the same compound in the different solvents we tested. For the same compound, solutions of the compound in different solvents have the same $\chi_{polymer-solute}$, since the polymer and solute components do not change. We therefore compare the degree of partitioning with, $\chi_{polymer-solvent}$, which we estimate by the difference in δ between the polymer and solvent. For the partitioning of rhodamine (Table 5), there is no obvious trend between solubility parameter and partition ratio. (Note that the solvents in Table 5 are listed from left to right in order of decreasing solubility parameter.) The partitioning of dansyl chloride did not change with slight variations in solubility parameter of the solvents tested.

Although we did not see a trend between solubility parameter and partition ratio for the solvents we tested, we generally do not expect the partitioning of solutes in PDMS to be a deterring factor for performing organic reactions in microfluidic channels made in PDMS, since the range of compatibilities for polymer−solute systems is much smaller than that of solvent−solute systems.[50] For instance, the critical parameter for the complete mixing of two small molecules (solvent and solute) in the regular solution model is $\alpha = 2$, such that if $\alpha < 2$, the two molecules will mix and make a clear solution; otherwise, they will partition.[51] The critical parameter for a polymer−solute mixture in the Flory−Huggins model, however, is $\chi = 0.5$; thus, for a polymer to mix homogeneously with a solute requires $\chi < 0.5$, a smaller range than for a solvent−solute mixture.[52] Because the range of values that is required to make a mixture homogeneous is smaller for a polymer-solute system than for a solvent−solute system, it is generally more common for a solute to be miscible with a solvent than a polymer.[8,48]

Extraction of PDMS Oligomers into Organic Solvents. When PDMS oligomers are cross-linked to form the polymer, not all of the oligomer strands are incorporated into the cross-linked network. The cross-linked (cured) PDMS, therefore, contains un-cross-linked, low molecular weight oligomers that are included in the bulk polymer. When PDMS is in contact with an organic solvent, that solvent may extract these un-cross-linked oligomers from the bulk. We wished to determine the extent of dissolution of PDMS in a solvent, because these oligomers might contaminate the products of reactions carried out in PDMS.

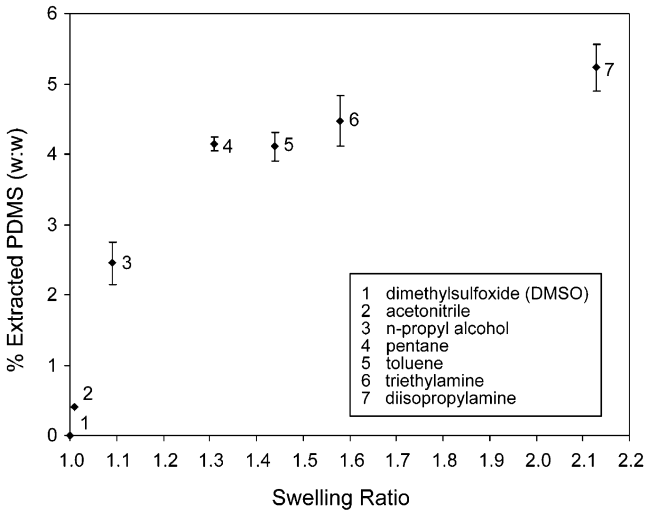


Figure 3. Relationship between the percent extracted PDMS (w/w) and the swelling ratio (*S*) of various solvents in Table 1.

We tested the extent of dissolution of PDMS in various solvents by immersing pieces of PDMS (5 cm × 3.5 cm × 0.3 cm, *lwh*) in the solvents for 24 h and determining the amount of un-cross-linked PDMS by measuring the difference in the weight of the polymer before and after extraction (see Experimental Section). The extent of dissolution of PDMS was also calculated by analyzing the solvent used for extracting the PDMS by ^{1}H NMR; this method gave values in agreement with the values obtained by weight measurements within experimental error. Figure 3 plots the weight percent of PDMS extracted against the swelling ratio

(50) There are some solutes, however, that are more likely than others to partition into PDMS. For example, solutes that have a chemical structure similar to the extremely soluble solvents (e.g., diisopropylamine and triethylamine) will likely partition into the polymer more than solutes that have characteristics of the low-solubility solvents (such as alcohols and ketones). The high solubility of amines in PDMS may explain why the partition ratio of rhodamine was quite low in the PDMS−water mixture (i.e., rhodamine favored the PDMS phase over the water phase, Table 5).

