Template Recognition in Inorganic−Organic Hybrid Films Prepared by the Sol−Gel Process

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Inorganic−organic hybrid sol−gel processing has been utilized to fabricate thin, porous, chemically selective silicate films. These materials have been fabricated using a template-based approach that involves the formation of a cross-linked matrix around a specific reagent followed by removal of that reagent. The silica sol consisted of a hybrid mixture of functionalized organosilicon precursors (phenyltrimethoxysilane and methyltrimethoxysilane), a network former (tetramethoxysilane), and the template molecule, dopamine (DA). Silicate thin films were prepared by spin casting an aliquot of the composite sol on the surface of a glassy carbon electrode. Dopamine was extracted from the dried film via soaking in phosphate buffer, and the affinity and selectivity of the DA-templated films were characterized using cyclic voltammetry. The results show that the DA-templated films have an increased affinity for dopamine over that of structurally related molecules including serotonin, epinephrine, and dihydroxynaphthalene. The DA-templated films show little to no affinity for negatively charged or large analytes including ascorbic acid, DOPA, DOPAC, catechol violet, and the peptide Tyr-Gly-Gly. In contrast, nontemplated films or templated films prepared with the organic modifier isobutyltrimethoxysilane show little to no response toward dopamine in solution. It is believed that film porosity and specific hydrophobic and electrostatic interactions play an important role in controlling molecular permeation through these materials.

Introduction

During the past decade considerable interest has been focused on the design and development of specialized materials with improved molecular specificity.[1,2] These materials hold considerable promise for the construction of highly selective chemical sensors, efficient chromatographic stationary supports, specific binding assays, and controlled-transport membranes. One promising approach for the creation of synthetic host systems with tailor-made physicochemical properties involves template polymerization.[3−8] In this approach a polymer network is assembled around a suitable "template" molecule or structure. Upon removal of the template, microcavities with a specific size, shape, and/or chemical functionality remain in the cross-linked host.

One of the first examples of "molecular" templating was the work of Dickey, who showed that silica gel synthesized in the presence of a specific dye molecule had an enhanced affinity for that particular dye once it had been removed from the silica host.[9] The mechanism for selectivity may involve a "footprint" mechanism as originally proposed by Dickey[9] or it may involve an association (or recrystallization) type mechanism as argued by Hodgson and co-workers.[10] Since that time a number of other studies have utilized related procedures and shown enhancements in template readsorption relative to control samples for silica-based materials.[11−13]

Analogous to these procedures, template-based polymerization routes have also been used to create periodic mesoporous silica and nanoporous silica membranes for catalyst and transport applications.[3,4] In the former approach, amorphous silica was formed around surfactant micelles, which, upon removal, create the array of uniform mesopores.[3−4,14−15] In the latter approach, organosilicon precursors were combined with the inorganic precursors to form an organic−inorganic

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hybrid material.[3,16] Upon pyrolysis of the organic functional groups, molecular-sized voids were created in the silica host material.[16] Through careful control over the template concentration and the sol−gel processing conditions, the pore size and pore connectivity can be controlled in these materials.[3]

In many situations it is desirable to introduce discrete functionalities into a polymeric host to improve the molecular specificity of the resultant material. Specific recognition sites have been introduced into highly cross-linked polymeric matrixes via the use of molecular imprinting technologies as first described by the research groups of Wulff and Mosbach.[5−7,17−18] In this approach, polymerizable functional monomers (i.e., methacrylic acid, vinylpyridine), chosen for their affinity for the print molecule, were combined with a large excess of the cross-linking agent (i.e., ethylene glycol dimethacrylate) and a free radical initiator to form a rigid polymer. After the template was removed, complementary binding sites for the template remained.[5−8] The molecular recognition properties of these synthetically designed binding sites are attractive and thus these materials have been routinely applied to the development of chromatographic stationary phases.[5−7,19−22]

