Nanoparticle Transport

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Stimuli-Responsive Reversible Transport of Nanoparticles Across Water/Oil Interfaces**

Erik W. Edwards, Munish Chanana, Dayang Wang, and Helmuth Möhwald*

Water/oil interfaces have been used extensively as platforms for assembling systems that are capable of mimicking a variety of biologically relevant systems and phenomena. The study of the structure and behavior of molecules at water/oil interfaces may help to increase our comprehension of the behavior of biological membranes,[1] transmembrane proteins,[2] protein folding,[3] and the fundamental principles that govern wettability.[4] For many applications, for example, to cross a biological membrane or barrier, a particle has to be hydrophobic, but before and after it has to be hydrophilic. Thus, reversibility of the wetting properties with avoidance of aggregation is of paramount importance. Herein, we demonstrate the transfer of gold nanoparticles (NPs), capped with a stimuli-responsive polymeric coating, across the water/oil interface in both directions. The present work demonstrates an unprecedented surface wettability of NPs. The gold NPs reported here are highly colloidally stable in both aqueous and organic media, but spontaneously transfer from one bulk phase to the other upon forming a biphasic salty water–oil system.

Recently developed experimental[5,6] and simulation[7,8] tools are capable of providing information about water/oil interfaces at the molecular level. However, the molecular-scale probes used to study the complex processes that occur at interfaces are limited by size and time regimes that are difficult to access by standard microscopy techniques. As a result of their unique size-dependent physicochemical properties, inorganic NPs provide a promising alternative class of materials with the potential to serve as model materials or probes for biological systems.[9] Moreover, their nanoscale dimensions, on the order of 2–20 nm, allow for direct imaging by electron microscopy techniques.

The reproducible synthesis and functionalization of inorganic NPs have been pursued for well over a decade.[10,11] We and other groups now have a good understanding of how inorganic NPs can be functionalized so that they are interfacially active in biphasic water–oil systems.[12–19] Previous studies on inorganic NPs capped by stimuli-responsive ligands either have not investigated the interfacial properties of those NPs[20–24] or have focused on the interfacial attachment of NPs to the water/oil interface.[12–19] However, one area that has not been fully investigated is how to make NPs truly "smart" materials that can cross the barriers of biphasic systems, similar to the behavior of biomacromolecules. Thus, the rational design and synthesis of inorganic NPs that are capable of crossing immiscible water/oil interfaces may ultimately be necessary to fully access the potential diagnostic and therapeutic applications that are often cited for inorganic NPs.

The gold NP–polymer system used in the present study is shown schematically in Figure 1 A. Disulfide-functionalized homopolymers and random copolymers of oligo(ethylene glycol) methyl methacrylate (OEGMA) and 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) were synthesized by atom-transfer radical polymerization (ATRP) initiated by disulfide-functionalized initiators.[25,26] The PEGylated polymethacrylates (PEG = polyethylene glycol) obtained in this manner were used as stabilizers to form gold NPs with diameters between 2 and 10 nm through a one-step reduction process in methanol.[10] This grafting-to strategy was chosen to

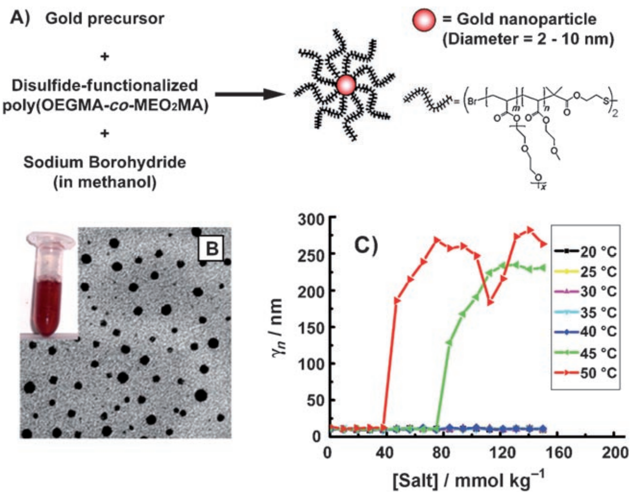

Figure 1. Synthesis and stability of poly(OEGMA-*co*-MEO_2MA)-capped gold NPs. A) Schematic depicting the synthesis of 2–10-nm-diameter gold NPs by the one-phase reduction of $HAuCl_4$ in the presence of disulfide-functionalized poly(OEGMA-*co*-MEO_2MA) and methanol. B) TEM and optical (inset) images showing gold NPs capped with poly(OEGMA-*co*-MEO_2MA) (8% OEGMA) dispersed in water. The TEM image shows a 100×100 nm area. C) Hydrodynamic radius r_h of poly(OEGMA-*co*-MEO_2MA)-capped gold NPs in solutions of varying salt concentration and at different temperatures, as measured by dynamic light scattering. The lines are provided to guide the eye.

