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Development of Macroporous Titania Monoliths Using a Biocompatible Method. Part 1: Material Fabrication and Characterization

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Monolithic titania could offer significant potential as a support for bioaffinity chromatography because of its stability, unlike silica, to a wide range of pH conditions and its ability to selectively bind phosphorylated proteins and peptides. However, traditional routes to monolithic titania utilize harsh conditions incompatible with most biomolecules. To address this, titania monoliths were prepared in a biocompatible sol−gel process from Ti(O*i*Pr)$_4$ and glycerol. Varied porosities could be introduced by the additional use of high-molecular-weight poly(ethylene oxide) in the sol, which led to the formation of two phases prior to gelation. Morphologies, including bimodal meso- and macroporous structures, and the polymerization of either the dispersed or condensed phases could be controlled by the fraction and molecular weight of PEO in the sol. The roles of glycerol and PEO are to retard hydrolysis and condensation reactions so that phase separation of titanium-rich species precedes gelation processes. PEO also facilitates aggregation of growing TiO$_2$ oligomers and particles.

Introduction

Inorganic silicate matrixes prepared through the sol−gel route have been widely employed for the entrapment of biomolecules.[1,2,3] The ease with which silica materials can be modified (i.e., by addition of polymers or organosilanes) and the ability to form these materials as films or bulk monoliths using sol−gel processes has been important in expanding the use of these materials for protein entrapment.

Although silica has been widely used for protein entrapment, monolithic silica materials are only stable between pH values of 2.5 and 7.5,[4] because of their tendency to dissolve at basic pH values. Erosion of silica is exacerbated by the presence of phosphate-based buffers.[5] The gels are also relatively brittle, particularly when formed as a macroporous material.

Titania is also readily formed using sol−gel processes.[6] A variety of researchers have demonstrated the effective synthesis of amorphous titania from standard monofunctional alcohols, usually ethanol, 2-propanol, or butanol derivatives. Titania-based materials have excellent pH stability,[7] thermal stability,[8] and superior mechanical strength compared to silica.[9] An additional advantage of using titania as a protein entrapment medium is its ability to selectively adsorb organophosphate compounds, such as nucleotides[10] and phospholipids,[11] allowing it to separate phosphate-containing compounds and phosphorylated proteins.[12] Furthermore, titania is amphoteric, allowing it to be an anion and cation exchanger at acidic and alkaline pH, respectively, whereas silica can only act as a cation exchanger.[13]

Titania has previously been used to entrap enzymes in a thin film format for biosensor applications.[14,15] However, although 15 years have passed since the first protein-doped silica monoliths were developed, there is still no report on the development of protein-doped titania monoliths, even though titania possesses many advantages compared to silica, as noted above. In part, this is due to the nature of the common titania precursor, titanium(IV) isopropoxide (Ti(O*i*Pr)$_4$), the hydrolysis/condensation kinetics of which are very rapid and difficult to control. Another issue is the inherent ability of the isopropyl alcohol byproduct to denature proteins. Finally, for chromatographic applications, synthetic control over porosity is required. Thus, the challenge is to develop a flexible, protein-friendly sol−gel route to make titania-based monoliths with well-defined pore structures.

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Alkoxytitanium species exhibit dramatically higher reactivity than alkoxysilanes toward water, which generally leads to the precipitation of the titania rather than the formation of a polymeric gel. Thus, formation of titania monoliths generally requires chelating ligands such as acetylacetone,[16] stearic acid,[17] citric acid,[18] carboxylic acids,[19,20,21] alkanolamines,[22] ethylene glycol,[18,23] diols,[24] or glycerol[16,25] to attenuate the reactivity of the titanium precursor by stabilizing a high coordination state of titanium.[6,16,26] Even though such chelating ligands can effectively reduce the reactivity of the titanium precursor, only chemical compositions leading to fast hydrolysis but slow condensation rates lead to polymeric gels; otherwise, colloidal sols, gels, or precipitates are formed.[26] As a result, there are only a few reports describing the formation of titania-based sol−gel monoliths.[19,27,28] However, even in these cases, large amounts of alcohol were used to dilute the concentration of titanium precursors, making this sol−gel route unsuitable for protein entrapment.

With respect to the porosity of titania monoliths, Nakanishi has recently reported the formation of macroporous titania starting from colloidal titanium dioxide particles.[29] This key paper demonstrates that macroporosity can be induced using PEO, as his group has previously demonstrated in a series of elegant papers on silica monoliths.[30−33] However, attainment of a macroporous morphology required processes that were inherently incompatible with biomolecule incorporation, and the resulting materials showed poor mechanical strength.

Improved biocompatibility in monolithic meso- and macroporous silicas arises from the use of sugar derivatives of the silicon-based starting materials rather than TEOS or TMOS. The groups of Brook and Brennan have described the preparation of a series of polyolsilanes based on glycerol,[34] sorbitol, and related materials.[35] Free proteins and protein-containing liposomes are dramatically more stable in silicas derived from these species than in analogous silicas prepared from TEOS.[36] Additional challenges arise in the fabrication of biocompatible monoliths, including monolith shrinkage, and nonspecific adsorption of (bio)molecules to the anionic silica surfaces. These can be addressed, respectively, in a biocompatible fashion by the incorporation of polyolsilanes that become covalently linked to the matrix and reduce shrinkage, and the addition of small amounts of polycationic polymers to the sol, which moderate adsorption processes at silica interfaces.[37]

The objective of our current research was to determine if processes analogous to those used for polyolsilane-derived silica could be applied to the preparation of biocompatible, protein-doped, monolithic titania. We report below the formation of meso- and macroporous titania monoliths prepared using glycerol to temper the condensation reaction kinetics and to improve biocompatibility and PEO to control porosity. The incorporation of γ-glutamyl transpeptidase into biocompatible titania monoliths and the determination of the enzymatic behavior of the bound protein forms the basis of the accompanying paper.[38]

Experimental Section

Chemicals: Titanium isopropoxide, glycerol (99.5%, anhydrous), and poly(ethylene oxide) (PEO) (average molecular weight 1000, 10 000, or 100 000 kD) were purchased from Aldrich. All water was distilled and deionized using a Milli-Q synthesis A10 water purification system. All other reagents were of analytical grade and used as received.

Procedures. *Formation of Titania Monoliths:* Meso- and macroporous titania materials were formed by a variety of routes. The nomenclature used throughout this report is as follows. Compounds are named by the glycerol:titanium molar ratio, e.g., 12:1 glycerol:Ti = **GT12**. The presence of 10 000 MW PEO in the sol is denoted by the presence of a P followed by the weight concentration in the sol. For example, 16:1:0.125 glycerol:Ti:PEO = **GT16-P0.125**. Titania samples prepared with a PEO molecular weight other than 10 000 are noted explicitly in the tables.

Titania sols were prepared by first mixing titanium(IV) isopropoxide and anhydrous glycerol at a specified molar ratio (1:2−1:32) at room temperature for 2 h. Each mixture was then independently dissolved in water or buffer to initiate hydrolysis. The optimized formula in the absence of PEO was a 1:16 Ti:glycerol ratio. In this particular system, glycerol (7.35 g, 80 mmol) was added to titanium isopropoxide (1.42 g, 5 mmol) in the absence of other solvents. The resulting mixture was stirred at room temperature for 2 h to give a milky solution. The sol slowly underwent reaction but, if stored at 4 °C, was usable for up to one week.