(51) Gaskell, D. R. *Introduction to the thermodynamics of materials*; Taylor & Francis: Washington, DC, 1995.

(52) Both α and χ are temperature-dependent, dimensionless parameters that represent the enthalpy term in the Gibbs free energy equation. The difference between the parameters is that α represents the pair−pair interaction energy in a solvent−solute solution (i.e., the solvent molecule−solute molecule interaction), while χ represents two types of interactions in a polymer−solvent solution: pair−pair interaction energy (i.e., the segment−segment interaction of the polymer) and the polymer volume and solvent volume interaction. Since χ involves volume interactions, it contains an entropic contribution, making it not as straightforward to interpret as the α term. For general discussion in this paper, however, we compare the values of α and χ directly. (For further discussion, refer to the section on Flory−Huggins Theory in: Young, R. J. *Introduction to Polymers*; Chapman and Hall: New York, 1991.)

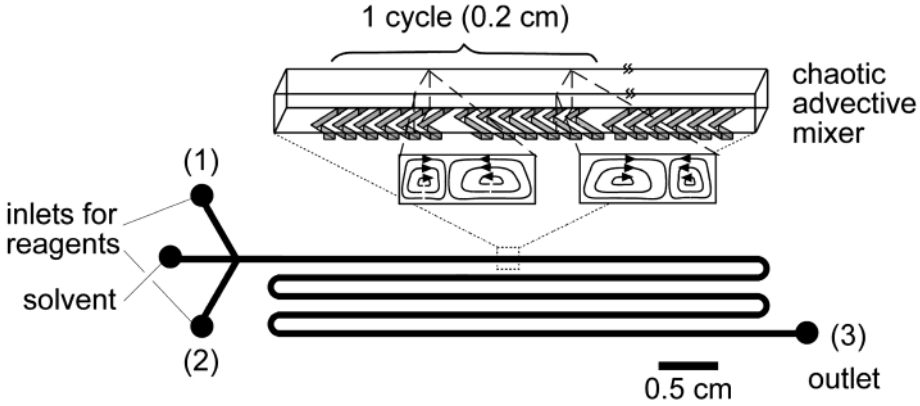


Figure 4. Schematic diagram of the microfluidic device used for the Diels−Alder reaction. The channels contain a chaotic advective mixer (CAM)—ridges that change their orientation with respect to the center of the channel every half-cycle. The streamlines of flow in the channel cross section are also shown. We inject solutions of the reagents 4-phenyl-1,2,4-triazoline-3,5-dione (position 1) and ergosterol (position 2) into the inlets using a syringe pump that is connected to the device via polyethylene tubing. The middle solvent inlet contains acetone and is only used to fill and rinse the channels. The adduct collects into a vial at the outlet (position 3) via polyethylene tubing.