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[*] Dr. E. W. Edwards, M. Chanana, Dr. D. Wang, Prof. Dr. H. Möhwald
Max Planck Institute for Colloids and Interfaces
14424 Potsdam (Germany)
Fax: (+49) 331-567-9202
E-mail: dayang.wang@mpikg-golm.mpg.de

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form polymer-stabilized gold NPs because a grafting-from strategy (surface-initiated ATRP) led to dense polymer brushes on the NP surface that rendered the particles insoluble in water.

After dialysis to remove free polymer and salts,[27] the polymer-coated NPs exhibited the solubility of the coating polymer. The particles could be suspended at high concentrations (ca. 10 mg mL^{-1}) in good solvents for the coating polymer, such as water, methanol, ethanol, tetrahydrofuran, and toluene, but could not be suspended in poor solvents, such as chloroform and *n*-alkanes. Figure 1 B shows a representative optical image of a water suspension of the poly(OEGMA-*co*-MEO$_2$MA)-capped gold NPs and a TEM image of those particles. For the particles shown in Figure 1 B, the poly(OEGMA-*co*-MEO$_2$MA) had a lower critical solution temperature (LCST) of circa 37 °C and an OEGMA molar fraction of 8 %.

The solubility of PEG in aqueous media results from hydrogen bonding between the polymer and surrounding water. It is well-known that the addition of salt and heating can weaken hydrogen bonds, thus reducing the water solubility of PEG. In the present study, one may envision that adding salt or heating results in a decreased solubility of gold NPs capped by PEGylated polymethacrylates in water, ultimately leading to aggregation. The hydrodynamic radius of poly(OEGMA-*co*-MEO$_2$MA)-capped gold NPs at various temperatures and NaCl concentrations was analyzed by dynamic light scattering. As shown in Figure 1 C, the NPs exhibit long-term stability at room temperature in the presence of aqueous NaCl at concentrations as high as 0.15 mol kg^{-1} NaCl. When the environmental temperature was significantly higher than the LCST of the polymeric capping layer, the NPs began to aggregate into large clusters above a certain salt concentration depending on the temperature. At 45 °C, particle aggregation occurred at 0.08 mol kg^{-1} NaCl, whereas at 50 °C aggregation started at 0.04 mol kg^{-1} NaCl.

Upon adding toluene to salt-containing aqueous solutions of gold NPs capped with PEGylated polymethacrylate, followed by standing at room temperature for 48 h, the NPs spontaneously transferred to the toluene phase (Figure 2 A). The degree of particle transfer was dependent on the aqueous salt concentration but independent of the specific salt. The number of particles transferred to the toluene phase increased with salt concentration and time in a nearly linear manner (Figure 2 B and C).

Furthermore, the relative fractions of the two monomers contained in the capping copolymer had a pronounced influence on the kinetics of the NP transfer from water to toluene. PEGylated polymethacrylates with a greater fraction of OEGMA required a greater salt concentration and/or a longer standing time for transfer from water to toluene. Additionally, heating biphasic mixtures of toluene and salty aqueous suspensions of the polymer-capped gold NPs accelerated the transfer of the particles to the toluene phase and resulted in a greater degree of particle transfer (Figure 2 D).[28]

Dynamic light scattering of gold NPs capped with PEGylated polymethacrylate in salty aqueous solutions and toluene revealed that the hydrodynamic radius of the particles was the same before and after transfer across the water/oil interface. This finding indicates that NP transfer from the aqueous phase to the organic phase does not result from the aggregation of the particles in the aqueous phase and redispersion in the toluene phase.