In this work we show that a similar strategy can be used to create silica based materials with improved permeability, molecular selectivity, and response time. The approach utilizes sol−gel technology to fabricate a stable, rigid host matrix via the hydrolysis and condensation of suitable organosilicon and silicon alkoxides.[23−27] By combining organosilicon reagents (i.e., functionalized monomer) with the inorganic precursor (i.e., network former) specific chemical functionalities can be introduced into the rigid polymer network, thus tailoring its physicochemical characteristics and improving molecular specificity and selectivity.[25−27] Two distinct advantages sol−gel technology affords is the ease with which thin films and/or bulk gels to be readily fabricated and the mild polymerization conditions that allow specific reagents to be readily introduced within the highly cross-linked, porous host structure without the problems of thermal or chemical decomposition.[28,29] The ability to form thin films is important in chemical sensor applications due to the inherent reduction in the path length for reagent diffusion. In a prior investigation, we have shown that dopamine-templated films prepared from the hydrolysis and cocondensation of phenyltrimethoxysilane with tetramethoxysilane exhibited a strong affinity for dopamine and little affinity for ascorbic acid.[30] In this report, we provide a more detailed account of the preparation of these unique materials as well as their molecular selectivity.

Experimental Section

Reagents and Equipment. Tetramethoxysilane (98%), phenyltrimethoxysilane (97%), methyltrimethoxysilane (99%), ethoxyethanol, catechol (CA), dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), L-ascorbic acid (AA), epinephrine (EN), norepinephrine L-bitartrate (NE), serotonin creatinine sulfate (serotonin, ST), 2,3-dihydroxynaphthalene (DHN), 3-(3,4-dihydroxyphenyl)-L-alanine (DOPA), peptide tyrosylglycylglycine (TGG), pyrocatechol violet (CaV, indicator grade), ruthenium hexaammine (95%), and ruthenium(II) tris(bipyridine) were purchased from either Aldrich or Sigma Chemical Co. and used as received. Hydrochloric acid, potassium ferricyanide, potassium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Fisher Scientific. All analyte solutions were prepared daily in pH 7.4, 0.1 M phosphate buffer and purged with nitrogen for 30 min prior to use. Water was purified to type I using a Labconco Water Pro PS four-cartridge system. A one-chamber, three-electrode cell was used. The working, reference, and auxiliary electrodes consisted of a glassy carbon electrode ($A = 0.2$ cm^2),[31] silver−silver chloride (1.0 M KCl), and platinum mesh, respectively. Prior to use, the glassy carbon electrodes were polished with 0.05 μm alumina in deionized water and sonicated for at least 10 min in deionized water and dried in an oven. Cyclic voltammograms were recorded with a BAS 50 electrochemical workstation. Film thickness was measured with a surface profilometer (Tencor, Alpha Step 500). UV−vis absorption spectra of the silicate film on 2 cm × 2 cm quartz substrates were collected with a HP 8453 diode-array spectrophotometer.

Procedures. A stock solution of the organic−inorganic hybrid sol was prepared by mixing tetramethoxysilane (3.0 mL, TMOS) with phenyltrimethoxysilane (0.37 mL, PTMOS), methyltrimethoxysilane (0.30 mL, MTMOS), ethoxyethanol (3 mL, EE), water (0.7 mL), and hydrochloric acid (1.0 mL of 0.1 M). The sol was stirred for approximately 2 h. To 1.7 mL of this stock solution was added 19 mg of dopamine (DA). The final molar ratio of TMOS:PTMOS:MTMOS:DA was 1:0.1:0.1:0.025. The doped sol was stirred for 5 min and a ca. 50 μL aliquot placed on a precleaned glassy carbon electrode. After 30 s, the electrode was rotated using an in-house-built rotator for 120 s at ca. 7000 rpm. The resultant thin film was dried in air for 1 day under ambient conditions (relative humidity ca. 30−50%) and then placed in phosphate buffer (0.1 M, pH 7.4) for 1 day to leach out the dopamine. After template removal, the electrode was rinsed with water and dried at 60 °C for 2 h and 100 °C for 18 h.