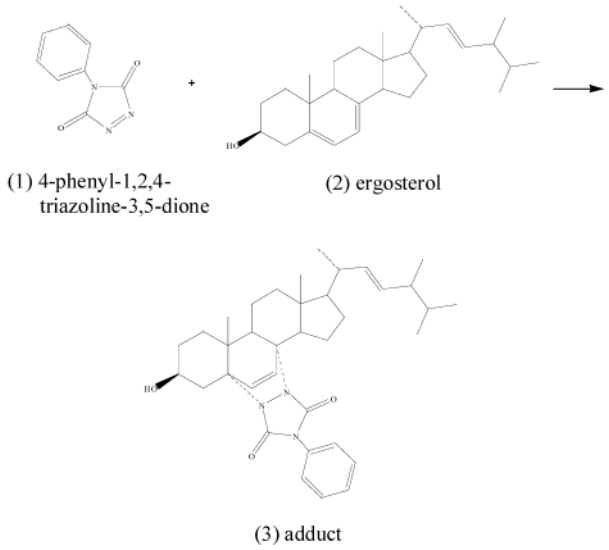
of PDMS in each solvent. Generally, the amount of extracted PDMS increases as the swelling ratio increases. We anticipated this trend.[53]

We suspect that the extent of dissolution of PDMS in a microchannel will be less than the amounts reported in Figure 3. For example, if the low-solubility solvents 21−38 are used in microfluidic applications, the extent of dissolution of PDMS in a microchannel will be <2.5% (w/w) (i.e., less than the highest swelling solvent of the low-solubility group, 1-propanol). In a microchannel, the surface area in contact with the solvent is smaller (on the order of 10^{-1} smaller for a 25-cm-long channel with a width and height of 100 μm) than the surface areas used in the extractions in Figure 3. A smaller surface area in contact with a low-solubility solvent makes extraction slower.

We compared the dissolution of a PDMS slab extracted with ~400 mL of 1-propanol (2.5% extracted PDMS (w/w) with 24 h of mixing, Figure 3) with the dissolution of PDMS from 1-propanol flowing through a microfluidic channel (dimensions 25 cm × 75 μm × 75 μm, *lwh*) that was bonded to glass. After allowing a solution of 1-propanol to flow through the channel at 5 μL/min for 24 h, the amount of un-cross-linked PDMS that was collected in the solution at the outlet was only 0.02% of the original weight of the PDMS, determined by ^{1}H NMR. This amount of un-cross-linked PDMS correlates to 0.05% (w/w) of the total amount of solvent allowed to flow through the channel.

To reduce or eliminate contamination from PDMS oligomers, the microfluidic channels that are embedded in PDMS can first be extracted with a highly soluble solvent (e.g., diisopropylamine or pentane) and then deswelled back to the original shape of the polymer. We performed this extraction procedure (using diisopropylamine) on a microfluidic network made in PDMS before testing the dissolution of PDMS. A solution of 1-propanol was then allowed to flow under the same conditions as those used with the device made in unextracted PDMS. The amount of un-cross-linked PDMS collected at the outlet of the device that was extracted was negligible (<10^{-3}% (w/w) of the total amount of solvent allowed to flow through the channel). We therefore do not believe that contamination of the product with PDMS will be an issue when performing organic reactions in microchannels fabricated of PDMS that have previously been extracted with a highly soluble solvent.

Applications in Synthesis. We demonstrate the compatibility of PDMS with organic solvents by performing a Diels−Alder reaction in a microfluidic channel made in PDMS (Figure 4).[54,55] The reagents 4-phenyl-1,2,4-triazoline-3,5-dione (14.9 mg, 0.085 mmol)



in acetone (0.2 mL) and ergosterol (22.3 mg, 0.056 mmol) in 1:1 acetone/benzene (0.9 mL) were injected into the inlets (positions 1 and 2) with flow rates of 11 and 44 μL/min, respectively. The reaction took place along the channel, with mixing aided by a chaotic advective mixer (CAM)[56] that had been incorporated into the channel. The solvent inlet contained acetone

(53) The *amount* of un-cross-linked PDMS in the bulk polymer depends on the ratio of PDMS prepolymer to cross-linking agent (a 10:1 (w/w) ratio is recommended), as well as the degree of mixing of the two components. A well-mixed solution of PDMS will contain less un-cross-linked PDMS than a solution that is not well-mixed. The amount of *extracted* PDMS depends on the efficiency of the solvent to swell the polymer.