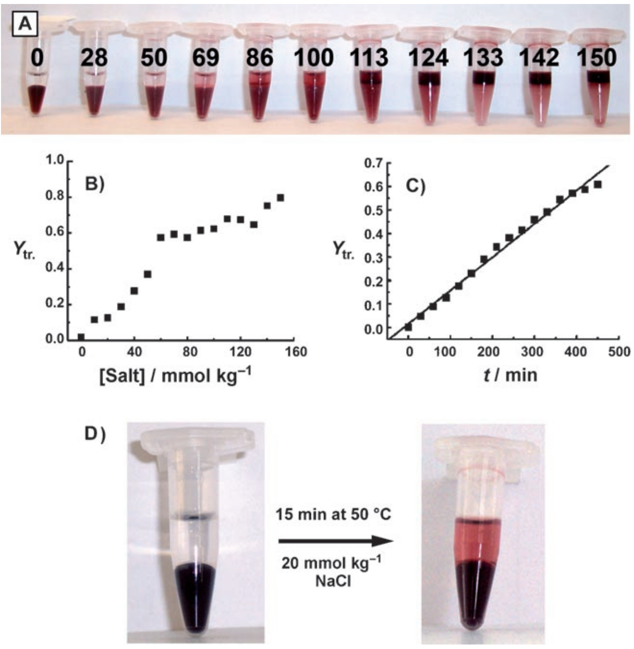

Figure 2. Poly(OEGMA-*co*-MEO$_2$MA)-capped gold NPs spontaneously transfer across the salty water/toluene interface. A) Optical image of gold NPs capped with poly(OEGMA-*co*-MEO$_2$MA) (8 % OEGMA, LCST ≈ 37 °C), originally dispersed in aqueous NaCl solution, 2 days after creating a biphasic system with toluene. The NaCl concentrations, in mmol kg^{-1}, are shown on each vial. B) Fraction $Y_{tr.}$ of poly(MEO$_2$MA)-capped gold NPs transferred across the salty water/toluene interface after 1 h with vigorous shaking, as measured by UV/Vis spectroscopy, as a function of salt concentration. C) Fraction $Y_{tr.}$ of poly(MEO$_2$MA)-capped gold NPs transferred across the salty water/toluene interface as a function of time, initially in salt solutions with a concentration of 150 mmol kg^{-1}, as measured by UV/Vis spectroscopy. The solid line is a linear fit to the data. D) Optical image of gold NPs capped with poly(OEGMA-*co*-MEO$_2$MA) (8 % OEGMA, LCST ≈ 37 °C), originally dispersed in a 30 mmol kg^{-1} solution of NaCl in water, 15 min after the introduction of toluene at room temperature and 15 min after heating the biphasic mixture at 40 °C.

To gain insight into the unique interfacial behavior of gold NPs capped with PEGylated methacrylic polymers at the interface between salty water and toluene, we measured the surface energy of different PEGylated polymers grafted to planar gold substrates. According to the van Oss–Chaudhury–Good (VOCG) model the overall interfacial energy of the surface, γ_{SL}^{tot}, can be expressed as shown in Equation (1).[29,30]

$$\begin{aligned}\gamma_{SL}^{tot} = & ((\gamma_S^{LW})^{1/2} - (\gamma_L^{LW})^{1/2}) \\ & + 2\,((\gamma_S^{+}\gamma_S^{-})^{1/2} + (\gamma_L^{+}\gamma_L^{-})^{1/2} - (\gamma_S^{+}\gamma_L^{-})^{1/2} - (\gamma_S^{-}\gamma_L^{+})^{1/2})\end{aligned} \tag{1}$$

In Equation (1) the subscripts S and L denote the surface energy components of the solid and liquid, respectively, γ^{LW} is the Lifshitz–van der Waals component of the surface energy,

γ^+ is the electron-acceptor parameter of an acid–base interaction, and γ^- is the electron-donor parameter. The calculated values of γ_{SL}^{tot} for poly(MEO$_2$MA), poly(OEGMA-*co*-MEO$_2$MA), and poly(OEGMA) with pure water, salty water, and toluene, as well as the calculated values of γ^{LW}, γ^+, and γ^- for the polymer-grafted planar gold surfaces, are presented in Table 1. The details of the derivation of Equation (1) in the VOCG model and the calculated values of γ^{LW}, γ^+, γ^-, and γ_{SL}^{tot} are presented as Supporting Information.