Formation of titania monoliths from Ti−glycerol sols was done using two different procedures. In Procedure 1, mesoporous samples

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were prepared that did not contain PEO. As a representative example, PEO-free titania **GT16** was formed as follows. To **GT16** (8.79 g, 5 mmol of Ti) was added H_2O (1.44 g, 80 mmol, $R = 16$); the mixture was sonicated at room temperature until it became a clear homogeneous solution. The mixture was left at room temperature; a white, opaque, and homogeneous gel was obtained in about 1 h. The resulting hydrogel was then aged in a closed container for 2 days and soaked in H_2O (10 mL) for 4 h; this process was repeated 9 times, 4 h each, with freshwater. The gel was then allowed to dry in air to give a yellow, translucent monolith. Monoliths formed with different R values (4−32) were also prepared.

PEO-containing titania monoliths with bimodal meso/macroporous morphologies were prepared by Procedure 2 as described below. Initially, survey experiments to ascertain the effect of glycerol on titania aging times were undertaken with fixed ratios of H_2O to $Ti(OiPr)_4$ to PEO 10 000 MW of 12:1:1 ($R = 12$), whereas the glycerol ratio was varied from 8 to 16. A second set of experiments probed the effect of different amounts of water using **GT12-P1** ($R = 10-16$). As an example of a typical macroporous titania material, the preparation of **GT16-P0.5** is described. To **GT16** (8.79 g, 5 mmol of Ti) was added H_2O (0.440 g, 24.4 mmol, $R = 5$), and the mixture was sonicated at room temperature until it turned to a clear homogeneous solution. An aqueous solution of poly(ethylene oxide) (0.25 g in 1.0 mL of H_2O) was added. The molar ratio of PEO to Ti was 0.5%, with a total water content of 80 mmol. The mixture was left at room temperature; phase separation was observed within 15 min. After a further 15 min, a white opaque gel was obtained. The resulting hydrogel was then aged in a closed container for 2 days. The aged gel was soaked in H_2O (10 mL) for 4 h; this process was repeated 9 times, 4 h each, with freshwater. The gel was then allowed to dry in air to give an opaque monolith. Analogous processes were used to prepare **GT12-P1** derivatives, with the exception that the glycerol concentration in the sol was reduced to 1:12 Ti:glycerol.

Role of Poly(ethylene oxide): The role of PEO concentration on monolith structure was established using Procedure 2. Initially, PEO of molecular weight 10 000 was used; the PEO:Ti molar ratio was varied from 0.125 to 1.0% (**GT16-P0.125**−**GT16-P1**). The experiments were repeated using PEO of molecular weight 100 000; the PEO:Ti molar ratio was 0.005−0.05% (**GT16-P0.005-100**−**GT16-P0.05-100**) and with PEO of molecular weight 1000 at 5% concentration (**GT16-P5-1**). Other molar ratios were kept constant.

Effect of pH and Buffer on Gelation Kinetics: The roles of pH and buffer concentration on phase separation time, gelation time, and monolith structure were also established using more biologically relevant conditions. To the hydrolyzed titanium−glycerol sol **GT16** (8.79 g, 5 mmol of Ti) was added a specified amount of aqueous PEO (10 000 MW, final concentration ranging from 0.5 to 3.25 wt %) in pH 7.0 HEPES buffer (0.94 mL) at various concentrations. The mixture was sonicated at 0 °C until it turned to a clear homogeneous solution. A solution of PEO of molecular weight 10 000 in 25 mM HEPES buffer at pH 7.0 (0.4 g in 0.5 mL buffer) was added. The mixture was left at room temperature to gel. The resulting hydrogel was then aged in a closed container for 2 days. The aged gel was soaked in H_2O (10 mL) for 4 h; the water was replaced 9 times. The gel was then allowed to dry in air to give an opaque monolith and characterized by porosimetry methods as described below.

The synthetic process is amenable to the preparation of monoliths of a variety of sizes and geometries. Generally, the monoliths were prepared in 20 mL vials with a diameter of about 2.4 cm. After being dried, the samples had sizes that ranged from about 1.1 to 2.0 cm in diameter and 0.45−1.1 cm in thickness. The aged, washed, and dried materials were rigid, highly macroporous, and not surprisingly, relatively friable. The compressive strength of disks prepared using a typical formula **GT16-P0.8** was 0.208 ± 0.013 MPa.

Crystallinity as a Function of Thermolysis Conditions: **GT16** and **GT16-P0.5** were prepared in a similar manner using Procedure 2 with or without PEO added. Separate samples of the resulting gels, after washing with water and drying in air, were heated at 200, 480, or 600 °C for 2 h (at a heating rate of 20 °C/h), respectively. The resulting materials were characterized by powder X-ray diffraction using a Bruker D8 Advance with $CuK\alpha_1$ radiation to assess the effect of temperature on crystallinity.

Characterization of Titania Materials: Thermogravimetric analysis (TGA) was performed using a Thermowaage STA409. The analysis was performed under air, with a flow rate of 50 mL/min. The heating rate was 10 °C/min from room temperature to 900 °C. SEM and TEM photographs were obtained on a JEOL 840 scanning electron microscope and JEOL 1200EX transmission electron microscope, respectively.

Prior to N_2 sorption and mercury intrusion porosimetry measurements, all the samples were degassed at 100 °C under a vacuum overnight. Nitrogen adsorption−desorption isotherms were recorded on a Quantachrome Nova 2000. The specific surface area was calculated using the multipoint Brunauer−Emmett−Teller (BET) method. Pore size distributions were calculated by the Barrett, Joyner, and Halenda (BJH) method. Pore volumes were determined from the amount of N_2 adsorbed at $P/P_0 = 0.99$. Macropore intrusion volumes and macropore size distributions were measured by mercury intrusion porosimetry on a Poremaster GT 60 over a pressure range of 0.10−60 000 psi and analyzed using the Washburn Equation.

Results

Effect of Glycerol and Water Levels: In previous work, we described the preparation of sugarsilanes (polyolsilanes) such as diglycerylsilane (DGS, Gly_2Si) by direct transesterification of TMOS or TEOS with glycerol. The low-boiling alcohols were simply removed by distillation.[35] Hydrolysis of these compounds to give silica could be accomplished at neutral pH without catalysts and followed very different condensation pathways than TEOS or TMOS.

Titania is similarly formed by a sol−gel process initiated by the hydrolysis of alkoxytitanates, of which $Ti(OiPr)_4$ is an example.[6] We initially attempted to prepare a series of titanium glycerol derivatives ($(Ti(glycerol)_y$, $y = 1-4$) using the protocol that was so effective with silanes. Transesterification of $Ti(OiPr)_4$ with glycerol or other sugars was attempted under a wide variety of conditions with or without the utilization of solvents such as THF or DMSO. In contrast to the silanes, attempts to transesterify the more Lewis acidic $Ti(OiPr)_4$ with glycerol led to a milky suspension that was not soluble in water. Thus, it was necessary to form titania directly from a dispersion of $Ti(OiPr)_4$ in glycerol without removal of the 2-propanol. As noted below, the Ti:glycerol ratio was critically important in controlling the subsequent condensation kinetics, which in turn were associated with morphological control of the resulting monolith.

