Monoglyceride Synthesis by Heterogeneous Catalysis Using MCM-41 Type Silicas Functionalized with Amino Groups

Anne Cauvel,[†] Gilbert Renard,[‡] and Daniel Brunel*[,†]

Laboratoire de Matériaux Catalytiques et Catalyse en Chimie Organique, UMR 5618 CNRS-ENSCM and CPI Groupe Synthèse Organique Enzymatique − Ecole Nationale Supérieure de Chimie-8, rue Ecole Normale, F-34296 − Montpellier Cédex 5, France

Received July 23, 1996

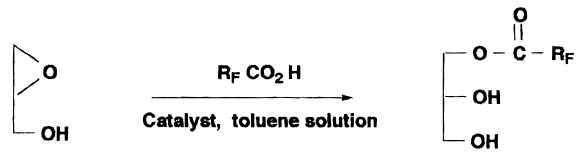
The availability of a selective synthesis of monoacylglycerols under mild heterogeneous catalysis would provide an important breakthrough in the fields of agrochemicals and pharmaceuticals. These syntheses are generally achieved through regiospecific esterification of glycerol with fatty acids using enzymatic catalysis.[1,2] However, the workup of this method presents some drawbacks, among which are the use of a biphasic system, dilute media, and large reactors. On the other hand, the selective chemical esterifications of glycerol to α- and *β*-monoglycerides described in the literature are difficult to achieve because they require that two hydroxyl groups be selectively blocked prior to the esterification of the third.[3]

The nucleophilic ring-opening of glycidol with fatty acids provides another interesting chemical route to monoacyl glycerol, since 2,3-epoxy alcohols are readily available by epoxidation of the corresponding allylic alcohols. The regioselective ring-opening can be assisted by titanium isopropoxide acting as a mediator.[4] The rate enhancement and the regioselectivity of the ring opening reaction have been explained by complexation of the epoxy alcohol to the metal center of the Ti(O-*i*-Pr)$_4$ which acts as a weak Lewis acid. However, the reaction yield is low due both to formation of byproducts and to difficulties in separation linked to the use of large amounts of titanium salts.[5]

Another method based on glycidol involves the use of tertiary amines[6] or ammonium salts[7] as the catalyst for the addition of fatty acids. However, the homogeneous conditions of this reaction remain unfavorable for easy recovery of the product. However the immobilization of the amino functions on a mesoporous mineral support could afford an active and useful heterogeneous catalyst for achieving this kind of reaction.

We herein report the use of MCM-41 type silicas (Micelle-Templated Silica, MTS) functionalized with primary and tertiary amino groups as catalysts for glycidol ring-opening with fatty acids under mild reaction conditions (Scheme 1).

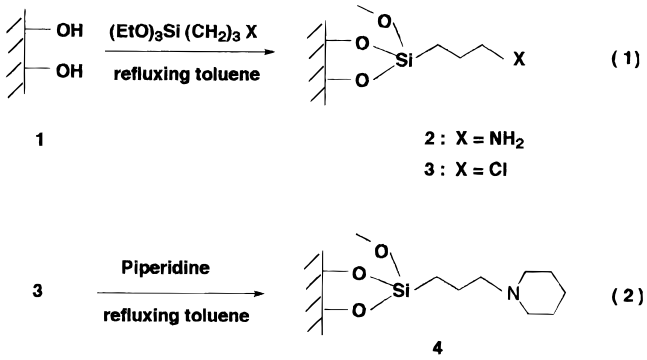
Scheme 1



Catalyst : MCM-41- Type silica - bound amino groups

$R_F CO_2 H$: Fatty acid

Scheme 2



Results and Discussion

Synthesis of the parent mesoporous MCM-41-type silica (MTS) (**1**) was achieved following Mobil's method[8] using amorphous silica and cetyltrimethylammonium hydroxide solution. The surfactant micelles which template the hydrothermal condensation of silica were subsequently eliminated by thermal degradation in air (823 K) to liberate a monodispersed mesoporous system featuring regular hexagonal arrays of uniform channels. The important textural characteristics of this MPS material are its high surface area (941 m^2 g^{-1}) and large mesoporous volume (0.73 mL g^{-1}) contained in channels having an average diameter of 31 Å. The surface silanol groups allow covalent linkage of functionalized organic moieties through Si−O−Si bonds by applying the usual methods of silica functionalization (Scheme 2, eq 1).[9,10] The mesoporous silica functionalized with primary 3-aminopropyl groups (NH_2-MTS) (**2**) and 3-chloropropyl groups (Cl-MTS) (**3**) were obtained through the treatment with toluene solutions of 3-amino- and (3-chloropropyl)triethoxysilane, respectively. Modification of compound **3** through the partial nucleophilic displacement of the chlorine atom with piperidine (Scheme 2, eq 2) yields grafted tertiary amino groups, *i.e.*, the 3-piperidinopropyl moiety (Pip-MTS) (**4**). Both materials **2** and **4** were subsequently treated with hexamethyldisilazane vapor at 453 K in order to selectively poison the residual OH groups[11,12] of the unmodified silica surface, yielding solids **5** and **6**, respectively (Scheme 3).