(54) Gilani, S. S. H.; Triggle, D. J. *J. Org. Chem.* **1966**, *31*, 2397−2398.

(55) Morris, D. S.; Williams, D. H.; Norris, A. F. *J. Org. Chem.* **1981**, *46*, 3422−3428.

and was only opened initially to fill the channels and to rinse the channels when the injections of reagents were stopped; this inlet remained closed during the time when the reagents were injected. The dione solution turned from bright red to a yellow-pink upon reaction with ergosterol in the channel; this color change was observed to take place within seconds inside the channel and not at the outlet.[57] The reaction mixture was collected at the outlet (position 3) into a vial via polyethylene tubing. The adduct was identified in the 1H NMR spectrum of the reaction mixture by the appearance of two peaks from the hydrogen of cyclohexene (1 H, d, 6.2 ppm; 1 H, d, 6.4 ppm); the formation of these peaks is typical of Diels−Alder reactions.[54] The two peaks from cyclohexadiene of ergosterol (1H, d, 5.4 ppm; 1H, d, 5.6 ppm) did not appear in the spectrum, indicating a 100% conversion of the limiting reagent (ergosterol) to the product. Unreacted 4-phenyl-1,2,4-triazoline-3,5-dione was also identified in the reaction mixture by ^{1}H NMR.

In this experiment, we used a microchannel that was first extracted with pentane to remove the un-cross-linked PDMS oligomers. ^{1}H NMR spectra of the reaction mixture collected at the outlet confirmed that the presence of PDMS was negligible. We also did not encounter problems of swelling of PDMS, even though we used benzene, a highly swelling solvent.[58] The microfluidic channel did not deseal from the glass substrate during the time that was allowed for the reaction to occur (15 min).

Although we did not integrate analyte detection into this microfluidic device, detection methods such as mass spectrometry,[5,59,60] or ones based on fluorescence,[61,62] electrochemistry,[63−65] or absorbance,[66,67] can be coupled to microfluidic systems for identifying reagents and products of organic reactions. Other steps that may be important for chemical synthesis, such as heating, cooling, and filtration, may also be integrated into microfluidic systems made in PDMS, since PDMS is a material that allows easy integration and interfacing of components.[1,2]

CONCLUSIONS

We have determined a range of solvents that is compatible with a range of operations in PDMS, including performing organic synthesis in microfluidic channels made in PDMS. Of the three parameters that determine the compatibility of PDMS with a solvent—i.e., the swelling of PDMS in the solvent, the partition of solute between a solvent and PDMS, and the dissolution of PDMS oligomers in the solvent—the swelling of PDMS had the greatest influence. Generally, low-solubility (weakly swelling) solvents are most compatible with performing organic reactions in microfluidic channels made in PDMS, although some mixtures of low- and high-solubility solvents are also compatible. We demonstrated this compatibility by performing a Diels−Alder reaction in PDMS microchannels. Acids and bases do not swell PDMS, but reactions that require amines or certain strong acids are not compatible, as these reagents dissolved the polymer.

High-solubility solvents are useful for extracting PDMS oligomers from the bulk of the cross-linked polymer. This extraction process helps to reduce or eliminate contamination (from PDMS oligomers) of solutions that flow through microchannels made in PDMS. Since PDMS deswells approximately back into its original shape when the swollen polymer is cycled through decreasingly soluble solvents, the shape of the microchannels is not disturbed after extraction. We also found that extraction of PDMS changes the surface properties of PDMS: surfaces of extracted PDMS that were oxidized with an air plasma retained $\theta_a^{H_2O} < 30°$ in air for 4 days after plasma treatment and sealed better than nonextracted PDMS. Extracted PDMS may be useful for those wanting hydrophilic channels for microfluidics or those interested in modifying the surface of PDMS.