Results and Discussion

Template Film Preparation and Characterization. The method used to fabricate the templated silicate films involves preparation of the sol, physical entrapment of the template, and gelation (cross-linking) of the sol. In these experiments, the catechol amine, dopamine (DA), was utilized as the template because of the important role it plays in neurotransmission and the need to develop new methods that allow its dif-

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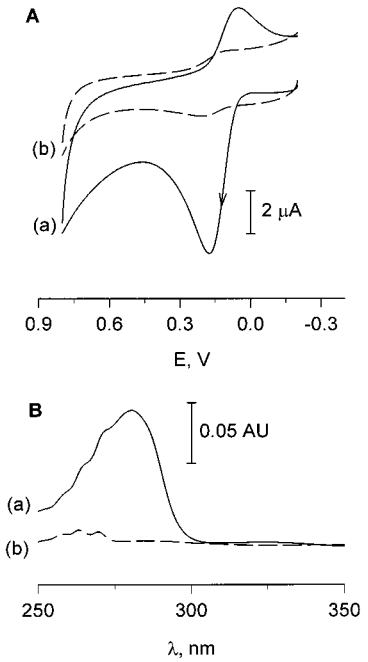

Figure 1. Cyclic voltammograms (panel A) and UV absorption spectra (panel B) of gel-encapsulated dopamine acquired (a) 2 min and (b) 24 h after placing the film in a 0.1 M, pH 7.4 phosphate buffer; scan rate, 100 mV/s.

ferentiation in the presence of numerous interferents including ascorbic acid, DOPAC, and DOPA.[32] The stock sol solution was prepared by combining PTMOS and MTMOS with TMOS in ethoxyethanol. PTMOS was utilized as the functionalized monomer due to its hydrophobicity and likely affinity for the aromatic functionality on the template, whereas EE was utilized as the solvent due to its both polar and nonpolar solvating properties. MTMOS was incorporated into the sol to introduce additional hydrophobicity and stability to the resultant materials. In general, films prepared with MTMOS were ca. an order of magnitude more stable in solution than films prepared without MTMOS. After DA was added to the sol, an aliquot was cast on the surface of a glassy carbon electrode to form a thin uniform film. Film thickness as measured via surface profilometry was ca. 450 nm. After sufficient drying, DA was extracted from the inorganic−organic host matrix by simply placing the film in buffer solution for an extended period of time.

Figure 1A shows cyclic voltammograms (CVs) of the DA-encapsulated silicate films immediately after placing the electrode in buffer and after a 24 h period. A clear response due to the quasireversible, two-electron oxidation of gel-encapsulated dopamine can be observed. As the film sits in phosphate buffer, the Faradaic oxidation current drops and after 24 h only a small response is observed. This loss in voltammetric signal is indicative of DA leaching from the silicate matrix as the films sits in buffer solution. As shown in prior work, gel-encapsulated redox probes will slowly leach out of the compact silicate matrix as the film sits in solution.[31] Leaching of small molecules from sol−gel-derived materials is not uncommon and is, in fact, one of the major

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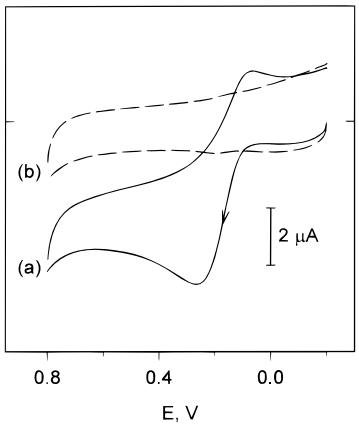

Figure 2. Cyclic voltammograms of 0.1 mM dopamine in 0.1 M, pH 7.4 phosphate buffer at (a) a templated film and (b) a nontemplated film; scan rate, 100 mV/s.

limitations to the use of these materials in chemical sensor applications.[28−29,31]

DA leaching from the hybrid film can be confirmed via UV−Vis absorption spectroscopy, as shown in Figure 1B. In these experiments, the hybrid film was prepared in an identical manner with the exception that composite sol was cast on quartz slides. The UV spectrum for gel-encapsulated DA is shown in Figure 1B. A clearly distinguishable absorbance can be observed prior to soaking the film in buffer. After placing the film in buffer for 24 h, the absorbance of gel-encapsulated DA is greatly diminished. From the CV and UV results, it can be estimated that ca. 90−95% of the DA leaches out of the rigid matrix during the 24 h time period. After the template is removed from the silicate host, the material is further cured by placing the electrode in an oven overnight. As described below, the additional heat treatment reduces the number of apparent pinholes in the film via additional cross-linking and thus improves the long-term stability and the selectivity of the templated films.