Monolithic titania was prepared by the hydrolysis of glycerol−$Ti(OiPr)_4$ mixtures using two distinct protocols: simple hydrolysis and hydrolysis in the presence of high-molecular-weight poly(ethylene oxide) (PEO). Extensive

Table 1. Effect of H_2O:Ti Molar Ratio on Gelation Time (hydrolysis of GT16)

H_2O:Ti molar ratio	gel time (min)
4	2095
8	345
12	180
16	60
20	50
32	<1

experimentation was needed to optimize titania formation from glyceroxytitanium species, and past experience with silicon provided no helpful guidance: for example, condensation/gelation of Si(glycerol)$_4$ was inconveniently slow, whereas the analogous processes of 1:4 Ti:glycerol were uncontrollably fast.

Gelation time, t_g, was defined as the time elapsed between the point when all chemicals were added together and the time when the monolith lost the ability to flow. As the molar ratio of glycerol increased from 1:2 to 1:16 Ti:glycerol at a fixed water concentration, there was an increase in t_g. Lower glycerol levels led to exceptionally fast gelation and produced only TiO_2 particulates. Recipes using a higher glycerol molar ratio of 1:32 exhibited retarded condensation rates, but did not exhibit other obvious advantages. The 1:8 ratio mixture gelled over a convenient period of time, but led to a fragile monolith susceptible to cracking. The optimal stoichiometry for an effective and practical titania precursor was found to be about 1:16 Ti:glycerol, **GT16**, although when PEO was also present in the sol (see below), it was possible to utilize less glycerol (e.g., a 1:12 ratio was suitable, i.e., **GT12-P1)**. The presence of buffer rather than distilled water also affected gelation times (see below). Monoliths prepared at higher glycerol concentrations were more resilient.

The kinetics of monolith formation were examined by hydrolyzing **GT16** as the titania precursor at room temperature with varying ratios of water:Ti. The amount of water present was a key factor in controlling the gelation time and resulting morphology of the monolith (Table 1). When the water concentration was kept very low (H_2O:Ti, 4:1), gelation took about 1.5 days. By contrast, increasing the amount of water by a factor of 4 (16:1 H_2O:Ti) decreased the gelation time by a factor of 35, to 1 h.

Gelation and Phase-Separation Behavior in PEO-Doped Gels. The second process for forming titania exploits Nakanishi's utilization of poly(ethylene oxide) (PEO) to change the condensation behavior of silica in sol−gel processes.[29,35,36] Overlaid on the conversion of sol to gel via condensation is a phase-separation process leading to a titanium-rich phase that ultimately forms a gel and a titanium-poor phase that is removed at the end of gelation. Nakanishi reports that high-molecular-weight PEO (>10 000 Da) is necessary to induce macroposity in silica[28,30−33] and used 100 000−1 000 000 MW PEO for the formation of macroporous titania.[29] We report below the formation of monoliths using either 10 000 or 100 000 MW PEO at various concentrations, which were incorporated at different weight ratios into the sol.

Initial experiments reprised the examination of the titanium isopropoxide:glycerol molar ratio on the gelation time, with PEO concentration fixed at 1 wt %, as shown in Figure 1A.

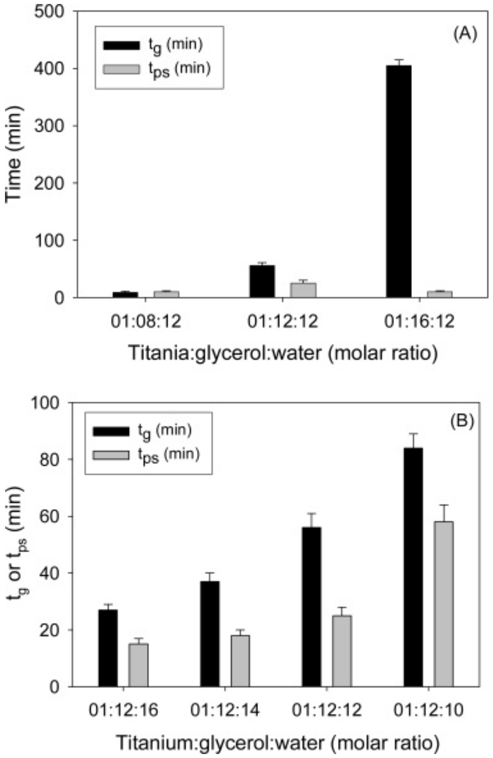

Figure 1. Effect of sol components on titania sol gelation behavior (by ratio Ti:Glycerol:H_2O): (A) 1 wt % PEO 10 000 MW using distilled water; (B) 1 wt % PEO 10 000 MW in HEPES buffer (pH 7.0, 25 mM). The data were obtained from three measurements on independent samples, and the error bars represent one standard deviation from the mean.

In addition to the key gelation time parameter t_g (defined above) is the phase separation time, t_{ps}, which is defined as the time required for the transparent sol to become translucent, again relative to the point where all components were mixed ($t = 0$). As shown in Figure 1B, increasing the titanium:glycerol molar ratio in the starting sol from 1:8 to 1:16 increased the t_g from 9 to 405 min, whereas t_{ps} did not change drastically (ranging from 10 to 25 min). Thus, the difference in gelation and phase-separation times, the coarsening time $t_g - t_{ps}$, varies from −1 min at lower glycerol levels (i.e., gelation occurs just prior to phase separation) to as long as 380 min at high glycerol levels. Gelation occurred almost immediately when the titanium:glycerol molar ratio was lower than 1:8; thus, ratios lower than this were not investigated when PEO was present. Higher concentrations of glycerol tend to suppress condensation, increasing both t_g and t_{ps}. Figure 1B and Table 2 show the effect of water concentration on the gelation behavior of the titanium sol in the presence of PEO (**GT12-P1)**. Both t_g and t_{ps} decreased with increasing water concentration in the titanium sol, consistent with more rapid hydrolysis in the presence of higher levels of water coupled with higher rates of condensation as the glycerol concentration was diluted.