Although problems of swelling and compatibility of organic solvents is less of a concern in microfluidic systems fabricated in glass or silicon, the cost of fabrication in these materials is high. The cost and ease of fabrication in PDMS is low, but PDMS is limited to certain ranges of solvents. As interest in performing organic reactions on-chip continues to grow, it seems likely that PDMS will be used in fabricating microreactors for organic reactions that involve solvents compatible with PDMS. Reactions requiring highly and extremely soluble solvents may require glass or silicon.

EXPERIMENTAL SECTION

Materials. Sylgard 184 Silicone, a two-part PDMS elastomer, was purchased from Essex Brownell (Edison, NJ). For all experiments requiring solid PDMS, we used a 10:1 (by weight) mixture of PDMS base/curing agent that was degassed under vacuum and cured at 70 °C for 24 h. Solvents were obtained from Sigma-Aldrich Co. (St. Louis, MO), Fisher Scientific Co. (Pittsburgh, PA), and Mallinckrodt, Inc. (Chicago, IL) and used as received.

Swelling Measurements. We measured swelling (at 25 °C) by comparing the lengths of solid pieces of PDMS before and after being immersed in a solvent. The PDMS pieces were made by soft lithography and are in the shape of hexagons;[32,68] the length from one edge of the hexagon to the opposite edge was measured (typically, 4 mm from one edge to the opposite edge, and 1 mm thick for unswollen pieces). We immersed these PDMS pieces in

(56) Stroock, A. D.; Dertinger, S. K. W.; Ajdari, A.; Mezic, I.; Stone, H. A.; Whitesides, G. M. *Science* **2002**, *295*, 647−651.

(57) Since the reagents flow at a rate of ∼44 mL/min and are adequately mixed in the channel, it should take ∼40 s for the reagents to reach the outlet for a channel with dimensions 200 μm × 75 μm × 20 cm (*whl*). The time for reaction is ≪ 40 s (Gilani, S. S. H.; Triggle, D. J. *J. Org. Chem*. **1966**, *31*, 2397−2398). Thus, the reaction should take place in the channel and not at the outlet. Observations of color change within the channel, and not at the outlet, agree with this analysis.

(58) We may not have observed swelling of PDMS with benzene in this experiment because of the short length of time in which the solvent was in contact with the polymer (15 min for the experiment performed here, versus 24 h for the swelling experiment performed in Figure 1, where swelling was observed).

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(67) Bowden, M. a. D., D. *Sens. Actuators, B* **2003**, *B90*, 170−174.

(68) Bowden, N.; Oliver, S. R. J.; Whitesides, G. M. *J. Phys. Chem. B* **2000**, *104*.

each solvent for 24 h at 25 °C; under these conditions, swelling reached equilibrium (i.e., the dimensions of the PDMS solid did not change with time).[69] The pieces were imaged while immersed in the solvent, using a CCD camera connected to a stereoscope; the lengths of the pieces were measured directly on the digitized image, using Nikon ACT-1 Version 2.12 software (Nikon Corp.). (If the PDMS piece was removed from the solvent, we found that the dimensions of the piece decreased within seconds as the solvent evaporated from the PDMS.) We measured the lengths of five different pieces of PDMS for each solvent; an average of these measurements gave the reported value with a typical relative error of ±1% for the different solvents.

Contact Angle Measurements. Advancing contact angles were measured on static drops of water using a Ramé-Hart goniometer with a Matrix Technologies Electrapipet to control the advancement of the drop. Typically, $N = 30$ measurements were taken for each of the data points in Figure 2. We measured the advancing contact angles of water on pieces of PDMS (1.5 cm × 1.5 cm × 0.2 cm, *lwh*) that were extracted or nonextracted and oxidized or nonoxidized. The pieces of extracted PDMS were extracted (at 25 °C) for 1 day in ∼100 mL of diisopropylamine with stirring, deswelled in stirred solutions of ∼100 mL of ethyl acetate for 1 day and then acetone for 2 days (∼100 mL each day; solvent was changed after 1 day), and dried in an oven (90 °C) for at least 2 days to remove the residual solvent from the bulk of the polymer. The oxidized surfaces were oxidized for 60 s in a SPI Plasma Prep II plasma cleaner that was used under vacuum (∼2 mTorr) (SPI Supplies, West Chester, PA).

