Chem. Mater. **2006,** *18,* 5817−5819 5817

Solid Lipid Nanoparticles of *p*-Hexanoyl Calix[4]arene as a Controlling Agent in the Photochemistry of a Sunscreen Blocker

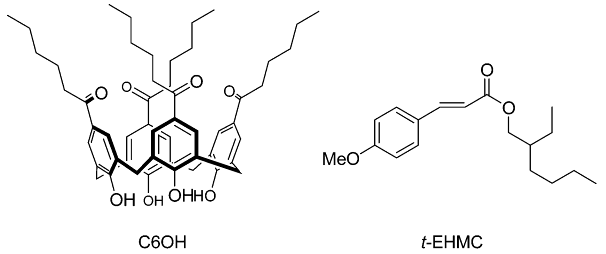
Michaela Pojarova,† Gennady S. Ananchenko,*,† Konstantin A. Udachin,† Malgosia Daroszewska,† Florent Perret,‡ Anthony W. Coleman,‡ and John A. Ripmeester†

Steacie Institute for Molecular Sciences,
National Research Council Canada, 100 Sussex Drive,
Ottawa, K1A 0R6 Canada, and Institut de Chimie et
Biologie des Proteins, 7 Passage du Vercors,
F-69367 Lyon Cedex 07, France

Received August 23, 2006
Revised Manuscript Received October 18, 2006

Solid lipid nanoparticles (SLNs),[1] among others (micelles, liposomes, polymeric nanoparticles), are new carrier systems for biologically active compounds such as drugs, cosmetic ingredients, and so forth. Typical SLN can be prepared from solid lipids (triglycerides, fatty acids, waxes) and stabilized by nontoxic surfactants (poloxamer, lecithin). Disadvantages are the relatively high water content, drug expulsion after polymorphic transitions during storage, and insufficient loading capacity.[1] The latter can be overcome with the application of SLN based on calix[4]arenes[2] which very easily complex small molecules and ions. The amphiphilic *para*-alkanoyl calix[4]arenes have been reported to be nontoxic and non-immunogenic[3] and can be synthesized by Friedel−Crafts acylation of the upper rim.[4] The crystalline inclusion complexes of amphiphilic calixarenes have been studied extensively,[5−7] and it is quite reasonable to compare these with SLN prepared from the same compounds[2,3,8] and loaded with the same guests. Aiming to explore practical applications of calixarene based SLN as carriers for sunscreens,[9] we have chosen one of the most used UV absorbers, *trans*-2-ethylhexyl-4-methoxy-cinnamate (*t*-EHMC),[10,11] as a guest and *p*-hexanoyl calix[4]arene as a host (Scheme 1). In the present Communication, the preparation and characterization of *p*-hexanoyl calix[4]arene-based SLNs loaded with *t*-EHMC (SLN-EHMC) are reported along with the influence of the calixarene nanocapsules on the photochemical stability and phototransformation pathways of the sunscreen agent.

Scheme 1. Structures of *p*-Hexanoyl Calix[4]arene (C6OH) and *t*-EHMC



The complex of C6OH with *t*-EHMC (2C6OH·1*t*-EHMC) crystallizes in the monoclinic $P2_1/n$ space group with unit cell parameters 15.55 Å, 22.34 Å, 15.61 Å, and 90.7°. The unit cell contains four molecules of calix[4]arene and two molecules of EHMC, whereas two molecules of calixarene enclose one molecule of EHMC inside the nanocapsule[5,6] (Figure 1). The methoxy group and the terminal methyl group of the 2-ethyl residue are included deeply in the cavity of the calixarene, providing CH_3-π stabilization of the guest in the nanocapsule. The complex is stable and does not decompose up to the melting point of the material (ca. 175 °C).

The SLNs were prepared by the solvent displacement method according to ref 2 with a starting ratio between calixarene and EHMC of 1:0.5 and 1:1. The ratios of calixarene to cinnamate in isolated SLN-EHMC were 1:0.6 (SLN-EHMC-0.6) and 1:1.2 (SLN-EHMC-1.2), respectively.