To characterize the affinity of the DA-templated films toward DA, the cured templated film was placed in a 0.1 mM DA solution in pH 7.4, 0.1 M phosphate buffer. As can be seen in Figure 2, distinct diffusion-based redox waves can be observed due to the partitioning of DA into the film and oxidation at the electrode surface. This CV was acquired after the film had been in solution for 5 min. The peak current for the oxidation of DA achieves a near constant value within the first 3−4 min after the film is placed in solution, indicative of the relatively fast response and affinity of the templated film toward DA. In contrast to these results, *nontemplated* silicate films show no affinity for DA, as evident from the lack of Faradaic response when the modified electrode is placed in a solution of 0.1 mM DA (Figure 2, curve b). In this experiment, the films were prepared under identical conditions as described in the Experimental Section, with the exception that DA was not added to the sol. The lack of response is characteristic of the compact nature of the silicate host structure. This is consistent with previous work that has shown that, when properly dried silicate films are placed in a solution of 1 mM potassium ferricyanide or ruthenium hexaammine, no voltammetry is observed for a significant period of time, indicative of the inability

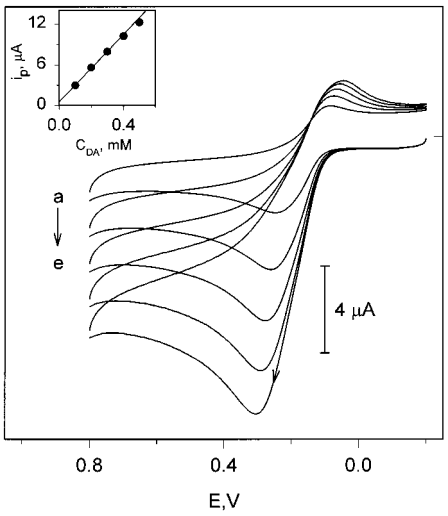

Figure 3. Cyclic voltammograms of (a) 0.1, (b) 0.2, (c) 0.3, (d) 0.4, (e) 0.5 mM dopamine in 0.1 M, pH 7.4 phosphate buffer at a templated film; scan rate, 100 mV/s. (Inset) Plot of anodic peak current vs dopamine concentration. The solid line represents the linear regression fit to the experimental data (●).

of the redox probe to reach the underlying electrode surface.[33]

The peak oxidation current for the DA-templated films is directly proportional to the DA solution concentration up to ca. 0.5 mM, as shown by the calibration curve depicted in Figure 3. At concentrations greater than or equal to ca. 0.5 mM, a slight roll-off in current is observed. The stability of the templated films is good. The affinity of the films for DA remained intact for ca. 48 h when the film was stored in buffer between use and ca. 7 days when stored in a desiccator between use.

To establish the importance of the phenyl functionality and to verify that the observed affect is not simply due to an increase in porosity resulting from dopant leaching, templated films were prepared using isobutyltrimethoxysilane (BTMOS) as the organic modifier instead of PTMOS. BTMOS was chosen because it is a bulky, hydrophobic modifier and thus similar to PTMOS. Figure 4 shows the response of a DA-templated BTMOS silicate film in 0.1 mM DA. The voltammetric response of the BTMOS-templated film toward DA in solution is slight after heat treatment but significantly less than that observed at the templated PTMOS silicate films. This is consistent with our preliminary work that showed templated films prepared from only TMOS had only a slight affinity for DA.[30,34] If the response of the PTMOS-derived DA-templated films was the result of a net porosity increase, similar voltammetric responses would have been observed for both control experiments. The fact that different responses are observed suggests that the PTMOS plays an important role in governing the permeation of DA into the hybrid silicate film.