Table 1: Surface energy components and interfacial energies with solvents of the surface-grafted polymers used as model systems for the polymer-capped NPs investigated.[a]

	MEO$_2$MA	OEGMA-*co*-MEO$_2$MA (10:90)	OEGMA
γ^{LW} [mN m^{-1}]	40.8 ± 0.6	40.5 ± 0.2	42.1 ± 0.1
γ^+ [mN m^{-1}]	0.0	0.0	0.0
γ^- [mN m^{-1}]	29.1 ± 0.8	35.0 ± 0.6	40.6 ± 0.9
$\gamma_{polymer-water}^{tot}$ [mN m^{-1}]	−0.5 ± 0.8	−5.8 ± 0.6	−10.0 ± 0.9
$\gamma_{polymer-0.5MNaCl}^{tot}$ [mN m^{-1}]	6.4 ± 0.6	1.6 ± 0.6	−2.1 ± 0.8
$\gamma_{polymer-toluene}^{tot}$ [mN m^{-1}]	1.4 ± 0.1	1.0 ± 0.1	1.3 ± 0.1

[a] The error values represent 95 % confidence intervals.

Table 1 reveals that the value of $\gamma_{polymer-water}^{tot}$ for each polymer is less than the value of $\gamma_{polymer-toluene}^{tot}$. This result indicates that the gold NPs with a PEGylated polymethacrylate capping are preferentially wetted by the aqueous phase of a biphasic system consisting of pure water and toluene, and explains why the polymer-capped NPs do not spontaneously transfer across pure water/toluene interfaces. As salt is added to the aqueous phase, the interfacial energy between the polymer-capped NPs with the aqueous phase, $\gamma_{polymer-0.5\,M\,NaCl}^{tot}$, increases such that it is comparable to or greater than $\gamma_{polymer-toluene}^{tot}$. The particles are then preferentially wetted by the toluene phase. In this scenario, it is energetically favorable for particles to transfer from salty water to toluene. A comparison of the $\gamma_{polymer-0.5\,M\,NaCl}^{tot}$ values listed in Table 1 indicates that the addition of salt has a stronger influence on $\gamma_{polymer-water}^{tot}$ of poly(MEO$_2$MA) relative to the toluene phase than on $\gamma_{polymer-water}^{tot}$ of poly(OEGMA-*co*-MEO$_2$MA) and poly(OEGMA) relative to the toluene phase. This finding is consistent with the experimental observation that the particles with a polymer cap containing a higher fraction of OEGMA require a higher salt concentration to cross the salty water/toluene interface.

We found that gold NPs capped with poly(MEO$_2$MA), poly(OEGMA-*co*-MEO$_2$MA), and poly(OEGMA) do not spontaneously transfer from toluene back to a pure water phase, as both the methacrylate backbone and the PEGylated side group of the polymer cap are wetted by toluene. To transfer the NPs from toluene back to water, one must promote hydrogen bonding between the particles and the aqueous phase. To accomplish this, we replaced the aqueous phase with 2 wt. % citric acid solution (pH ≈ 4) after transferring poly(OEGMA)-capped gold NPs from NaCl solutions (5 mol kg^{-1}) to toluene. The NPs were found to spontaneously transfer back to the citric acid solution overnight. This process was accelerated by vigorous shaking (Figure 3 A–C). The spontaneous transfer of poly(OEGMA)-capped gold NPs from toluene to 2 wt. % citric acid is documented in Figure 3 D. This reversible transfer can be repeated at least five times without aggregation. Gold NPs capped with poly(MEO$_2$MA) and poly(OEGMA-*co*-MEO$_2$MA) have not been transferred back to such citric acid solutions in our experiments to date.