The comparison of the powder X-ray diffraction (XRD) patterns of unloaded SLN, SLN loaded with *t*-EHMC, and the crystalline complex 2C6OH·1*t*-EHMC (Figure 2) reveals that the guest causes ordering of the SLN into microcrystalline material similar to 2C6OH·1*t*-EHMC. Since the latter is a nanocapsular complex, one can expect that SLN-EHMC also are agglomerations of nanocapsules that are partially ordered. The size of the nanoparticles is expected to be ca. 270 nm or smaller.[2,3b]

---

* E-mail: gennady.ananchenko@nrc-cnrc.gc.ca.
† National Research Council Canada.
‡ Institut de Chimie et Biologie des Proteins.

(1) (a) Wissing, S. A.; Kayser, O.; Müller, R. H. *Adv. Drug Delivery Rev.* **2004**, *56*, 1257. (b) Mehnert, W.; Mäder, K. *Adv. Drug Delivery Rev.* **2001**, *47*, 165. (c) Müller, R. H.; Mäder, K.; Gohla, S. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 161. (d) zu Mühlen, A.; Schwarz, C.; Mehnert, W. *Eur. J. Pharm. Biopharm.* **1998**, *45*, 149. (e) Müller, R. H.; Radtke, M.; Wissing, S. A. *Adv. Drug Delivery Rev.* **2002**, *54*, S131. (f) Manjunath, K.; Reddy, J. S.; Venkateswarlu, V. *Methods Find. Exp. Clin. Pharmacol.* **2005**, *27*, 127.

(2) Shahgaldian, P.; Da Silva, E.; Coleman, A. W.; Rather, B.; Zaworotko, M. J. *Int. J. Pharm.* **2003**, *253*, 23.

(3) (a) Shahgaldian, P.; Da Silva, E.; Coleman, A. W. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *46*, 175. (b) Shahgaldian, P.; Gualbert, J.; Aïssa, K.; Coleman, A. W. *Eur. J. Pharm. Biopharm.* **2003**, *55*, 181.

(4) Shahgaldian, P.; Coleman, A. W.; Kalchenko, V. I. *Tetrahedron Lett.* **2001**, *42*, 577.

(5) (a) Ananchenko, G. S.; Udachin, K. A.; Dubes, A.; Ripmeester, J. A.; Perrier, T.; Coleman, A. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 1585. (b) Ananchenko, G. S.; Udachin, K. A.; Pojarova, M.; Dubes, A.; Ripmeester, J. A.; Jebors, S.; Coleman, A. W. *Cryst. Growth Des.* **2006**, *6*, 2141.

(6) Ananchenko, G. S.; Udachin, K. A.; Ripmeester, J. A.; Perrier, T.; Coleman, A. W. *Chem.*−*Eur. J.* **2006**, *12*, 2441.

(7) Dubes, A.; Udachin, K. A.; Shahgaldian, P.; Coleman, A. W.; Ripmeester, J. A. *New J. Chem.* **2005**, *29*, 1141. Shahgaldian, P.; Coleman, A. W.; Rather, B.; Zaworotko, M. *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 241.

(8) Dubes, A.; Moudrakovski, I. L.; Shahgaldian, P.; Coleman, A. W.; Ratcliffe, C. I.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 6236.

(9) Wissing, S. A.; Muller, R. H. *J. Controlled Release* **2002**, *81*, 225. Wissing, S. A.; Müller, R. H. *Pharmazie* **2001**, *56*, 783. Wissing, S. A.; Müller, R. H. *Int. J. Pharm.* **2003**, *254*, 65. Wissing, S. A.; Müller, R. H. *Int. J. Cosmet. Sci.* **2001**, *23*, 233.

(10) Perugini, P.; Simeoni, S.; Scalia, S.; Genta, I.; Modena, T.; Conti, B.; Pavanetto, F. *Int. J. Pharm.* **2002**, *246*, 37.