Other Parameters that Affect the Condensation/Aggregation/Gelation Profile. In addition to glycerol and water concentration, parameters such as the PEO concentration, operating temperature, ionic strength, and pH were all found to affect the gelation behavior. For example, increasing temperature resulted in faster condensation, similar to what is observed for silica systems (data not shown). For convenience, the ambient temperature was routinely used for

Table 2. Varying the Content and Molecular Weight of Poly(ethylene oxide)

sample	PEO:Ti molar ratio (%) (PEO MW, kD)	phase separation time t_{ps} (min)	gelation time t_g (min)	$t_g - t_{ps}$	nominal fused particle size (nm)	shrinkage (%) (dried)[a]
GT16-P1	1.0 (10)	5	16	11	1150	(cracked)
GT16-P0.8	0.8 (10)	5	10	5		59
GT16-P0.6	0.6 (10)	8	28	20		65
GT16-P0.5	0.5 (10)	15	30	15	470	82
GT16-P0.4	0.4 (10)	20	30	10		70
GT16-P0.25	0.25 (10)	35	41	6	175	90
GT16-P0.125	0.125 (10)	33	52	19	60	
GT16-P0.05-100	0.05 (100)	50	80	30		
GT16-P0.005-100	0.005 (100)	30	45	15	115	
GT16-P5-1	5 (1)	N/A	53	N/A	65	
GT16	0				70	95

[a] Dried at room temperature in air for 60 days.

the formation of titania. The concentration and molecular weight of PEO was also a strong contributor to both t_g and t_{ps} . Both t_g and t_{ps} dropped as the concentration of PEO (10 000 MW) was increased: there was an increase and then a decrease in $t_g - t_{ps}$ (Figure 2A). The absolute concentration of EO monomer units was less important in mediating these changes than the molecular weight. Thus, decreasing the [EO] by a factor of 100, using 0.5% MW 10 000 PEO vs 0.005 MW 100k PEO, led to increases in t_g and t_{ps} by only a factor of 2 (**GT16-P0.5** vs **GT16-P0.005-100,** Table 2). By contrast, an 8-fold reduction in [EO] using PEO of the same MW (10 000) led to a 6-fold reduction in the t_{ps} and 3-fold reduction in the t_g value (**GT16-P1** vs **GT16-P0.125**, Table 2).

Unlike silica, increases in ionic strength tended not to result in significant changes in the gelation times of titania. As the buffer (HEPES) concentration was increased from 5 to 50 mM, there was a decrease in the t_g from 40 to about 30 min. (Figure 2). The phase-separation time decreased in step with t_g, from ~11 to 5 min. The difference $t_g - t_{ps}$ was higher at all buffer concentrations than when sols were prepared from deionized water (Figure 2B). The nominal fused particle size was only marginally affected by buffer concentration. As the concentration varied from 5 to 50 mM, fused particles sizes ranged from about 500−600 nm with no obvious trend being evident (see the Supporting Information). Shifts in pH to more basic conditions led first to a decrease in t_g as pH approached neutrality and then significant increases in t_g at pH 9 (Figure 2C). The value of t_{ps} followed a similar pattern, but to a much lower degree. The difference $t_g - t_{ps}$ increased with increasing pH (see the Supporting Information). Interestingly, the nominal fused particle size is consistent over the pH range 5−7 (550 nm), and then decreases with increasing pH (pH 8, 400 nm; pH 9, 300 nm; see the Supporting Information).

Monoliths were prepared using this process in a variety of sizes and geometries, including capillary columns and disks of dimensions as large as 1−2 cm diameter and 0.5−1 cm thick; thin films would typically crack during the shrinkage that accompanied aging and drying.

Morphology Control in Titania Monoliths. The morphology of the titania gel was affected by the presence of 10 or 100 kDa PEO in the sol. It was not possible to form macroporous titania gels starting with 1000 MW PEO (Table 2). With 1:12 Ti:glycerol (**GT12)** as the starting sol, SEM images of the titania gel in the absence of PEO demonstrated no features (pores or particles) at the resolution of the SEM instrument (Figure 3). Increasing PEO concentration to 1 wt %, **GT12-P1**, led to a gel with a rough surface, where mesopores may exist, but there were no detectable macropores observable under SEM. Although the gel monolith in the wet state has an opaque appearance, suggesting the presence

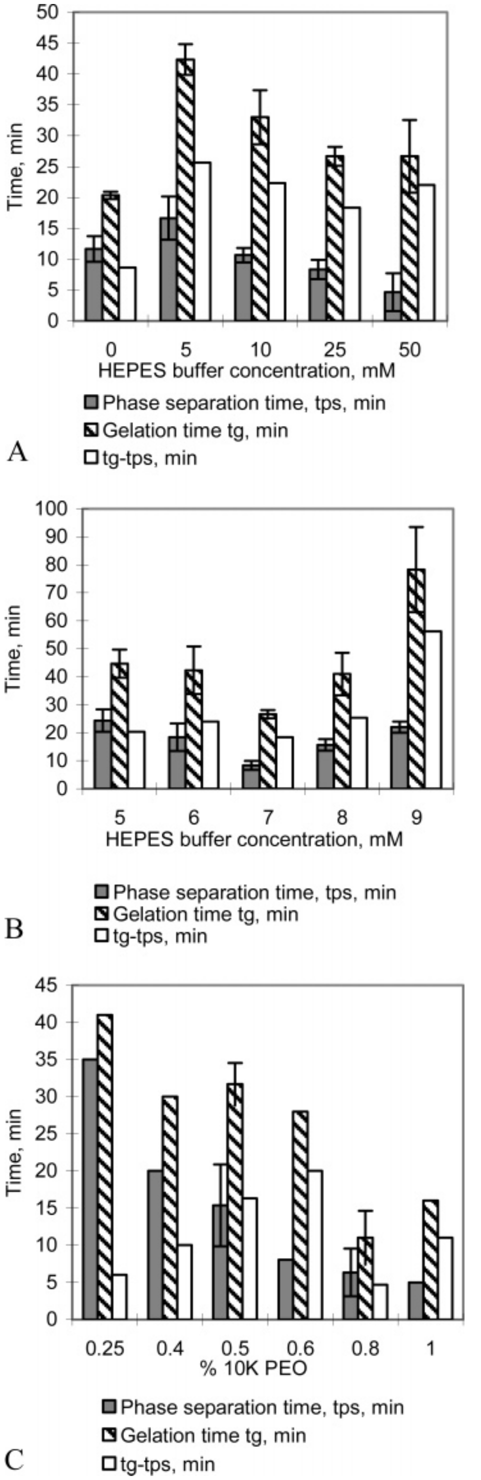

Figure 2. Effect of (A) quantity of 10 000 PEO, (B) buffer concentration (ionic strength), and (C) pH on gelation and phase separation times. Note that the *x*-axes are not to scale. Error bars represent one standard deviation from the mean of data taken from three measurements on independent samples.