Template Film Affinity and Selectivity. To evaluate the ability of the DA-templated films to discriminate among structurally related or biologically significant compounds, the templated films were exposed to 0.1 mM

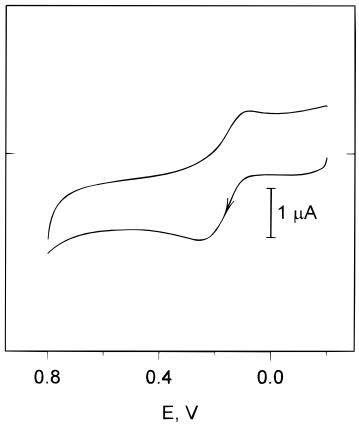

Figure 4. Cyclic voltammograms of 0.1 mM dopamine in 0.1 M, pH 7.4 phosphate buffer at a templated film prepared from isobutyltrimethoxysilane (BTMOS). Mole ratios of precursors used to prepare sol, 1:0.1:0.025 (TMOS:BTMOS:DA); scan rate, 100 mV/s.

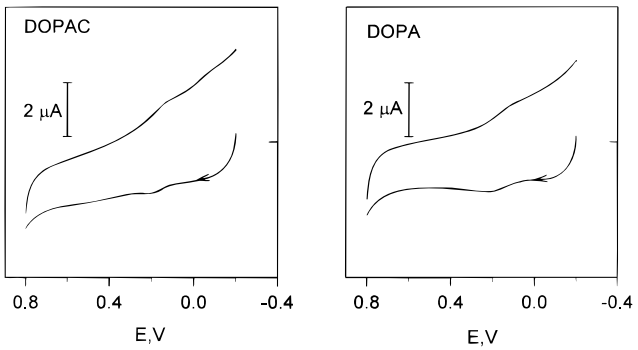

Figure 5. Cyclic voltammograms of 0.1 mM 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-(3,4-dihydroxyphenyl)-L-alanine (L-DOPA), respectively, at a templated film; solution conditions, 0.1 M phosphate buffer, pH 7.4; scan rate, 100 mV/s.

solutions of different analytes. Figure 5 shows the CVs of DA-templated films in pH 7.4 solutions of AA, DOPA, and DOPAC. Very little, if any, Faradaic current can be observed at the modified electrodes, indicative of the inability of these analytes to partition into the film. At a bare, polished glassy carbon electrode, 0.1 mM DOPAC, DOPA, and AA are irreversibly oxidized at $E_{p,a} \sim 0.5$ V in pH 7 phosphate buffer and give a *Faradaic* peak current of ca. 3 (AA) to 5 μA (DOPAC and DOPA). The appearance of the small voltammetric feature at ca. 0.3 V in the CVs shown in Figure 5 is due to the DA, which remains encapsulated in the film after the 24 h leach.

Excellent discrimination between AA and DA can be observed, as noted in Figure 6. In an equal molar mixture of AA and DA, only the DA response can be observed, and this peak current is nearly identical to that observed for the templated film in a solution containing only DA. This discrimination is important in bioanalytical applications, which often require DA to be measured in the presence of AA.[32] In previous work, the similarly prepared templated films showed a slightly greater response toward AA and the other negatively charged analytes relative to that reported in this paper.[30] In addition, the voltammetric response of the templated film in a solution of DA + AA was considerably larger than that obtained in the presence of DA alone. The major difference between the two methods of fabrication lies in the heat treatment used in the

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(34) Attempts to make control films solely from TMOS using the current methodologies were unsuccessful, because the films cracked during the heating step.