(11) (a) Pattanaargson, S.; Limphong, P. *Int. J. Cosmet. Sci.* **2001**, *23*, 153. (b) Broadbent, J. K.; Martincigh, B. S.; Raynor, M. W.; Salter, L. F.; Moulder, R.; Sjöberg, P.; Markides, K. E. *J. Chromatogr., A* **1996**, *732*, 101. (c) Damiani, E.; Rosati, L.; Castagna, R.; Carloni, P.; Greci, L. *J. Photochem. Photobiol., B* **2006**, *82*, 204. (d) Tarras-Wahlberg, N.; Stenhagen, G.; Larkö, O.; Rosén, A.; Wennberg, A.-M.; Wennerström, O. *J. Invest. Dermatol.* **1999**, *113*, 547.

10.1021/cm061993o CCC: $33.50

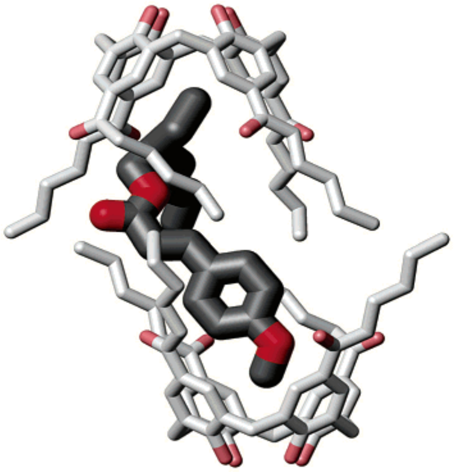


Figure 1. Capsular structure of inclusion complex of *p*-hexanoyl calix[4]-arene with *t*-EHMC (2C6OH·1*t*-EHMC). Disorder and H-atoms are omitted for clarity.

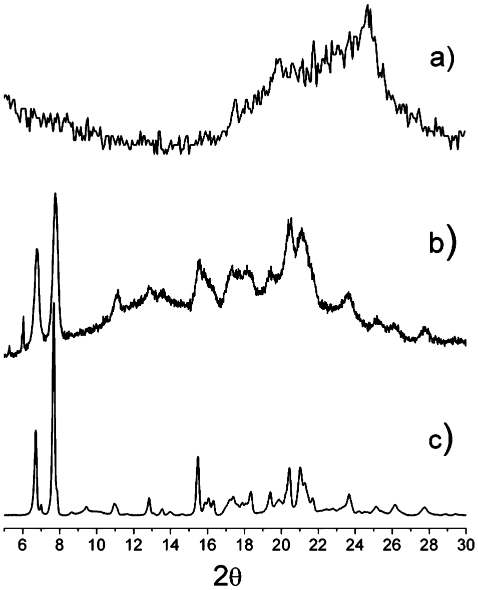


Figure 2. Powder XRD patterns of C6OH SLNs: unloaded SLN (a), SLN-EHMC-1.2 (b), and crystalline inclusion complex 2C6OH·1*t*-EHMC (c).

The nanocapsular structure of SLN loaded with EHMC can be also confirmed by comparison of ^{13}C CP MAS NMR spectra of SLN-EHMC-1.2 and the crystalline complex (2C6OH·1*t*-EHMC; Figure 3). The resonances in the NMR spectrum of SLN are broader; however, the chemical shifts are the same as those in 2C6OH·1*t*-EHMC. Moreover, an approximately 5 ppm upfield shift of the methoxy-CH_3 and terminal CH_3 in the 2-ethyl group agrees with single-crystal XRD data where these two groups are found to be included deeply in the calixarene cavity.[5,6] It was mentioned previously[8] that the guest can change the degree of order of calixarene molecules in the nanoparticles, and this generally agrees with other types of SLN[12] where the degree of crystallinity depends strongly on formulations and on the conditions of preparation of the nanoparticles.

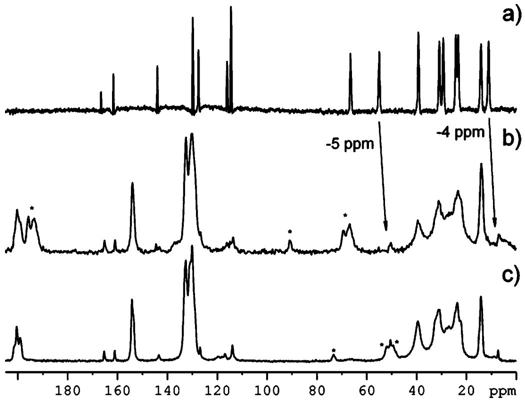


Figure 3. ^{13}C CP-MAS spectra of SLN-EHMC-1.2 (b) and the crystalline inclusion complex 2C6OH·1*t*-EHMC (c) in comparison with the ^{13}C NMR spectrum of pure *t*-EHMC taken in the CP-MAS NMR probe without spinning (a). Spinning side bands are marked with *.