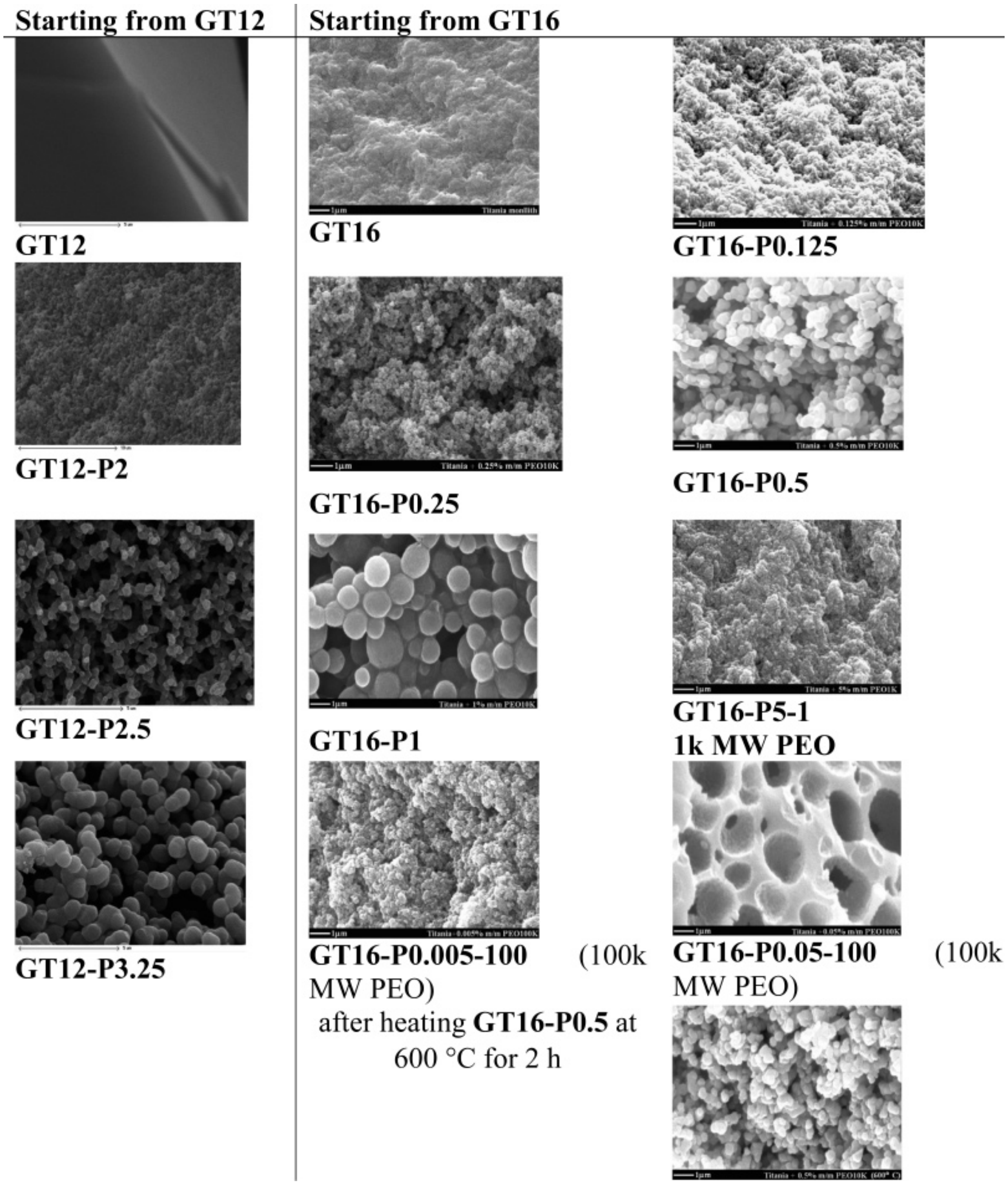

Figure 3. SEM photographs of the morphology of titania monoliths as a function of the glycerol:Ti molar ratio, PEO MW, and PEO concentration.

of macropores, the monoliths become translucent after drying, indicating the disappearance of macropores because of either collapsing or shrinking (see below). Increasing the PEO concentration led to a rougher surface, with some detectable macropores that were about a few hundred nanometers in diameter, as shown in Figure 3. When a PEO concentration of 2.25 wt % was utilized, a clearly interconnected gel network was obtained, with throughpores of 1−2 μm in diameter, **GT12-P2.25**. Titania gel monoliths with interconnected gel networks appeared over a limited range of PEO concentrations, where spinodal decomposition occurs. Further increases in PEO concentration led to a morphology of particle aggregates, with feature sizes (particle size) increasing from about 400 nm to about 800 nm when PEO concentration increased from 2.5 to 3.25 wt %, **GT12-P2.5** and **GT12-P3.25**.

Similar changes were observed with the **GT16** series of compounds, but at much lower PEO concentrations (Figure 3). With this system, macroporous structures were already formed with PEO 10 000 MW at concentrations of 0.5%, **GT16-P0.5**. Comparable morphologies were observed with 100 000 MW PEO at even lower concentrations (e.g., **GT16-P0.125** (0.125% 10 000 PEO) ≈ **GT16-P0.005-100** (0.005% 100 000 MW PEO). Nominal fused particle size also increased with PEO content in this series (e.g., **GT16-P1**, 1150 nm vs **GT16-P0.5**, 470 nm, Figure 3 and Table 2). Note that if higher concentrations of high MW (100 000) PEO are utilized, it is possible to gel the continuous (**GT16-P0.05-100)**) rather than the dispersed phase (**GT16-P1**).

Porosimetry Studies. Titania gels were also characterized by nitrogen adsorption−desorption (BET) porosimetry and mercury intrusion data (Figure 4). Isotherms of all titania gel monoliths were of type IV with a H3 hysteresis loop (data not shown). Analysis of the nitrogen desorption data using the BJH model (Figure 4A) showed that the titania gels contained mesopores at all PEO concentrations, with mesopore diameters centered at 2.2 nm. Titania gels derived from 1:12 Ti:glycerol sols containing 2 or 2.25 wt % 10 000

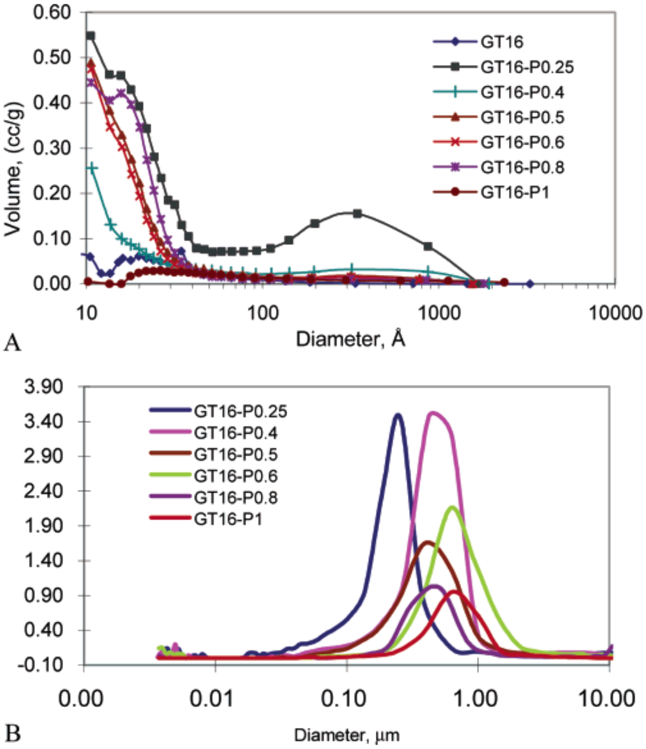

Figure 4. 1:16 Ti:glycerol molar ratio with PEO values ranging from 0 to 1%. (A) BET data. (B) Hg intrusion porosimetry data.

PEO, and gels derived from 1:16 Ti:glycerol sols containing 0.25 wt % 10 000 PEO possessed larger mesopores centered at 33 nm. Pore volume increased with increasing PEO concentration, reaching a maximum pore volume at concentration of 2.25 wt % 10 000 MW PEO for 1:12 Ti:glycerol and 0.25 wt % for 1:16 Ti:glycerol (Table 3). Further increases in PEO concentration led to a decrease in pore volume and the disappearance of large mesopores.