The nature of the organic moieties anchored to the solid support and the structure of the hydrocarbon chains were analyzed by infrared (IR) and MAS-NMR spectroscopies.

[†] Laboratoire de Matériaux Catalytiques et Catalyse en Chimie Organique.

[‡] CPI Groupe Synthèse Organique Enzymatique.

(1) El Zant, A.; Pina, M.; Graille, J.; Grimaud, J.; Renard, G. *Oléagineux* **1988**, *43*, 355.
(2) Gancet, C. *Stud. Surf. Sci. Catal.* **1991**, *59*, 93.
(3) Mattson, F. H.; Volpenhein, R. A. *J. Lipid Res.* **1962**, *3*, 281.
(4) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(5) Burgos, C. E.; Ayer, D. E.; Johnson, R. A. *J. Org. Chem.* **1987**, *52*, 4973.
(6) (a) Lock, C. M.; Mank, A. P. J.; Ward, J. P. *Chem. Phys. Lipids*, **1985**, *36*, 329. (b) Trubnikova, N. A.; Kuzkina, L. I. Deposited document cited in *Chem. Abstr.* **1979**, *91*, 192785 h.
(7) Lock, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115.
(8) Beck, J. C.; Chu, C. T.-W.; Johnson, I. D.; Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C. To Mobil Oil Corp.: WO91/11390, **1991**.
(9) W. Hertl, *J. Phys. Chem.* **1968**, *72*, 1248.
(10) (a) Brunel, D.; Cauvel, A.; Fajula, F.; Di Renzo, F. *Stud. Surf. Sci. Catal.* **1995**, *97*, 173. (b) Cauvel, A.; Brunel, D.; DiRenzo, F.; Fajula, F. Organic Coatings. Proceedings of 53rd International Meeting of Physical Chemistry. *Am. Inst. Phys.* **1996**, *354*, 477.
(11) Morrow, B. A.; McFarlan, A. J. *Langmuir* **1991**, *7*, 1695.
(12) Haukka, S.; Root, A. *J. Phys. Chem.* **1994**, *98*, 1695.

S0022-3263(96)01400-4 CCC: $14.00

Scheme 3

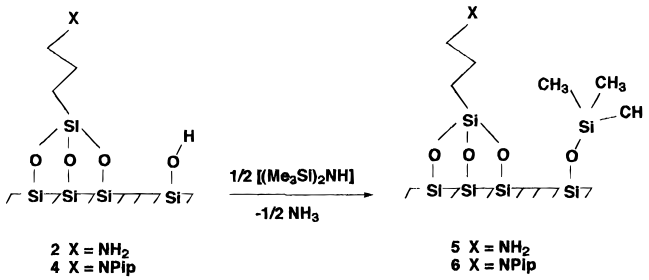


Table 1. Monoglyceride Production by Heterogeneous Catalysis Using Surface-Modified Mesoporous Silicas 1−6[a]

entry	catalyst	MG yield %[b] (6 h)	MG yield %[b] (24 h)
1	1	0[c]	0[c]
2	2	15	16[c]
3	**2**[d]	58	70[c]
4	3	0	0
5	4	59	67[c]
6	5	57	62[c]
7	**5**[d]	52	78[c]
8	6	84	90[c]
9	**6**[d]	84	85[c]
10[e]	6	49	85

[a] Catalyst (1g) activated at 423 K in vacuo; lauric acid (2 g); glycidol (0.75 g); toluene (25 mL); temperature 393 K. [b] % Yield as a function of initial mole content of lauric acid. [c] No residual glycidol was detected in the liquid phase. [d] corresponds to the catalyst that was reused after separation from the reaction liquid phase by filtration after 24 h of reaction time. It was washed with toluene, ethanol, and diethyl ether successively and then reactivated.[a] [e] Same reaction conditions as *a*, except temperature was reduced to 353 K, and undecylenic acid was used in place of lauric acid.