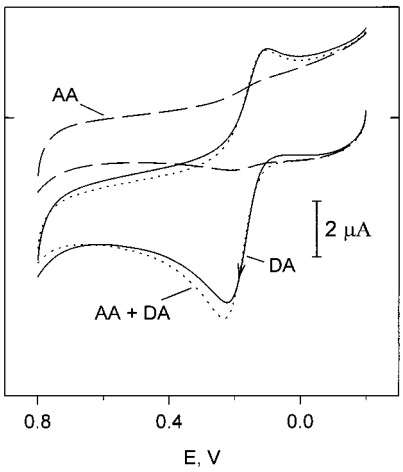

Figure 6. Cyclic voltammograms of 0.1 mM ascorbic acid (AA), 0.1 mM dopamine (DA), 0.1 mM AA, and 0.1 mM DA at a templated film; solution conditions, 0.1 M phosphate buffer, pH 7.4; scan rate, 100 mV/s.

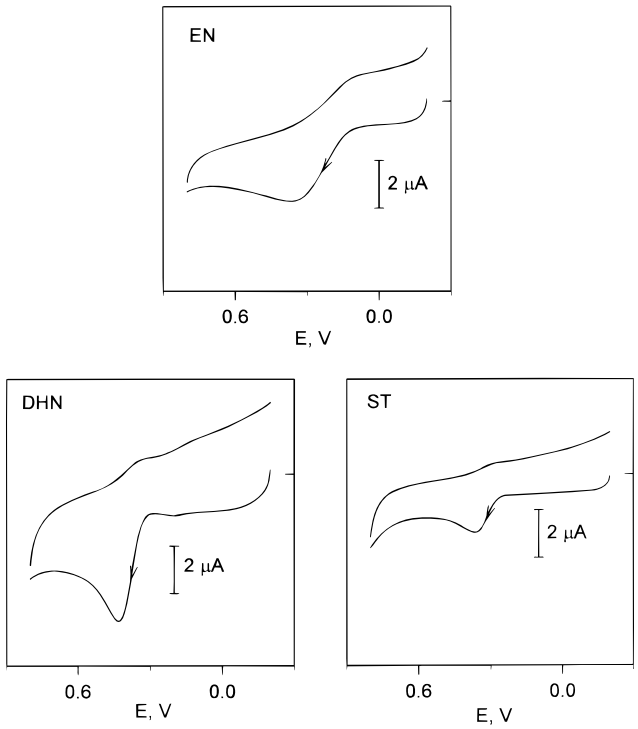

Figure 7. Cyclic voltammograms of 0.1 mM epinephrine (EN), 2,3-dihydroxynaphthalene (DHN), creatanine sulfate (serotonin, ST), respectively, at a templated film; solution conditions, 0.1 M phosphate buffer, pH 7.4; scan rate, 100 mV/s.

present work. When the film is heated after template removal, additional cross-linking will occur between neighboring unreacted silanol groups, thus reducing the number and size of pinholes in the film. Templated films prepared using current methodolgies, but without heat treatment, show a greater Faradaic response when in 0.1 mM solutions of AA, DOPAC, or DOPA.

The voltammetric response of the DA-templated films to solutions of other structurally related catechol and catechol amines can be observed in Figures 7−9. The DA-templated films show some affinity for small structurally similar catechol amines and aromatic catechols such as EN, ST, and DHN. All these analytes have an aromatic ring and are very similar in size and polarity to dopamine. When exposed to solutions of larger

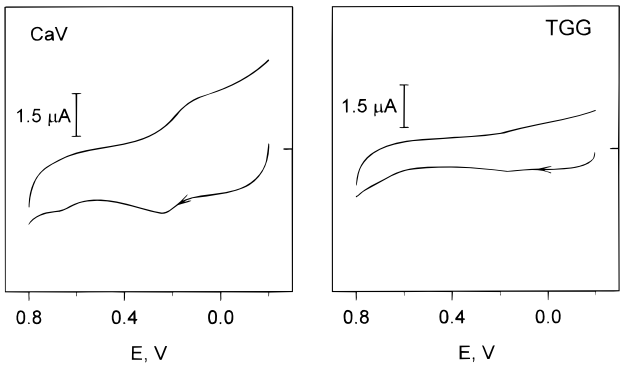

Figure 8. Cyclic voltammograms of 0.1 mM pyrocatechol violet (CaV) and peptide tyrosylglycylglycine (TGG), respectively, at a templated film; solution conditions, 0.1 M phosphate buffer, pH 7.4; scan rate, 100 mV/s.