Titania gels derived from 1:12 Ti:glycerol containing PEO concentrations higher than 1.75 wt %, and 1:16 Ti:glycerol with PEO concentrations greater than 0.125% appeared to be opaque upon drying at 150 °C overnight, indicating the presence of macropores. These macropores were beyond the detection limit of nitrogen sorption analysis. Therefore, those gels were examined by Hg intrusion porosimetry, with pore size distribution data shown in Figure 4B and Table 3 (see the Supporting Information). In all cases, the titania gels possessed a narrow pore size distribution. Regardless of the initial sol formulation, the macropore size first increased and then decreased with PEO concentration. A similar trend of increasing followed by decreasing pore size with increases in PEO concentration has been reported for silica systems[35] and reflects a change from bicontinuous to particle aggregate morphologies, as demonstrated by the SEM images shown in Figure 3.

The effects of pH, buffer concentration, and PEO concentration on pore size and surface area were examined. There was initially little effect on porosity, median pore size, and total intruded volume as the pH was modified from 5 to 9, until neutrality was approached, at which point all factors began to decrease (see Figure 2 and the Supporting Information). A similar profile was observed for changes in median pore size as a function of buffer concentration. Pore size dropped as buffer concentration was increased. By contrast, the total surface area increased as a function of buffer concentration. There was no significant change in total intruded volume as a function of buffer concentration.

Highly mesoporous gels were self-supporting monoliths that were somewhat fragile. Thus, rigid disks (after aging and drying) derived from **GT16-P0.8** of about 1 cm diameter and 0.5 cm thickness showed compressive strengths of 0.208 ± 0.013 MPa.

Crystalline Character of Monolithic Titania. The aged materials contained measurable quantities of PEO. Extensive washing was required to remove unbound glycerol and PEO, which otherwise remains sequestered within the monolith. Allowing the samples to dry at 25 °C for 60 days was accompanied by shrinkage of the titania gel, which was more severe than the analogous silica compounds. Shrinkage at room temperature was inversely proportional to the amount of PEO present in the gel (Table 2). The residual PEO and glycerol act to plasticize the gel. However, shrinkage could

Table 3. Effect of PEO:Ti Ratio on Pore Size Distribution as Measured by BET and Mercury Intrusion Porosimetry before and after Calcination at 600 °C

	nitrogen adsorption			mercury intrusion porosimetry		
sample	BET surface area (m^2/g)	total pore volume ($\times 10^{-2}$ cc/g)	average pore size (nm)	total surface area (m^2/g)	total intruded volume ($\times 10^{-2}$ cc/g)	median pore size (nm)
			Dried at Room Temperature			
GT16	51.4	4.2	3.3	15.9	2.1	3.6
GT16-P0.25	467.0	42.4	3.6	51.7	144.9	226.2
GT16-P0.4	370.9	33.2	3.6	29.4	172.5	497.4
GT16-P0.125	201.8	15.6	3.1	11.7	98.2	427.3
GT16-P0.6	331.1	20.5	2.5	24.4	111.0	674.9
GT16-P0.8	205.3	13.2	2.6	6.7	50.0	444.4
GT16-P1	12.0	2.3	7.6	3.3	45.2	690.9
GT16-P0.05-100	11.7	2.2	7.4	51.4	59.2	396.5
GT16-P5-1	217.2	12.5	2.3			
			Calcined at 600 °C			
GT16	20.4	3.0	6.0	14.6	2.5	5.1
GT16-P0.25	21.5	6.9	12.8	11.8	37.7	145.8
GT16-P0.4	14.2	3.8	10.6	9.3	80.3	375.1
GT16-P0.125	11.4	3.2	11.3	5. 7	49.4	393.6
GT16-P0.6	5.3	1.3	9.5	4.3	49.5	482.0
GT16-P0.8	6.3	1.4	9.0	15.5	30.5	324.6
GT16-P1	7.2	1.3	7.2	2.2	28.6	533.0
GT16-P0.05-100	17.3	2.7	6.3	5.3	29.7	336.6

be induced thermally, even in PEO-rich gels, and is directly correlated with thermal treatments (both time and temperature of exposure) that remove the organic constituents (Table 3), as is clearly seen in the before and after micrographs of a gel calcined at 600 °C (Figure 3).

Thermolysis of the organically modified titania gel also affects the crystallinity of the matrix. The X-ray diffraction patterns of samples **GT16** and **GT16-P0.125**, prepared under ambient conditions, suggest that these samples are amorphous: no crystalline domains were present. Heating the samples at a relatively low temperature (200 °C) did not change the amorphous structure (see the Supporting Information). However, heating the samples to higher temperatures caused them to convert to a phase of imperfect crystallinity that was dominated by the anatase phase. The XRD patterns of both samples **GT16** and **GT16-P0.5** after heating at 480 °C for 2 h showed broad and overlapping peaks at $2\theta = 38$ and 62°. Sample **GT16-P0.5**, prepared with PEO, showed a higher degree of crystallinity than sample **GT16**, prepared without PEO. When treated for 2 h at 600 °C, still higher degrees of crystallinity, consistent with anatase,[39] were observed. This suggests that the plasticization effects of PEO may facilitate anatase crystallization.

The TEM and selected area electron diffraction (SAED) of samples **GT16** and **GT16-P0.5** prepared without calcination similarly show the absence of crystalline diffraction rings, whereas after heating at 600 °C for 2 h, both show the presence of an anatase diffraction ring (Table 3, see the Supporting Information). TEM also shows that the crystal size is dependent upon the temperature treatment to which the monolith is exposed and whether PEO was in the sol: for compounds cured at 400 °C for 2 h, crystal sizes in sample **GT16** are slightly bigger than those in sample **GT16-P0.5**.

DTA data (Figure 5) of sample **GT16** at 594 °C show a broad exothermic peak (from 468 to 685 °C), whereas that for sample **GT16-P0.5** show a narrow exothermic peak at 464 °C (onset 441 °C, end 482 °C). These results (see the Supporting Information) suggest that upon heating, the PEO-induced macroporous structure has a higher crystallization rate than the titania prepared without PEO.

The TGA results of samples **GT16** and **GT16-P0.5** are shown in Figure 5. For sample **GT16**, prepared without PEO, there are three major zones of mass loss, with a total mass loss of 32.9%. The mass loss below 200 °C is ascribed to desorption of absorbed water (8.8%). The mass loss from 200 to 350 °C (12.0%), associated with an exothermic peak at 276.6 °C, is attributed to the decomposition of absorbed glycerol. The mass loss from 350 to 600 °C arises from the decomposition of unhydrolyzed organics and the dehydration of titanium oxyhydrate (12.2%).[40] There are two exothermic peaks, at 370 and 594 °C. The former peak is attributed to the combustion of unhydrolyzed organics, whereas the latter is attributed to the crystallization from amorphous to anatase phase.