The organic chain contents and compositions of the functionalized materials were determined by elemental analysis and thermogravimetry. During the different modifications, no loss of the previously anchored chains or the regular porous structure was observed. These new composite MTS materials exhibit unusually large sorption capacities and, owing to their large pore diameters, are well-suited for conducting reactions between large molecules such as fatty acids and glycerides.

The catalytic activities and regioselectivities of the various solids were determined during the addition of lauric acid to glycidol in toluene solution at 393 K. The product obtained was identified as the α-monoglyceride 2,3-dihydroxypropyl laurate by GC-MS and by ^{1}H and ^{13}C NMR. The yields of monoglyceride (MG) as a function of lauric acid consumed were determined by GC, after reaction times of 6 and 24 h as summarized in Table 1.

The activity of the grafted primary amino groups (entry 2) toward the catalytic production of monoglyceride is revealed by comparison with the inactivity of the corresponding solid grafted with chloro groups, which we present as a control (Table 1, entry 4). It should be noted that the yield of monoglyceride is improved when the same catalyst **2** is reused (entry 3). During the first cycle (entry 2), the reaction of glycidol with lauric acid in a 1:1 ratio leads to a lower yield due to the fast disappearance of glycidol in the reaction solution. This phenomena can be explained by the competitive reaction of glycidol with residual silanol groups resulting in either polymerization or grafting reactions. This assumption is supported by the total transformation of glycidol, without lauric acid conversion, observed during the reaction performed with unmodified MTS **1** (entry 1). Moreover, the study of the reaction using glycidol alone in toluene solution catalyzed with the Cl-MTS material **3** showed the formation of an oligomeric product deposited on the catalyst particles after filtration of the reaction liquid phase. This oligomer was slightly soluble in ethanol and was analyzed by GPC with dimethylacetaldehyde as the liquid phase. The product showed an average molecular weight of 1500 g mol^{-1}. The elemental analysis and the ^{13}C NMR spectrum of the crude product show that it corresponds to a polymer of glycidol. Characterization of the washed catalyst carried out by IR and NMR spectroscopies further suggests that the residual silanols are partially blocked by grafted glycerol molecules. This observation may explain how the reused catalyst leads to higher MG yield (entry 3). The residual silanol groups are partially blocked during the first cycle, leading to reduced polymerization of glycidol during the second cycle.

The higher efficiency of the grafted tertiary amine (entry 4) over the primary amine is consistent with lower accessibility of the glycidol molecules to the surface silanols owing to steric hindrance caused by the piperidyl groups.

In order to improve the initial selectivity of the catalyst toward fatty acid addition on the epoxide ring, the catalysts **2** and **4** were treated with hexamethlyldisilazane, which is known to be reactive toward most of the OH groups of various silicas. As expected, the corresponding catalysts **5** and **6** produced higher monoglyceride yields (entries 6 and 8) than the parent solids (entries 2 and 5).

As catalyst **6** revealed the best catalytic behavior for lauric monoglyceride production, it was also tested for unsaturated monoglyceride preparation via the addition of undecylenic acid to glycidol. In this case, the reaction proceeded at a lower temperature (353 K) than with lauric acid, but the yield of monoglyceride was slighty lower (entry 10).

From a synthetic point of view, a supplementary experiment was performed wherein catalyst **6** was reactivated after two runs. Four times more glycidol−lauric acid solution containing a slight excess of glycidol than the normal scale was used in this synthetic run. The yield of monoglyceride in the reaction mixture after 24 h was actually higher than 95%. Filtration and evaporation of the solvent, followed by recrystallization of the crude product from hexane provided the pure lauric monoglyceride in 70% yield.

Our results show, therefore, that immobilization of amino functions on mesoporous silica provides an effective, nonenzymatic catalyst for epoxide ring-opening of glycidol by fatty acid addition. The catalyst displays high activity and regioselectivity.

Experimental Section

Instrumentation. Powder X-ray diffraction experiments have been carried out by using CGR Thêta-60 diffractometer with monochromated Cu Kα radiation ($\lambda = 1.54$ Å). Adsorption−desorption isotherms for nitrogen at 77 K were determined in a volume device Micromeritics Asap 2000. Thermogravimetric studies were carried out on a Setaram SF 85 balance under air flow. ^{13}C MAS-NMR measurements of the modified solids were carried out on a Bruker Model AM 300 spectrometer operating at 75.470 MHz with Fourier transform. The instrument setting were the following: 90° pulse of 4.80 ms; proton decoupling power: 30 G; contact time: 5.10^{-3} s; delay time 5 s; rotor spinning speed: 5 KHz. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 250 MHz spectrometer in $CDCl_3$ for fatty acid glycerides and in D_2O for oligomeric glycidol. IR spectra were

recorded on a FT-IR Nicolet 320 spectrometer with self-supported wafer of the solids outgassed under vacuum.