The photochemistry of *t*-EHMC is well understood[11] and is quite similar to that of other cinnamic acid derivatives.[13−16] Upon irradiation of *t*-EHMC the main product of photodegradation is the corresponding cis isomer,[11] which is less efficient in absorbing light[10,11] and decreases the effect of the UV blocker. In addition to the cis−trans isomerization, the formation of small amounts of dimeric product has also been observed.[11b] According to the literature[11a] the cis/trans ratio after irradiation of pure *t*-EHMC with sunlight is approximately 1:1.

In our experiments, both the crystalline complex 2C6OH·1*t*-EHMC and SLN-EHMC-0.6 were irradiated with UV light ($\lambda = 320-390$ nm) for 2 h at an intensity of 2.5 W/cm^2 in a similar manner as described previously.[6] The ratio of the two isomers after the irradiation proved to be 40% cis- and 60% trans isomer of EHMC. The formation of dimers was not detected. This agrees with the X-ray data that one molecule of *t*-EHMC is encapsulated and there are no other EHMC molecules nearby to give dimeric products. Upon irradiation of SLN-EHMC-1.2, the formation of photodegradation products was observed in addition to the cis−trans isomerization. The total fraction of these products was approximately 10%, as estimated from a ^{1}H NMR spectrum of the reaction mixture, and, hence, photodegradation can be considered as a minor process which only takes place if excess *t*-EHMC is present in the material. HPLC-MS analysis of the reaction mixture revealed that two major photodegradation products are the corresponding cyclobutanes—products of [2+2] photocycloaddition of EHMC.

Aiming to assign the stereochemistry of the dimers, we carried out the photolysis of a larger amount of *t*-EHMC in a sodium dodecylsulfate (SDS) micellar solution and isolated the products which had the same retention times as those after the irradiation of SLN. Using the published data about

---

(12) Sauppe, A.; Wissing, S. A.; Lenk, A.; Schmidt, C.; Müller, R. H. *Bio-Med. Mat. Eng.* **2005**, *15*, 393. Cavalli, R.; Caputo, O.; Marengo, E.; Pattarino, F.; Gasco, M. R. *Pharmazie* **1998**, *53*, 392. Freitas, C.; Müller, R. H. *Eur. J. Pharm. Biopharm.* **1999**, *47*, 125. Zimmerman, E.; Souto, E. B.; Müller, R. H. *Pharmazie* **2005**, *60*, 508.

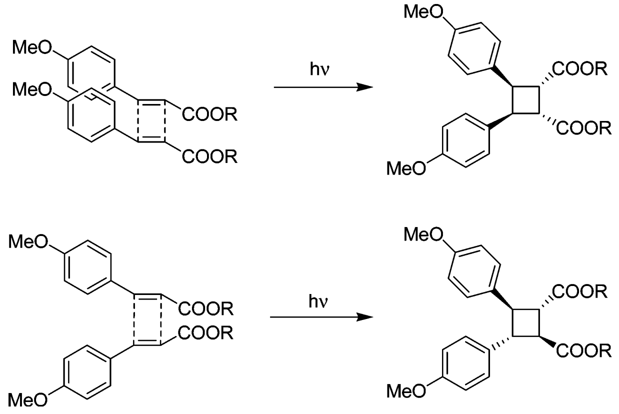
(13) Dilling, W. L. *Chem. Rev.* **1983**, *83*, 1. McCullough, J. J. *Chem. Rev.* **1987**, *87*, 811. Inoue, Y. *Chem. Rev.* **1992**, *92*, 741.

(14) Nakamura, T.; Takagi, K.; Itoh, M.; Fujita, K.; Katsu, H.; Imae, T.; Sawaki, Y. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2751. Ramesh, V.; Weiss, R. G. *J. Org. Chem.* **1986**, *51*, 2535. D'Auria, M.; Vantaggi, A. *Tetrahedron* **1992**, *48*, 2523.