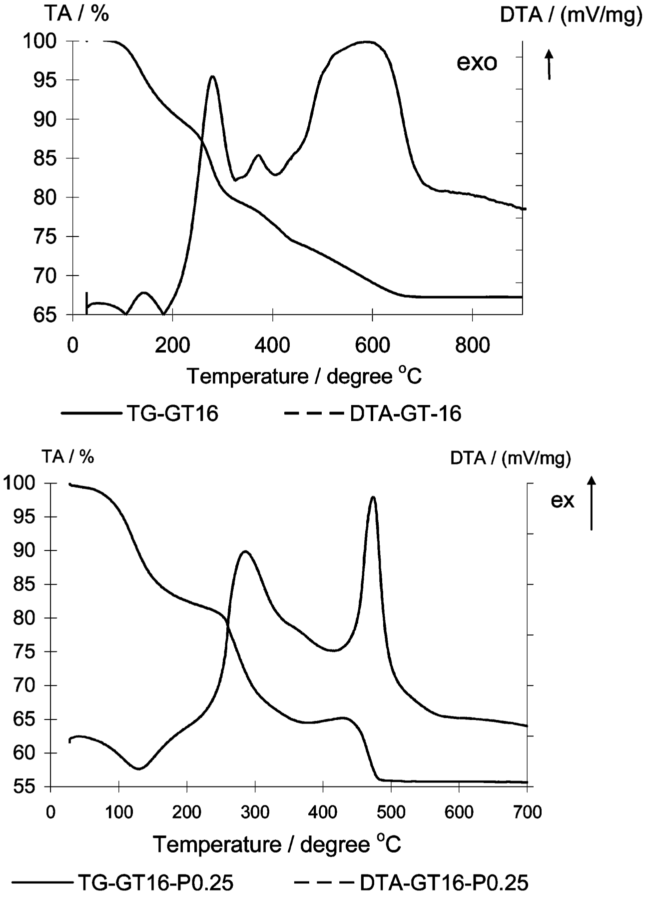

Figure 5. Thermal analysis of **GT16** and **GT16-P0.25**.

For sample **GT16-P0.5**, which was prepared with PEO, mass losses up to 400 °C, but particularly those associated with a broad exothermic peak at around 270 °C, were attributed to the removal of absorbed water, residual organics, and PEO (35%). Mass losses from 400 to 500 °C are consistent with dehydration of titanium oxyhydrate (9%). The exothermic peak at 464.6 °C is attributed to crystallization during conversion of the amorphous to the anatase phase.[41]

Discussion

Formation of a titania gel from $Ti(OiPr)_4$ and glycerol involves several concurrent events. At a molecular level, hydrolysis and condensation occur to build up oligomeric structures along the pathway $Ti{-}OiPr \rightarrow TiOH \rightarrow Ti{-}O{-}Ti$. When oligomers achieve a certain size, they precipitate from the solution, forming primary particles that simultaneously grow and, in the absence of effective particle stabilizers, are captured by larger particles. Ultimately, a monolith is formed when the concentration of grown particles is sufficiently high and the ability to stabilize large particles is sufficiently low that they flocculate and are subsequently bound together by further condensation/growth processes to form self-supporting spanning clusters. Most of the monoliths prepared have a fused bead structure (Figure 3, see the Supporting Information), which is characterized both by the

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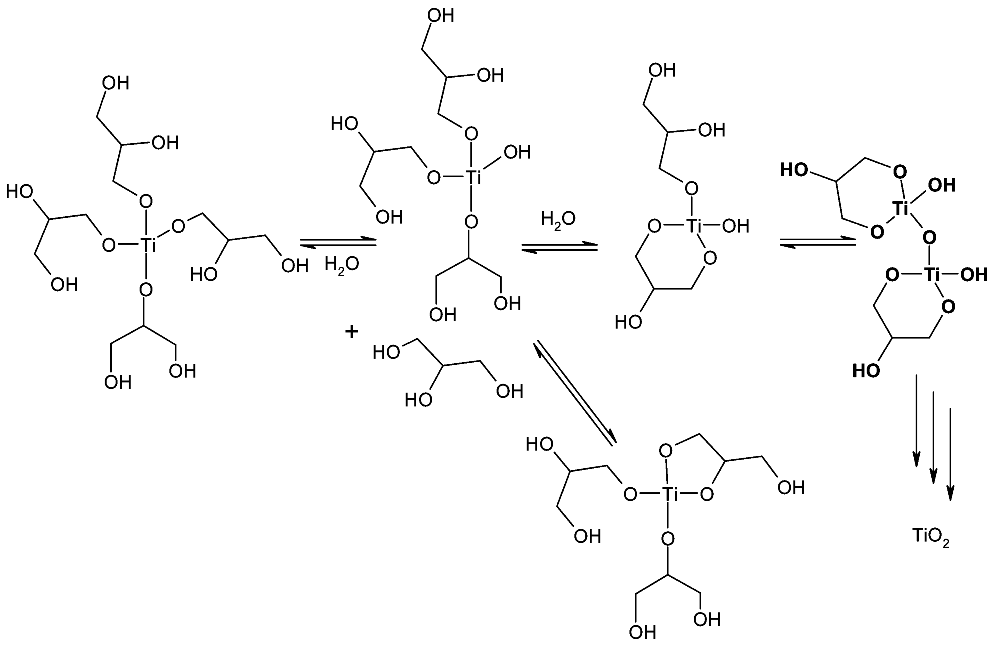
(39) Joint Committee on Powder Diffraction Standards. JCPDS 21-1272; International Centre for Diffraction Data: Newtown Square, PA; http://www.icdd.com.

(40) Mueller, R.; Kammler, H. K.; Wegner, K.; Pratsinis, S. E. *Langmuir* **2003**, *19*, 160−165.

(41) (a) Hsu, L. S.; Shet, C. Y. *Opt. Lett.* **1985**, *10*, 638−640. (b) Yao, B.; Zhang, L. *J. Mater. Sci.* **1999**, *34*, 5983−5987. (c) Liu, Y.; Li, J.; Wang, M.; Li, Z.; Liu, H.; He, P.; Yang, X.; Li, J. *Cryst. Growth Des.* **2005**, *5*, 1643−1649.

Scheme 1



nominal size of the particles and by the degree to which the fused particles are monodisperse. The density of packing (macroporosity) and internal void volume (mesoporosity) are also characteristics of the gel. The role of glycerol, PEO, and reaction conditions (e.g., pH, buffer concentration) in controlling these effects are examined in turn below.

Alkoxytitanium species undergo hydrolysis and condensation reactions extremely rapidly, much more rapidly than alkoxysilanes. Nakanishi and co-workers seeded their titania sol, also containing Ti(O*i*Pr)$_4$, with ~7 nm TiO$_2$ particles; otherwise, gelation and phase separation were too fast to permit controlled monolith formation.[29] The presence of polyols, such as glycerol, and use of low water concentrations in mineral sols affects the hydrolysis and condensation kinetics. Overall gelation rates for silica, which are a composite of the rates of hydrolysis, condensation, and particle aggregation, are retarded as a function of glycerol concentration.[35] Glycerol similarly retards these processes in the formation of TiO$_2$ monoliths.

Glycerol is used in the titanium−glycerol sol−gel route as a chelating ligand, which decreases the hydrolysis/condensation rate by transesterifying onto the primary titanium precursor (i.e., Ti(O*i*Pr)$_4$ + HOCH$_2$CHOHCH$_2$OH → HOCH$_2$CHOHCH$_2$OTi(O*i*Pr)$_3$), forming a less-water-sensitive secondary precursor, as proposed by Sanchez and co-workers.[16] There is an additional role played by glycerol. Unlike monofunctional alcohols, with which hydrolysis in aqueous solvents is essentially irreversible, the polyol can participate in intramolecular reactions that reform alkoxytitanates (Scheme 1). Thus, the presence of polyols additionally distorts the equilibrium for hydrolysis and condensation toward starting materials. Finally, glycerol increases the viscosity in the medium, moderating collisions between growing titania oligomers and particles.

