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Dipolar Molecules as Impellers Achieving Electric-Field-Stimulated Release

Yingchun Zhu,*,† Huijuan Liu,† Fang Li,† Qichao Ruan,† Hua Wang,‡ Masahiro Fujiwara,§ Lianzhou Wang,|| and G. Q. (Max) Lu||

Key Lab of Inorganic Coating Materials, Shanghai Institute of Ceramics, CASS, Shanghai 200050, China, Key Lab for Special Functional Materials, Ministry of Education, Henan University, Kaifeng 475004, China, National Institute of Advanced Industrial Science and Technology (AIST), Ikeda, Osaka 563-8577, Japan, and ARC Centre of Excellence for Functional Nanomaterials, School of Chemical Engineering and AIBN, The University of Queensland, St Lucia, QLD 4072, Australia

Received September 7, 2009; E-mail: yzhu@mail.sic.ac.cn

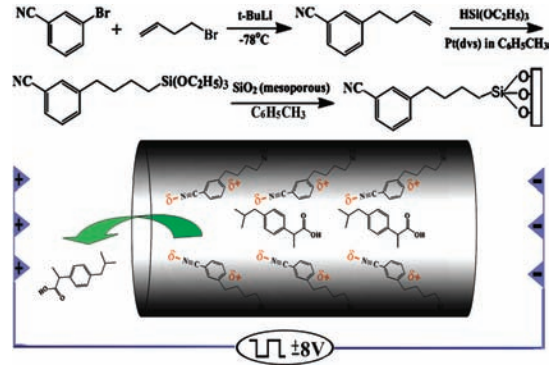
Stimuli-responsive release systems are gaining increasing interest as drug delivery systems that allow intelligent release of drugs. Many promising controlled-release systems have been developed by employing functional molecules to supply drugs in response to external stimuli, such as UV or visible light,[1] pH,[2] and others.[3] These functional molecules act as smart gates or molecular impellers that regulate the release of guest molecules by responding to endogenous and exogenous activation.

Electric fields are widely used as power and signal sources, based on which electrotherapy has been developed to cure various diseases, such as brain diseases, voice and swallowing disorders, chronic resistant wounds, tumors, and so on.[4] However, studies on electric-field-stimulated release are quite limited despite the achievements involving electrochemical processes.[5] Here we report a new electric-field-stimulated release system that uses external electric fields to control the release process. We assemble functional molecules with permanent electric dipole moments in channels of mesoporous silica; these molecules can respond to an external alternating electric field applied on the hybrid system. The flexible molecular chains swing to push the guest molecules out of the pore voids. The electric-field-responsive release system can be remotely controlled by external electric fields.

Molecules with permanent electric dipole moments (μ) have the ability to reorient or switch with an electric field and have found a wide range of applications in electric and optical devices.[6] Molecular chains terminated with cyano groups ($\mu = 4.18$ D) have strong permanent electric dipole moments. Polymers with cyano group-terminated side chains are typically used in liquid-crystal displays and antiferroelectric photonics and electronic devices because of their fast and reversible electrical and optical response based on their excellent dielectric properties.[6] In the present work, we synthesized functional molecules of 4-(3-cyanophenyl)butylene and grafted them onto the meso channels of ordered mesoporous silica for electric-field-controlled drug release.

The synthesis of 4-(3-cyanophenyl)butylene and the assembly of the hybrid materials are illustrated in Scheme 1. The whole procedure was processed under anhydrous and oxygen-free conditions, and all of the organic solvents were freshly distilled from metal hydrides to remove water and oxygen. 4-Bromo-1-butene (0.62 mL, 6 mmol), ether (25 mL), and *tert*-butyllithium (10 mL, 1.4 M in pentane, 14 mmol) were sequentially added into a Schlenk tube under an Ar atmosphere at −78 °C. A yellow solution was obtained after the reaction mixture was stirred for 2 h. 3-Bromobenzonitrile in ether (10 mL, 6 mmol) was then added dropwise by syringe, and reaction for 4 h afforded a red solution. After the reaction was quenched, the red solution was washed with NaCl solution, extracted with ether, and dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography on silica gel using 1:2 (v/v) chloroform/petroleum ether as the eluent to yield 4-(3-cyanophenyl)butylene as a yellow product that was identified by NMR analysis (see the Supporting Information). The 4-(3-cyanophenyl)butylene (0.21 mL, 1.3 mmol) was reacted with triethoxysilane (0.25 mL, 1.43 mmol) in toluene under an Ar atmosphere using Pt as the catalyst, resulting in grafting of the molecules with a permanent electric dipole moment onto the inner surfaces of mesopores of ordered mesoporous silica to form a functional mesoporous silica system (FMSS) (Scheme 1) (for experimental details, see the Supporting Information).

Scheme 1. (top) Synthesis of 4-(3-Cyanophenyl)butylene and (bottom) Release Mechanism of the Functional Mesoporous Silica System under an Alternating Square-Wave Electric Field



Dielectric property investigations using a Solartron impedance/gain-phase analyzer were carried out to determine the dynamic behavior of the permanent electric dipoles fixed on the mesoporous silica (Figure 1a,b). Three relaxation processes can be observed in Figure 1b. The relaxation at a frequency of $\sim 10^3$ Hz is the reorientation of the whole axis of the functional molecular chains, while the weak one at a frequency of $\sim 10^4$ Hz should be the relaxation of the end cyano groups, which reorient by a rotation process.[7] Such dielectric behavior is quite similar to that of side-group polymers with CN-terminated side groups.[7] The abrupt increase in both dielectric constant and loss at frequencies lower than 10^2 Hz may be the contribution of ionic conductivity in mesoporous silica, which may induce a supercapacitor effect. The 4-(3-cyanophenyl)butylene contains a cyano group with a strong inherent moment parallel to the long molecular axis, which enables the reorienting of molecules in response to external electric fields.