Swelling of PDMS Bonded to Glass. To test whether a solvent desealed a piece of PDMS that was chemically bonded to a glass substrate, pieces of PDMS (4 cm × 3 cm × 0.3 cm, *lwh*) and glass slides (7.5 cm × 2.5 cm × 0.1 cm, *lwh*) were oxidized in an air plasma. The surfaces that were exposed to the plasma were brought together and sealed irreversibly by applying a small pressure for 1 min. These bonded pieces were then placed into the solvent for 24 h without stirring at 25 °C.

Extraction of Un-Cross-Linked PDMS. To test the extent of dissolution of PDMS in a solvent (Figure 3), we immersed pieces of PDMS (5 cm × 3.5 cm × 0.3 cm, *lwh*) into ∼400 mL of the solvent for 24 h at 25 °C while the solvent was stirred. The percent extraction (w/w) was determined by dividing the difference between the weight of the PDMS before and after extraction by the original weight of the PDMS. We also analyzed the solvent used for extracting the PDMS by evaporating off the solvent under vacuum, adding a known amount of internal standard (DMSO), and taking a ^{1}H NMR of the extracted PDMS in $CDCl_3$.[70] (The PDMS peak had a chemical shift of $\sigma = 0.1$ ppm.) The amount of extracted PDMS calculated by this method agreed with the values obtained by weight measurements, within experimental error.

To test the extent of extraction of PDMS by a solvent flowing through a microfluidic channel, we used a Harvard Apparatus 2000 syringe pump to produce a steady flow rate (5 μL/min for 24 h) of 1-propanol in the channel (25 cm × 200 μm × 200 μm, *lwh*). Microfluidic channels were made by soft lithographic procedures described elsewhere.[32,39] The solution was collected at the end of the channel, and the solvent was evaporated under vacuum. The amount of un-cross-linked PDMS was determined by adding a known amount of internal standard and taking a ^{1}H NMR in $CDCl_3$. The amount of un-cross-linked PDMS was 0.02% (w/w) of the original weight of PDMS, or 0.05% (w/w) of the total amount of solvent flowed through the channel.

Reactive Solvents. To determine which acids and bases reacted with PDMS, pieces of PDMS in the shapes of hexagons (4 mm in length from one edge to the opposite edge) were immersed in 10 mL of acid or base for 24 h at 25 °C. The solvents that reacted with PDMS (18.0 M sulfuric acid and 13.4 M trifluoroacetic acid) formed a white precipitate after this time. To determine the product of the reaction of acid with PDMS, the precipitate was rinsed thoroughly with water and then dried in an oven (70 °C) for 24 h. Mass spectra and IR spectra of the precipitate give data that are consistent with the hypothesis that the products of both reactions consisted of low molecular weight oligomers having the structure $(CH_3)_3Si[OSi(CH_3)_2]_xOSi(CH_3)_3$.

Partitioning. For partitioning experiments, we used one part (the PDMS base) of a two-part PDMS elastomer, Sylgard 184 Silicone, from Essex Brownell. Rhodamine B chloride and fluorescein were purchased from Sigma-Aldrich Co., dansyl chloride was purchased from Fluka, and all solvents were purchased from Sigma-Aldrich Co. and used as received.

Partitioning of UV-active compounds (rhodamine, fluorescein, dansyl chloride) was tested in mixtures containing PDMS prepolymer and solvent. Solutions of each compound were made in water, propylene carbonate, nitromethane, ethanol, and acetonitrile. The wavelengths that gave maximum absorption, λ_{abs}, for each compound varied slightly in each solvent and were determined to be ∼554−588 nm for rhodamine, 490 nm for fluorescein, and 373 nm for dansyl chloride. Calibration curves containing a range of concentrations of each solute that gave absorbance (A) measurements (at λ_{abs}) between 0 and ∼1.5 were determined using a HP 8453 UV−visible spectrophotometer (Hewlett-Packard) and UV−visible ChemStation software (Agilent Technologies).