Preparation of Mesoporous MCM-41 Type Silica MTS 1. MTS-silica **1** was prepared by addition of Zeosil 175 MP precipitated silica (Rhône-Poulenc, 0.17 weight % Al) (21 g, 0.34 mol) to a stirred solution of cetyltrimethylammonium bromide (Aldrich) (11 g, 0.034 mol) and sodium hydroxide (4 g, 0.1 mol) in deionized water (200 mL). The reagents were mixed under stirring at 343 K and then heated in a stirred autoclave at 393 K for 16 h. After filtration and washing with deionized water to pH 9 and then with ethanol, the solid phase was dried at 353 K in air. The occluded organic template was decomposed by calcination at 823 K in flowing air for 7 h.

X-ray powder diffraction patterns matched well with those reported[13] for the monodispersed mesoporous system with d_{100} = 40.0 Å. The hexagonal lattice parameter was equal to 46.2 Å.

The nitrogen sorption isotherm of MTS is a type IV isotherm, showing monolayer and multilayer adsorptions on a very high area mesoporous surface and a sharp, reversible step at P/P_0 0.38 characteristic of capillary condensation within a regular mesoporous system.[13] The BET surface area (S_m) and the mesoporous volume Vol_m are 941 $m^2\ g^{-1}$ and 0.73 mL g^{-1}, respectively. The average pore diameter d of the mesoporous channels estimated by the relation $d = 4Vol_m/S_m$ was equal to 31 Å. Composition: Al/(Al + Si): 0.003; Na/(Al + Si): 0.0014. IR: 3742, 3536, 1974, 1866 cm^{-1}.[14]

Functionalization Procedure. (3-Aminopropyl)silyl-MTS 2 and 3-chloropropylsilyl-MTS 3. 2 and **3** were prepared by addition of the 3-amino- and and (3-chloropropyl)-trialkoxysilane (3 g) to a suspension of freshly activated MTS silica (3 g) in refluxing toluene (50 mL) and then stirred for 1.5 h. After distillation of a toluene fraction containing ethanol, the heating and distillation sequences were repeated two times. The modified solid was filtered, washed in a Soxhlet apparatus with diethyl ether and dichloromethane, and then dried at 393 K.

Characteristics of 2. IR: 3732, 3650,3375,3306, 2979,2936, 2867, 1974, 1836 cm^{-1}. ^{13}C CP-MAS-NMR δ (ppm) $Si^{\alpha}CH_2{}^{\beta}CH_2{}^{\gamma}CH_2NH_2$: $^{\alpha}C$ 8.9; $^{\beta}C$ 26.4; $^{\gamma}C$ 43.3. Anal. C, 6.90; N, 2.36; Si, 39.69. Thermogravimetry: % organic weight/dry mineral weight: 12.0. Surface area: 693 $m^2\ g^{-1}$; mesoporous volume: 0.45 mL g^{-1}.

Characteristics of 3. IR: 3732, 3650, 2970, 2940, 1974, 1836 cm^{-1}. ^{13}C CP-MAS-NMR δ (ppm) $Si(OCH_2CH_3)^{\alpha}CH_2{}^{\beta}CH_2{}^{\gamma}CH_2Cl$: OCH_2CH_3 58.7; OCH_2CH_3 16.3; $^{\alpha}C$ 8.9; $^{\beta}C$ 26.3; $^{\gamma}C$ 46.3. Anal. C, 7.22; Cl, 5.23; Si, 38.43. Thermogravimetry: % organic weight/dry mineral weight: 12.9. Surface area: 872 $m^2\ g^{-1}$; mesoporous volume: 0.53 mL g^{-1}.

(3-Piperidinopropyl)silyl-MTS 4. A suspension of activated **3** (3 g) in toluene (30 L) was refluxed and stirred in an excess of piperidine (1 g) for 6 h. The modified solid was then washed with water and then extracted with diethyl ether−dichloromethane mixture in a Soxhlet apparatus overnight. IR: 3731, 3649, 2945, 2892, 2867, 2818, 1974, 1866 cm^{-1}. Anal. C, 10.89; N, 1.45; Cl, 1.73; Si, 34.60. Thermogravimetry: % organic weight/dry mineral weight: 18.1. Surface area: 733 $m^2\ g^{-1}$; mesoporous volume: 0.43 mL g^{-1}.