† Shanghai Institute of Ceramics.
‡ Henan University.
§ National Institute of Advanced Industrial Science and Technology.
|| The University of Queensland.

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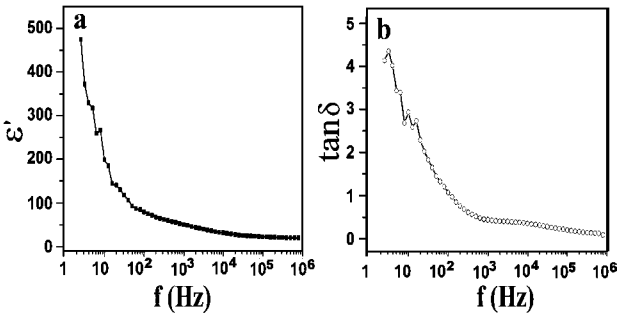

Figure 1. (a) Dielectric constant and (b) tangent of the dielectric loss as functions of frequency for 4-(3-cyanophenyl)butylene-modified mesoporous silica.

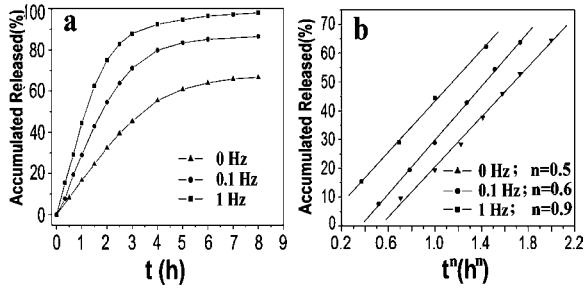

Figure 2. (a) Profiles for release of ibuprofen from 4-(3-cyanophenyl)butylene-modified mesoporous silica at different frequencies. (b) Release-kinetics profiles corresponding to the curves in (a).

The release of ibuprofen from FMSS was carried out in a cell composed of two mesh electrodes by applying electric fields with different frequencies (Figure 2a). The mesh electrodes were coated with insulator and placed 3 mm apart, and a voltage of ±8 V was used to provide electric fields but prevent electrochemical reactions in the solution. When a static electric field was applied, the ibuprofen was slowly released from FMSS in simulated body fluid, and ~62% of the stored ibuprofen was released in 8 h. When an alternating electric field with a frequency of 0.1 Hz was applied, we found that the rate of ibuprofen release from FMSS increased considerably, with ~85% of the ibuprofen released into the simulated body fluid in 6 h. More encouragingly, when an alternating electric field with a frequency of 1 Hz was applied, ~90% of the stored ibuprofen was released in 3 h and ~98% was released after 8 h. The results clearly indicate that the release rate can be rationally regulated simply by controlling the external electric field. In this case, very fast release was achieved by applying an alternating electric field with a frequency of 1 Hz.

The kinetics of ibuprofen release from FMSS was analyzed by fitting the Peppas equation in Figure 2b. The diffusion exponent (n) was 0.5 in the static electric field, corresponding to typical Fickian diffusion (natural diffusion) driven by the concentration gradient of ibuprofen in FMSS. In the cases of release using alternating electric fields with frequencies of 0.1 and 1 Hz, the diffusion exponents were 0.6 and 0.9, respectively. The increased diffusion exponents suggest a non-Fickian diffusion mechanism, which means that the diffusion under the alternating electric fields exceeded the concentration-gradient-controlled diffusion. As shown in Scheme 1, the 4-(3-cyanophenyl)butylene molecules grafted onto the mesopores may reorient in response to external electric fields because of the strong inherent dipole moment. The swinging of the flexible molecular chains consequently accelerates the release of ibuprofen from the meso channels.

Further release experiments showed that the release rate at 10 Hz was similar to that at 1 Hz, and no further acceleration of the release was observed for electric fields at 10^3 Hz. This implies that the reorientation of dipole molecules in the mesopores was possibly restrained by the loaded ibuprofen molecules and thus was unable to respond fully to higher frequencies. It is suggested that the relaxation time may be ~0.1 s when ibuprofen is loaded, so the release is accelerated at 10 Hz. The dipoles could well reorient at 1 Hz and result in fast release. At a frequency of 0.1 Hz, the release is also accelerated but to a lesser extent than that at 1 Hz because of the lower frequency. The dipoles cannot reorient when the period of the electric field is shorter than the relaxation time and do not stimulate release at 10^3 Hz. The control experiments using mesoporous silica without 4-(3-cyanophenyl)butylene molecules showed that alternating electric fields did not accelerate the release of ibuprofen from mesoporous silica. It is therefore clear that the release of guest molecules is controlled by the applied alternating electric field with appropriate frequencies.

In summary, we have demonstrated the external electric field-controlled release of guest molecules from mesoporous silica. In this system, the dipolar 4-(3-cyanophenyl)butylene molecules served as impellers to propel the release of guest molecules in response to external electric fields with different frequencies. Together with electrotherapy,[4] this new externally controlled release system offers a number of advantages, including local release in the target, external control, and the nonelectrochemical nature of the process, and thus may open up many application opportunities, including important in vivo tumor treatments.

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Supporting Information Available: Experimental details and supporting figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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