We chose to perform partitioning experiments with the concentration of solute that gave A ∼0.8 for each solvent. These concentrations were on the order of 0.01 mM (depending on the solvent) for rhodamine, 0.01 mM for fluorescein, and 0.2 mM for dansyl chloride. To a vial was added 3.0 g of the solvent containing the solute and 3.0 g of PDMS prepolymer. The contents were mixed for 2 min using a Vortex-Genie 2 (VWR Scientific) set to maximum. The mixture was covered from exposure to light, and the phases were allowed to separate for 24 h. The PDMS phase was removed from the solvent phase using a pipet and then placed in a cuvette for UV−visible; this phase was degassed under vacuum for 24 h (in the dark) to remove the air bubbles before performing absorbance measurements. Measurements of absorbance were obtained for both the solvent phase and PDMS phase. Three sets of partitioning experiments were performed for each of the solute−solvent combinations.

Organic Synthesis in Microfluidic Channels. All reagents were purchased from Sigma-Aldrich Co. and used without further purification. Microfluidic channels with CAM surface features were

(69) Typically, equilibrium swelling was reached within 1 h of being immersed in the solvent. For the amines, however, equilibrium swelling time varied from days to weeks.

(70) We assumed the PDMS to have an average molecular weight of 50 000 based on the viscosity of the polymer immediately after mixing with the curing agent (4000 mPa/s) (www.dowcorning.com) and the relationships between viscosity and molecular weight for PDMS (https://www.sigma-aldrich.com/aldrich/brochure/al_pp_viscosity.pdf).

fabricated in PDMS according to reported procedures.[56] The PDMS channels were extracted with pentane for 2 days, deswelled in toluene for 1 day, ethyl acetate for 1 day, and acetone for 1 day, and then dried in an oven (90 °C) for 2 days. The PDMS was oxidized in an air plasma for 60 s and then bonded irreversibly to glass.

We filled 0.250- and 1-mL syringes with solutions of 4-phenyl-1,2,4-triazoline-3,5-dione (14.9 mg, 0.085 mmol) in acetone (0.2 mL) and ergosterol (22.3 mg, 0.056 mmol) in a 1:1 solution of acetone/benzene (0.9 mL). The solutions were injected into the channels via polyethylene tubing, with flow rates of 0.011 (for the 0.25-mL syringe) and 0.044 mL/min (for the 1-mL syringe) for 15 min using a Harvard Apparatus 2000 syringe pump. The reaction proceeded inside the microchannels by evidence of a color change from the bright red 4-phenyl-1,2,4-triazoline-3,5-dione to a yellow-pink (product). The reaction mixture was collected at the outlet via polyethylene tubing into a vial; the adduct was identified by ^{1}H NMR in $CDCl_3$ by the appearance of two peaks due to the hydrogen from cyclohexene (1 H, d, 6.2 ppm; 1 H, d, 6.4 ppm). We estimate 100% conversion of the limiting reagent (ergosterol) to the product based on the disappearance of the two peaks from cyclohexadiene in ergosterol (1H, d, 5.4 ppm; 1H, d, 5.6 ppm). An excess of ~47% of 4-phenyl-1,2,4-triazoline-3,5-dione in the end reaction mixture was calculated by comparing the ratio of integration of the peaks from the phenyl group on 4-phenyl-1,2,4-triazoline-3,5-dione (~7.3 H (calculated), m, 7.4 ppm) to the expected integration (5 H, m, 7.4 ppm). This value is in agreement with the 52% excess of starting reagent of 4-phenyl-1,2,4-triazoline-3,5-dione, compared to the initial amount of ergosterol.

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