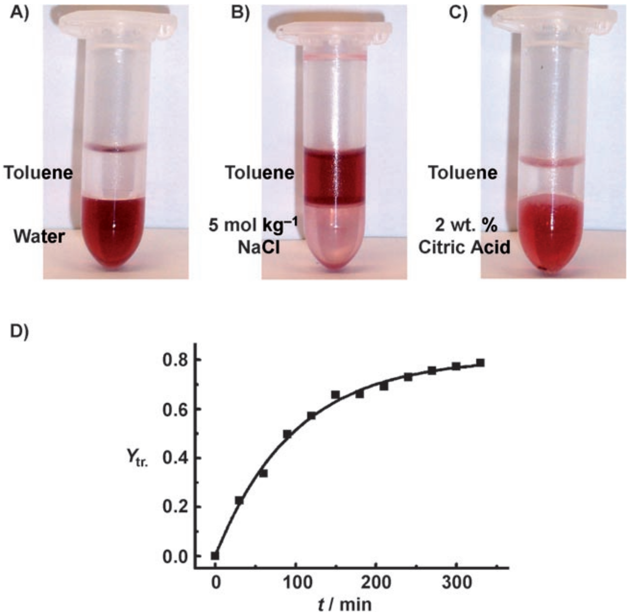

Figure 3. Poly(OEGMA)-capped gold NPs can be transferred from water to toluene and back again. A) Poly(OEGMA)-capped gold NPs dispersed in a solution (5 mol kg^{-1}) of NaCl in water after the introduction of toluene. B) The vial depicted in (A) after 5 min of vigorous shaking to induce the transfer of the poly(OEGMA)-capped gold NPs to the toluene phase. C) The same poly(OEGMA)-capped gold NPs after removing the toluene phase, placing it in a vial with 2 wt. % citric acid solution, and shaking vigorously for 5 min. The particles return to the aqueous subphase. D) Time evolution of the fraction $Y_{tr.}$ of poly(OEGMA)-capped NPs that transfer from toluene to 2 wt. % citric acid solution, as measured by UV/Vis spectroscopy. The line is an exponential fit to the data.

In summary, NPs capped with homopolymers and copolymers of MEO$_2$MA and OEGMA spontaneously transfer across salty water/toluene interfaces. The NP–polymer composite materials presented here represent the first report of NPs that are capable of reversible transfer across an immiscible interface without chemical modification or precipitation to induce that phase transfer. A particularly significant result is that even in the so-called “collapsed state” that induces the particles to transfer to toluene, the NPs do not precipitate in water. This may result in new applications for inorganic NPs, such as crossing biological barriers, which requires particles to be hydrophobic even as they remain soluble in biomimetic conditions. Thus, the technological significance of this work lies in the potential utility of the NP–polymer composite materials as carriers for drugs across biological barriers, as imaging agents in biological systems, and as probes to investigate interesting interfacial phenomena.

Experimental Section

Gold NPs were prepared by reducing $HAuCl_4$ in the presence of disulfide-functionalized PEGylated polymethacrylates with sodium borohydride as the reducing agent and methanol as solvent. Disulfide-functionalized polymer (100 mg) and $HAuCl_4$ (10 mg) were dissolved in methanol (100 mL). $NaBH_4$ (37 mg) in methanol (3 mL) was then added dropwise to the $HAuCl_4$/polymer solution under vigorous stirring. After stirring overnight, excess methanol was removed by rotary evaporation and the concentrated NP solution was dialyzed repeatedly against deionized water to remove $NaBH_4$ and free polymer. The resulting NP suspension was then filtered and the filtrate was heated above the LCST of the polymer to ensure that free polymer was removed.

Gold NPs capped with PEGylated methacrylates were transferred across the water/oil interface by adding NaCl solutions to highly concentrated aqueous suspensions of the NPs. After introducing toluene to the salty water NP suspensions, the particles spontaneously transferred to the organic phase. This process was accelerated in some experiments by vigorously shaking the salty water–oil mixture.

UV/Vis absorption spectra were recorded with a Cary 50 UV/Vis spectrophotometer. TEM images were obtained with a Zeiss EM 912 Omega microscope at an acceleration voltage of 120 kV. Dynamic light scattering experiments were performed on a Malvern HPPS 500 instrument. Contact angle measurements were made with a contact angle measuring G10 apparatus (Krüss, Germany) at ambient temperature.