Trimethylsilylation of 2 and 4 Solids with Hexamethyldisilazane (HMDS). The silylation procedure was a CVD method using dynamic vacuum.[15] The sample **2** or **3** (2 g) was laid on a glass scinter inside a vertical glass tube heated with an electric furnace. The solid was evacuated at 453 K for 2 h under reduced pressure (10^{-1} Torr). The organic silane vapor (HMDS) was then admitted through the heated solid under dynamic vacuum (1 Torr) by means of a heated connection with the reservoir containing the liquid silylating agent (6 g) heated at 308 K. After all the silazane compound was consumed (4 h), the solid was reevacuated (10^{-2} Torr) for 1 h.

Characteristics of 5. IR: 3650, 3375, 3306, 2960 (intense), 2935, 2868, 1974, 1866 cm^{-1}. ^{13}C CP-MAS-NMR δ (ppm) $(CH_3)_3$-Si: 0.2 (intense signal); $^{\alpha}C$ 8.9; $^{\beta}C$ 26.4; $^{\gamma}C$ 43.3. Anal. C, 9.79; N, 1.98; Si, 36.89. Thermogravimetry: % organic weight/dry mineral weight: 12.5. Surface area: 516 $m^2\ g^{-1}$; mesoporous volume: 0.32 mL g^{-1}.

Characteristics of 6. IR: 3655, 2960, 2941, 2862, 2803, 1974, 1866 cm^{-1}. ^{13}C CP-MAS-NMR δ (ppm) $(CH_3)_3Si$: 0.3 (intense signal); 10; 23.8; 40−70 (broad signal). Anal. C, 13.32; N, 1.36; Cl, 1.02; Si, 37.08. Thermogravimetry: % organic weight/dry mineral weight: 18.1. Surface area: 515 $m^2\ g^{-1}$; mesoporous volume: 0.26 mL g^{-1}.

Adsorption of Glycidol on Silanol Groups of MTS 1. The MTS **1** sample was analyzed after adsorption of glycidol followed by washing with ether−CH_2Cl_2 and vacuum evacuation. IR: 3500 (broad), 2920, 2875, 1974, 1866 cm^{-1}. No signal at 3742 cm^{-1}. Thermogravimetry: % organic weight/dry mineral weight: 60.

Analysis of the Oligomeric Solid Obtained during the Reaction of Glycidol Solution on Solid 3. After dissolution in methanol, filtration of the functionalized silica, and elimination of the solvent, the solid was analyzed by GPC using dimethylacetamide as liquid phase. The estimated mass average (M_w) and number average (M_n) molecular weights are 1500 and 800, respectively, with poly(methyl methacrylate) (PMMA) used as a standard. ^{13}C NMR ($CDCl_3$) δ (ppm): CH_2OH, 61.5, 61.8, 63.4; CH_2O, 71.0, 71.6, 72.9; $CHOH$, 69.6, 70,0, 71.2; CHO, 78.7, 79.3, 80.2, 81.9. Anal. Calcd C, 48.64; H, 8.10; O, 43.24. Found: C, 47.78; H, 8.61; O, 43.66.

General Procedure for the Catalyzed Addition of Lauric Acid to Glycidol. The reactions were performed in a glass flask under vigorous stirring. A 2 g (0.01 mmol) amount of lauric acid were added to a suspension of 1 g of solid catalyst in toluene (25 mL). A 750 mg (0.01 mmol) amount of glycidol were added when the temperature of the reaction mixture reached 393 K. The reaction mixture sample was analyzed after filtration using GC-MS (Hewlett Packard, GC series 5890, MS series 5970, Chem Station, windows series G 1034 C; column CP Sil-5CB (Chrompack), 25 m × 0.25 mm, gas: He) and GC (Delsi 30; FID, column Optima 1 (Macherey-Nagel), 25 m × 0.25 mm, gas: H_2) using dodecane as internal standard.