In a silica-based sol−gel system, macroporous morphology can be conveniently obtained in a controlled manner by inducing phase separation in parallel to the sol−gel transition.[30] The mechanism of phase-separation induced by the addition of PEO in tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS) systems has been extensively discussed.[31,32] Few studies have previously examined the possibility of controlling titania morphology using this approach. Kajihara et al. have prepared a macroporous TiO$_2$ films using a sol−gel dip-coating method from a titanium alkoxide-based solution containing poly(ethylene oxide).[33] As noted above, starting from 7 nm TiO$_2$ particles, Nakanishi formed macroporous titania monoliths by hydrolyzing Ti(O*i*Pr)$_4$ at very low pHs in the presence of high MW PEO (100 000−1 000 000 MW).[29]

The tendency for separation into titania rich and poor phases is strongly dependent on the compatibility of the PEO-titania oligomer complex with the solvent mixture. In the titanium-PEO system described above, it is expected that hydrogen bonding will occur between the hydroxyl groups of growing titania oligomers and the ether oxygens of PEO, increasing the repulsion between the complex and solvent mixture.[42] Polymerization of titania oligomers leads to a longer chain with more hydroxyl groups, further facilitating hydrogen bonding with PEO molecules. The titania-PEO complex becomes increasingly less compatible with the solvent mixture as polymerization continues and is eventually excluded from the solution, forming a gel phase.

While the interactions between titania and PEO are favorable, they are not strong. If PEO was strongly linked to TiO$_2$ particle surfaces, small particles would be (sterically) stabilized and one would expect an inverse correlation between particle size and PEO concentration. In fact, the opposite is observed. At higher levels of PEO fewer (larger) particles are formed, which ultimately fuse into a gel. Similarly, higher-molecular-weight and more viscous PEO leads to more effective flocculation of small particles into

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(42) Pelton, R.; Xiao, H.; Brook M. A.; Hamielec, A. *Langmuir* **1996**, *12*, 5756-5762.

larger aggregates that ultimately fuse. By contrast, as the PEO flocculant concentration is reduced, or the PEO MW lowered, more primary particles can independently grow before fusing into aggregates. Thus, PEO acts to facilitate depletion flocculation, ultimately controlling the nominal size of the fused particles. Glycerol, another viscous, hydrogen-bonding material, can amplify this effect. Thus, similar monoliths can be prepared when some high MW PEO is replaced with glycerol (e.g., **GT12-P3.25** ≈ **GT16-P1**).

The kinetics of hydrolysis and gelation and effects of particle aggregation caused by pH and buffer concentration are subordinate to the flocculating role of PEO. As the buffer concentration increases from 5 to 50 mM, there is little change in nominal fused particle size, nor in t_g or t_{ps}. pH similarly has little effect except at higher pHs (8−9), where more, smaller particles are formed and remain able to grow independently prior to fusion (see the Supporting Information). Note that the pH constraints of traditional methods are completely subverted by the utilization of glycerol. There is no need to use excessively acidic pHs to moderate titania growth. Instead, biocompatible pHs can be utilized. The driving force for both gelation and phase separation is condensation of titanium aggregates. Although the relationship between PEO MW and concentration has been previously noted for silica and titania, the effect has typically been correlated with coarsening time.[29,43]

Coarsening time $t_g - t_{ps}$ was not an effective predictor of structure for these monoliths (Figure 2). For example, comparable low values of $t_g - t_{ps}$ were observed with formulas containing 0.125 and 0.5% 10 000 MW PEO. However, the resulting monoliths are strikingly different, with nominal fused particle sizes of 60 and 475 nm, respectively. More instructive is the t_g value. As t_g drops, there is a correlation to larger nominal particle sizes, resulting from larger but fewer particles (Figure 2, Figure 3). Any constituent in the sol that impedes colloidal particle aggregation leads to more and smaller fused particles and a less macroporous structure. Thus, high pH is associated with increased surface charge and electrostatic stabilization of smaller particles, which are eventually captured at long t_g into a tightly fused mass. By contrast, high-molecular-weight PEO facilitates small particle flocculation, leading to very large particles at short t_g. The intersection of molecular and colloidal processes is dependent on the presence of glycerol and water.[44] Retarding the rate of condensation using glycerol and metering the water content in the sol permits colloidal aggregation processes to compete with titania growth. In the absence of glycerol, it is necessary to provide seed particles whose further reaction and agglomeration leads to macroporous monoliths.[29]

Increases in the PEO concentration were associated with reduced mesopore and increased macropore size (Table 3). This is consistent with the flocculation described above. The fusing of large, improperly packed particles engenders the formation of large macropores. Smaller particles pack more efficiently with consequently smaller macropore sizes. At low PEO concentration, the primary particles grow to larger sizes before associating. The nascent mesopores (interstices between particles) will be smaller when the aggregated particles are smaller. Increasing PEO concentration more effectively favors primary particle association at early stages of the process when they are smaller.

Titania gels formed by sol−gel processes undergo extensive shrinkage. In the absence of PEO, shrinkage of 95% was noted for **GT16.** The presence of small amounts of PEO moderates shrinkage, but the effect is lost as PEO concentration is increased (Table 2). The plasticization provided by the polymer is more efficacious when particles are small. Monoliths comprised of larger particles, with less surface contact area, were typically more fragile.

A similar role by PEO is played during extensive thermal heating. Gels formed at ambient temperature were amorphous. Upon heating, the onset of crystallization occurs at lower temperature in the sample containing PEO than in a monolith derived from glycerol alone (Figure 5). At this temperature, 441 °C, either residual PEO in the monolith or a more flexible structure resulting from the presence of PEO during monolith fabrication can facilitate reorganization of the titania into crystalline domains.

Conclusion

The gelation behavior and pore morphology of titania gels obtained by the titania−glycerol sol−gel route can be manipulated by changing the glycerol and water concentrations. The pore size distribution of the titania gel monoliths was also tunable through the addition of PEO, with mesoporous or mesoporous/macroporous biomodal/trimodal titania gel monoliths being obtained. Over a limited PEO concentration range, a monolithic gel with an interconnected titania gel network was obtained using a biocompatible processing method.

Balancing hydrolysis, condensation, and phase separation times of alkoxytitanium precursors allows for a high degree of control in the formation of titania monoliths. It is possible to target structures with specific macro- and mesoporosity using simple mixtures of readily available materials. Although these materials undergo significant degrees of shrinking, when properly formulated, they can be very tough even with macroporous morphologies. Thus, such materials have the potential of being used as chromatographic materials for HPLC or bioaffinity chromatography applications, as shall be outlined in detail in the accompanying paper.

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Supporting Information Available: X-ray diffraction patterns and TEM images; plots of the effects of PEO concentration, pH, and buffer concentration on pore size and volume; effect of buffer and pH on particle size. This material is available free of charge via the Internet at http://pubs.acs.org.

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