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[1] R. Zimmermann, L. Müller, B. Wullich, *Trends Mol. Med.* **2006**, *12*, 567.
[2] G. von Heijne, *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 909.
[3] E. Shakhnovich, *Chem. Rev.* **2006**, *106*, 1559.
[4] A. Poynor, L. Hong, I. K. Robinson, S. Granick, Z. Zhang, P. A. Fenter, *Phys. Rev. Lett.* **2006**, *97*, 266101.
[5] P. B. Miranda, Y. R. Shen, *J. Phys. Chem. B* **1999**, *103*, 3292.
[6] L. F. Scatena, G. L. Richmond, *J. Phys. Chem. B* **2001**, *105*, 11240.
[7] I. Kereszturi, P. Jedlovszky, *J. Phys. Chem. B* **2005**, *109*, 16782.
[8] R. L. Napoleon, P. B. Moore, *J. Phys. Chem. B* **2006**, *110*, 3666.
[9] A. P. Alivisatos, *Sci. Am.* **2001**, *285*, 59.
[10] H. Weller, *Angew. Chem.* **1993**, *105*, 43; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 41.
[11] M. Brust, M. Walker, D. Bethell, D. J. Schiffrin, R. Whyman, *J. Chem. Soc. Chem. Commun.* **1994**, 801.
[12] B. P. Binks, R. Murakami, S. Armes, S. Fujii, *Angew. Chem.* **2005**, *117*, 4873; *Angew. Chem. Int. Ed.* **2005**, *44*, 4795.
[13] H. Duan, D. Wang, D. Kurth, H. Möhwald, *Angew. Chem.* **2004**, *116*, 5757; *Angew. Chem. Int. Ed.* **2004**, *43*, 5639.
[14] H. Duan, D. Wang, N. Sobal, M. Giersig, D. Kurth, H. Möhwald, *Nano Lett.* **2005**, *5*, 949.
[15] E. Glogowski, J. B. He, T. Russell, T. Emrick, *Chem. Commun.* **2005**, 4050.
[16] E. Glogowski, R. Tangirala, J. He, T. Russell, T. Emrick, *Nano Lett.* **2007**, *7*, 389.
[17] F. Reincke, W. Kegel, H. Zhang, M. Nolte, D. Wang, D. Vanmaekelbergh, H. Möhwald, *Phys. Chem. Chem. Phys.* **2006**, *8*, 3828.
[18] F. Reincke, S. G. Hickey, W. K. Kegel, D. Vanmaekelbergh, *Angew. Chem.* **2004**, *116*, 464; *Angew. Chem. Int. Ed.* **2004**, *43*, 458.
[19] J. Wang, D. Y. Wang, N. S. Sobal, M. Giersig, M. Jiang, H. Möhwald, *Angew. Chem.* **2006**, *118*, 8131; *Angew. Chem. Int. Ed.* **2006**, *45*, 7963.
[20] M. Das, N. Sanson, D. Fava, E. Kumacheva, *Langmuir* **2007**, *23*, 196.
[21] M. Karg, I. Pastoriza-Santos, L. Liz-Marzan, T. Hellweg, *ChemPhysChem* **2006**, *7*, 2298.
[22] D. J. Kim, S. M. Kang, B. Kong, W. J. Kim, H. J. Paik, H. Choi, I. S. Choi, *Macromol. Chem. Phys.* **2005**, *206*, 1941.
[23] F. Y. Pong, M. Lee, J. R. Bell, N. T. Flynn, *Langmuir* **2006**, *22*, 3851.
[24] F. Seker, P. R. L. Malenfant, M. Larsen, A. Alizadeh, K. Conway, A. M. Kulkarni, G. Goddard, R. Garaas, *Adv. Mater.* **2005**, *17*, 1941.
[25] J. F. Lutz, A. Hoth, *Macromolecules* **2006**, *39*, 893.
[26] R. R. Shah, D. Merreceyes, M. Husemann, I. Rees, N. L. Abbott, C. J. Hawker, J. L. Hedrick, *Macromolecules* **2000**, *33*, 597.
[27] If free polymer remains in the NP solution it will affect the phase-transfer behavior of the NPs. NP solutions containing no free polymer remain clear when heated above the LCST of the polymer.
[28] That a greater degree of particle transfer occurs can be seen by comparing the vial in the right-hand panel of Figure 2D with the second vial shown in Figure 2A.
[29] C. J. Van Oss, M. K. Chaudhury, R. J. Good, *Chem. Rev.* **1988**, *88*, 927.
[30] C. J. Van Oss, R. J. Good, M. K. Chaudhury, *Langmuir* **1988**, *4*, 884.