Selective Preparation of Monolauric Glyceride. After two runs, the catalyst **6** was washed with toluene and methanol and then evacuated at 423 K under vacuum. Lauric acid (2.32 g, 0.012 mol) and glycidol (1.12 g, 0.015 mol) were added to a stirred suspension of **6** (290 mg) in toluene (29 mL) heated at 293 K during 24 h. After separation of the solid by filtration, the solvent was distilled and the crude solid (3.15 g) was recrystallized in hexane. The pure lauric glyceride (2.25 g) was obtained in 69% yield. IR ($CHCl_3$): 3580, 3450, 2928, 2855, 1730 cm^{-1}. NMR ($CDCl_3$): $^{\gamma}CH_2(OH)^{\beta}CH(OH)^{\alpha}CHO^1C(O)^2CH_2{}^3CH_2(CH_2)_8{}^{12}CH_3$. ^1H NMR δ (ppm): $^{12}CH_3$ 0.88; $(CH_2)_8$ 1.26; $^3CH_2$ 1.65; $^2CH_2$ 2.35; $^{\gamma}CH$ 3.65; $^{\beta}CH$ 3.95; $^{\alpha}CH_2$ 4.18. ^{13}C NMR δ (ppm): $^{12}CH_3$ 14; $(CH_2)_8$ 22.5−29.5; $^3CH_2$ 31.8; $^2CH_2$ 34; $^{\gamma}CH_2$ 63.2; $^{\alpha}CH_2$ 65; $^{\beta}CH$ 70; $^1C(O)$ 174. MS m/e 257, M − OH; 243, M − CH_2OH; 214, M − $C_2H_4O_2$; 201, M − $C_3H_5O_2$; 183, M − $C_3H_7O_3$; 134, M − $C_{10}H_{20}$; 98, M − $C_9H_{20}O_3$; 74, M − $C_{12}H_{24}O_2$; 43, C_3H_7. Anal. Calcd: C, 65.69; H, 10.95; O, 23.36. Found: C, 65.78; H, 11.09; O, 23.55.

Preparation of Undecylenic Monoglyceride. The crude solid (2 g) obtained during entry 10 and according to the same procedure used previously produced recrystallized undecylenic monoglyceride (1.5 g) in 56% yield. IR: 3570, 3420, 2930, 2855, 1733 cm^{-1}. NMR δ ($CDCl_3$): $^{\gamma}CH_2(OH)^{\beta}CH(OH)^{\alpha}CHO^1C(O)^2CH_2{}^3CH_2(CH_2)_6{}^{10}CH{=}{}^{11}CH_2$. ^1H NMR (ppm) $(CH_2)_6$ 1.27−1.59; $^3CH_2$ 2; $^2CH_2$ 2.31; $^{\gamma}CH$ 3.70; $^{\beta}CH$ 3.87; $^{\alpha}CH_2$ 4.10;.^{10}CH 5.78; $^{11}CH_2$ 4.95. ^{13}C NMR δ (ppm): $(CH_2)_6$ 24−29.1; $^3CH_2$ 33.6; $^2CH_2$ 34; $^{\gamma}CH_2$ 63.3; $^{\alpha}CH_2$ 64.9; $^{\beta}CH$ 70.1; $^{11}CH_2$ 114;^{10}CH 139; $^1C(O)$ 174.2. Anal. Calcd: C, 65.11; H, 10.08; O, 24.81. Found: C, 64.66; H, 9.13; O, 24.48.

Acknowledgment. The authors thank Annie Finiels for the ^1H and ^{13}C NMR measurements in $CDCl_3$ solution. They are grateful to Francesco Di Renzo for fruitful discussions on the characterization of the solid materials. One of us (A.C.) is indebted to Ademe for a postgraduate grant.

JO9614001

(13) (a) Beck, J. S.; Vartuli, J. C.; Roth, W. J.; Leonowicz, M. E.; Kresge, C. T.; Schmitt, K. D.; Chu, C. T.-W.; Olson, D. H.; Sheppard, E. W.; McCullen, S. B.; Higgins, J. B.; Schlenker, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 10834. (b) Chen, C.-Y.; Li, H.-X.; Davis, M. E. *Microporous Mater.* **1993**, *2*, 17. (c) Ortlan, A.; Rathousky, J.; Schulz, G.; Zukal, A. *Microporous mater.* **1996**, *2*, 117.

(14) *Characterization and chemical modification of the silica surface*; Vansant, E. F., Van Der Voort, P., Vrancken, K. C., Eds.; Elsevier: New York. *Stud. Surf. Sci. Catal.* **1995**, *93*, 65.

(15) Chamoumi, M.; Brunel, D.; Fajula, F.; Geneste, P.; Moreau, P.; Solofo, J. *Zeolites* **1994**, *14*, 282.