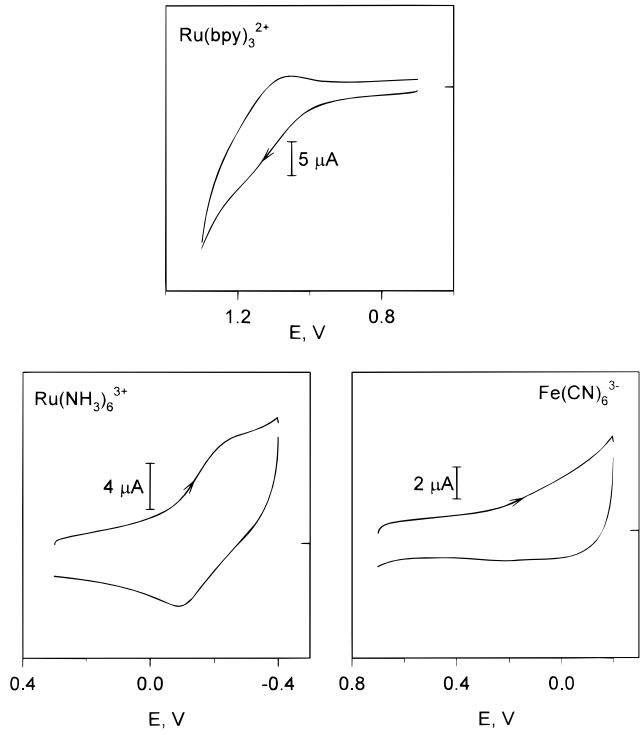

Figure 9. Cyclic voltammograms of 1 mM $Ru(bpy)_3^{2+}$, $Ru(NH_3)_6^{3+}$, and $Fe(CN)_6^{3-}$, respectively at a templated film; solution conditions, 0.1 M phosphate buffer, pH 7.4; scan rate, 100 mV/s.

catechols, such as catechol violet (CaV), or electroactive peptides, such as Tyr-Gly-Gly (TGG), however, little response was observed (Figure 8). At a bare, polished glassy carbon electrode, however, CaV gives a voltammetric response similar to that observed for DA ($E_{p,a} \sim 0.3$, $E_{p,c} = -0.09$ V), whereas TGG is irreversibly oxidized at $E_{p,a} \sim 0.66$ V in pH 7 phosphate buffer.

To further evaluate the molecular selectivity of the film, the response of the DA-templated films toward three structurally unrelated redox probes was also examined. Figure 9 shows the CV response of the templated films in 0.1 M, pH 7.4 phosphate buffer containing *1 mM* $Ru(NH_3)_6^{3+}$, $Ru(bpy)_3^{2+}$, and $Fe(CN)_6^{3-}$, respectively. As can be seen, very little Faradaic current is observed for any of these inorganic redox probes. This was a surprising result, particularly considering the high analyte concentration used in this experiment.

Table 1. Relative Response of Templated Films

analyte	% response[a] (relative to bare electrode)
dopamine (DA)	67
catechol (CA)	65
norepinephrine (NE)	33
epinephrine (EN)	32
dihydroxynaphthalene (DHN)	25
serotonin creatinine sulfate (ST)	23
ascorbic acid (AA)	0
(dihydroxyphenyl)alanine (DOPA)	0
dihydroxyphenylacetic acid (DOPAC)	0
catechol violet (CA)	0
Tyr-Tyr-Gly	0
$Ru(bpy)_3^{2+}$	4
$Ru(NH_3)_6^{3+}$	4
$Fe(CN)_6^{3-}$	0

[a] $N = 2$.