(15) Feldman, K. S.; Campbell, R. F.; Saunders, J. C.; Ahn, C.; Masters, K. M. *J. Org. Chem.* **1997**, *62*, 8814.

(16) Pattabiraman, M.; Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529.

Scheme 2



the selectivity of dimerization of cinnamic acid esters,[15-17] we identified the products of photolysis of *t*-EHMC in SLNs as the esters of two isomeric (β- and δ-) *p*-methoxytruxinic acids (Scheme 2), that is, syn- and anti-isomers, respectively.

Since the dimerization of *t*-EHMC in SLN is regioselective, it is reasonable to expect that the excess *t*-EHMC molecules in the particles is aligned between calixarene nanocapsules preferably in a head-to-head orientation[13] (Scheme 2). The pre-alignment of similar molecules using micelles, Lewis acids, supramolecular hosts, or (co-)-crystallization has been widely used to achieve higher regio- and stereoselectivity in such photoreactions.[14,16,18,19] Simple considerations of the structure from the point of view of van der Waals interactions reveals that there is no free space in the capsular pocket for the second molecule of *t*-EHMC. Therefore, one can expect that some *t*-EHMC is distributed between the capsules and distorts the crystal lattice to some extent. This extracapsular *t*-EHMC is able to give dimers with higher selectivity upon irradiation due to the restricted motion and probably due to the self-association of *t*-EHMC molecules. Of course, the presence of another phase of the complex with a different type of inclusion[20] cannot be ruled out completely, but no evidence was found from single crystal and powder XRD experiments.

In summary, we have demonstrated for the first time that SLNs based on amphiphilic calixarenes can be a good carrier system for cosmetically interesting substances. Unlike unloaded nanoparticles, the SLN loaded with *t*-EHMC (and probably other guests) is a microcrystalline material where the guest is entrapped in molecular nanocapsules constructed from two calixarene molecules. Thorough combination of components (C6OH and *t*-EHMC) during preparation of SLNs can control the photochemistry, eliminate the photodimerization, and improve the photoblocking properties of *t*-EHMC. In addition, the host (i.e., acylphenol) also may serve as an additional UV filter and, hence, can enhance the photoblocking properties of the guest. The amphiphilic calixarene may well be a promising additive for creams and lotions that can improve the efficacy of the corresponding cosmetic formulations.

Acknowledgment. This work was supported in part by the CNRS-NRC collaborative program.

Supporting Information Available: Experimental details of preparation of inclusion complexes and SLN; TGA analysis of 2C6OH•1*t*-EHMC and of SLN-EHMS; description of solid-state NMR and HPLC results; and ^{1}H NMR of isolated β- and δ-truxinates (PDF); CIF file and details of crystal structure of the complex 2C6OH•1*t*-EHMC. This material is available free of charge via the Internet at http://pubs.acs.org.

CM061993O

---

(17) Saito, H.; Mori, T.; Wada, T.; Inoue, Y. *Org. Lett.* **2006**, *8*, 1909.

(18) Vriezema, D. M.; Aragonés, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445.

(19) Papaefstathiou, G. S.; MacGillivray, L. R. *Org. Lett.* **2001**, *3*, 3835. Ramnath, N.; Ramamurthy, V. *J. Org. Chem.* **1984**, *49*, 2827. Muthuramu, K.; Ramnath, N.; Ramamurthy, V. *J. Org. Chem.* **1983**, *48*, 1872. Lewis, F. D.; Oxman, J. D.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 466. Papaefstathiou, G. S.; Friščić, T.; MacGillivray, L. R. *J. Am. Chem. Soc.* **2005**, *127*, 14160. Cohen, M. D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 386. Yang, J.; Dewal, M. B.; Shimizu, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 8122. Karthikeyan, S.; Ramamurthy, V. *J. Org. Chem.* **2006**, *71*, 6409.

(20) Brouwer, E. B.; Udachin, K. A.; Enright, G. D.; Ripmeester, J. A.; Ooms, K. J.; Halchuk, P. A. *Chem. Commun.* **2001**, 565.