As a means to semiquantitate the selectivity of the DA-templated films toward these analytes and others (catechol and norepinephrine) in solution, a direct comparison of the response of the analyte at a bare glassy carbon electrode to its response at a templated film modified electrode was made. In this comparison, the anodic peak current ($i_{p,a}$) at the templated film was divided by $i_{p,a}$ at a bare electrode in an identical 0.1 mM analyte solution. The results are tabulated in Table 1. As can be seen, the DA-templated films exhibit a large relative response (ca. 65−70%) toward the print molecule, dopamine. In addition, a large response is observed for catechol, presumably because of its small size and phenyl functionality (hydrophobicity). The next greatest affinity (30−35%) of the DA-templated films is toward EN and NE, which are nearly structurally identical to DA, with the exception that they contain an additional hydroxyl functional group and EN is a secondary amine. DHN and ST show a similar small affinity for the templated films. Little response, if any, is observed for the negatively charged or zwitterionic analytes (AA, DOPAC, DOPA and $Fe(CN)_6^{-3}$) or the larger analytes (CaV, TGG, $Ru(bpy)_3^{2+}$).

Given the current sol−gel processing and film preparation procedures, the silicate films in this work are likely to be relatively dense compact structures.[35] This is evident from the lack of response at the nontemplated films and is also consistent with the work of Brinker and co-workers,[35] who have noted that films prepared from acid-catalyzed sols are often nonporous.[36] The introduction of a template into the sol and the subsequent removal of the template from the gel via extended soaking in buffer undoubtedly increases the porosity of the material and creates specific pathways (i.e., channels and/or cavities) for template permeation into the film. As can be seen in Table 1, the hybrid materials prepared in this work show an affinity for molecules containing a phenyl group, particularly those that are small and positively charged or neutral. In contrast, the templated films show no response toward negatively charged analytes. In pH 7 phosphate buffer, the silicate films will likely have a negative charge, due to the presence of deprotonated silanol groups (pK_a ca. 2).[37] The compact negatively charged surface likely plays an important role in prevention of negatively charged analytes such as AA, DOPAC, DOPA, and $Fe(CN)_6^{-3}$ from reaching the underlying electrode surface. Likewise, the restricted surface pore sizes may also limit structurally similar, albeit larger, aromatic catechols or peptides from partitioning into the film.

The exact mechanism for the observed enhancement in current for DA relative to similarly structured molecules such as DHN, NE, or EN is not currently known. The mechanism may involve an association-type mechanism, as described by Hodgson and co-workers, whereby the unextracted DA in the silicate film act as "nucleation centers" to enhance adsorption of their own kind.[10] Alternatively, the observed results could possibly be explained in terms of a "lock-and-key" or a "footprint" mechanism as originally hypothesized by Dickey[9] and popularized in the field of molecular imprinting.[5−8] The lack of response of the film toward a small electroactive cation, i.e., $Ru(NH_3)_6^{3+}$, suggests that hydrophobicity could also play an important role in governing the affinity of these materials toward specific analytes. Perhaps the DA-templated hosts contain the correct balance of porosity and hydrophobicity to favor DA permeation and diffusion within the film. Future work will be directed toward understanding the molecular recognition properties of these unique hybrid materials.

Conclusions

The blending of inorganic precursors with organosilicon reagents enables unique materials to be fabricated with the desired chemical and physical characteristics. In this work, templated inorganic−organic hybrid materials that show a distinct chemical affinity for dopamine have been prepared. The thin film materials thus produced are stable in aqueous solution and have a relatively fast response time. These are important concerns in the development and design of viable chemical sensors. The mechanism by which these materials are able to discriminate among the different analytes evaluated in this work is believed to be due to the combined effects of porosity, hydrophobicity, and electrostatic repulsion. Two key attributes to this method for the preparation of templated materials are the flexible, mild solution chemistry and the ease with which materials in various configurations (e.g., films, fibers, monoliths) can be processed. It is anticipated that this work will increase the range of molecules that can be successfully templated and lead to promising developments in the design of more selective, stable, efficient materials for advanced applications.

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(36) Due to the very limited amount of silica on the electrode surface, however, we were unable to obtain pore size or surface area measurements for the materials used in this work. However, AFM images obtained of the nontemplated surfaces are similar to that pictured in previous work.[30]

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