Catalysis Letters 40 (1996) 109–114

Transesterification on "imprinted" silica

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Received 17 January 1996; accepted 11 April 1996

The transesterification reaction of ethyl phenylacetate to hexyl phenylacetate on an "imprinted" silica catalyst of the type first reported by Heilmann and Maier is investigated. In the presence of sulfuric acid co-catalysts, the data obtained here reveal that catalytic activity can be due to phosphorous species leached into solution; no evidence for molecular recognition and catalysis from an imprinted site in the silica is observed. In the absence of co-catalysts, no conclusion regarding the presence of an imprinted site in the silica can be ascertained because of the low level of activity relative to background autocatalysis.

Keywords: imprinting; transesterification reaction; nanostructured materials

1. Introduction

Almost half a century ago, F.H. Dickey working in the Pauling laboratories at Caltech produced the first nanostructured materials capable of molecular recognition. Dickey imprinted silica gels with a homologous series of orange dye molecules in order to prepare selective adsorbents [1]. Motivated by this pioneering investigation, Morihara and co-workers imprinted aluminum ion-doped silica gels that were able to catalyze acylation reactions as well as several enantioselective conversions [2–4]. These authors published a series of papers on what they aptly termed "footprint catalysis", referring to the specific adsorption sites left upon removal of the imprint. Although they have thus far obtained limited success in terms of catalytic activity and selectivity, improvements continue to be reported.

Recently, Heilmann and Maier (hereafter referred to as HM) exploited a slightly different approach than Morihara and colleagues and claim a selective silica catalyst for the transesterification of ethyl phenylacetate **1** with *n*-hexanol to produce hexyl phenylacetate **2** [5–7]. Compound **3**, 1-triethoxysiloxy-ethylhexyl-1-hydroxyphenylmethylphosphonate , was synthesized for use as the imprint because of its close resemblance to the proposed transition state **4** for the acid-catalyzed transesterification reaction (scheme 1).

The triethoxysiloxy moiety on **3** was used to supposedly covalently attach the proposed transition state analogue (TSA) into a silica gel when using an acid-catalyzed sol–gel process with an 100-fold excess of monomer tetraethylorthosilicate (TEOS). HM reported removal of the imprint molecule by decomposing the organic at 523 K to leave behind a silica-based solid (silica **A**) with well-defined three-dimensional cavities that were claimed to accelerate the transesterification reaction. A control material (silica **B**) that was synthesized without the TSA showed no catalytic activity.

HM claimed that the transesterification reaction proceeds rapidly in the presence of **A**. As a test for the selectivity of the imprinted site, the rates of transesterification of ethyl naphthylacetate vs. ethyl phenylacetate were studied using the catalyst. No reaction was observed when using the naphthyl compound. On the basis of these and other results, HM suggested that their solid had in fact demonstrated molecular recognition and "imprinted" catalysis. In this work, we investigate the HM system and provide additional detail, e.g., results from solid-state NMR spectroscopy and further reaction studies. Our results reveal that an alternative mechanism for catalysis is possible.

2. Experimental

The transition state analogue **4** and silicas were synthesized by closely following the procedures of HM [5–7]. Compound **3** was shown to be pure by a combination of NMR and IR spectra. HM report two types of catalytic experiments. The first type (type I) involved the use of sulfuric acid in a toluene solvent while the second (type II) was conducted in the absence of sulfuric acid and toluene in neat alcohols.

Here, experiments of type I were conducted at 386 K using either ethyl phenylacetate (Aldrich, 99+%) or ethyl naphthylacetate (TCI, 97%) in 60 ml anhydrous toluene (Aldrich, 99.8%) as a solvent with a 10 : 1 molar excess (100 mmol) of 1-hexanol (Aldrich, 98%). Experiments of type II were performed at 418 K using ethyl phenylacetate (Aldrich, 99+%) in a mixture of 10 : 1 molar excess (100 mmol) each of 1-hexanol (Aldrich, 98%), 1-octanol (Aldrich, 99+%) and 2-phenylethanol (Aldrich, 99%).

All reaction experiments were carried out under an

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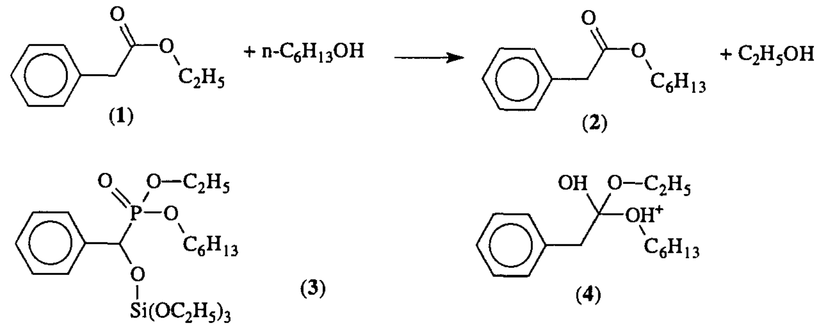


Scheme 1.

argon atmosphere. Care was taken to ensure that the reactions were conducted under strictly anhydrous conditions. Prior to use, the alcohols were filtered over an aluminum oxide column to remove traces of acid. The reaction mixture was vigorously stirred and the temperature maintained to within 1 K. Reactant and product concentrations were monitored by GC using a HP 5890 system equipped with a 12 m HP-1 capillary column.

A Scintag XDS-2000 diffractometer equipped with a Ge solid state detector was used to obtain powder X-ray (Cu Kα radiation) diffraction patterns. Thermogravimetric analysis was performed by heating the silicas in air from room temperature at a rate of 2 K/min to 873 K on a Dupont 951 TGA. FTIR measurements in the range of 400–4000 cm^{-1} were obtained on a Nicolet system 800 spectrometer using pelletized samples (1 wt% in KBr). Nitrogen adsorption at 77 K was performed on samples that were degassed at 473 K and 50 Pa using a Coulter Omnisorp 100. The pore size distributions of the silicas were obtained using the Horvath and Kawazoe analysis [8].

Solid-state NMR spectra were collected using a Bruker AM-300 instrument equipped with a high power assembly for solids. Samples were packed into 4 or 7 mm ZrO_2 rotors and spun in air. ^{29}Si single-pulse experiments were performed at 59.6 MHz with a 2.5–3 kHz spin rate, 40° pulse widths of 4–8.5 μs and relaxation delays of 5–60 s. ^{29}Si CP MAS spectra were obtained with proton decoupling at 2.5–3 kHz spin rates with a 5 μs pulse (^{1}H 90°), ^{29}Si contact times of 5 and relaxation delays of 5 μs. ^{31}P single-pulse experiments were performed at 121.5 MHz with a 7–8 kHz spin rate, 40° pulse widths of 4–8.5 μs and relaxation delays of 5–30 s.

3. Results and discussion

3.1. Catalyst characterization

Scanning electron micrographs of the crushed and sieved silica show that the particles are generally smaller than 13 μm and XRD experiments verified that they are amorphous. Two weight losses in the TGA data for untreated silica A confirm removal of the water and ethanol (up to $T \approx 420$ K) followed by decomposition of the organic TSA (from $T \approx 550$ to 600 K). These weight loss assignments were verified by FTIR measurements. The mass losses observed from the TGA for silica A are consistent with the amount of organic imprint present in the amorphous matrix.

Nitrogen adsorption isotherms are shown in fig. 1. The catalysts exhibit an isotherm similar to zeolite Y (shown on the figure for comparison) and have a void volume of 0.2 cm^3/g (same value as obtained by HM [5]). The pore size distribution determined by the method of Horvath and Kawazoe [8] shows a remarkably sharp

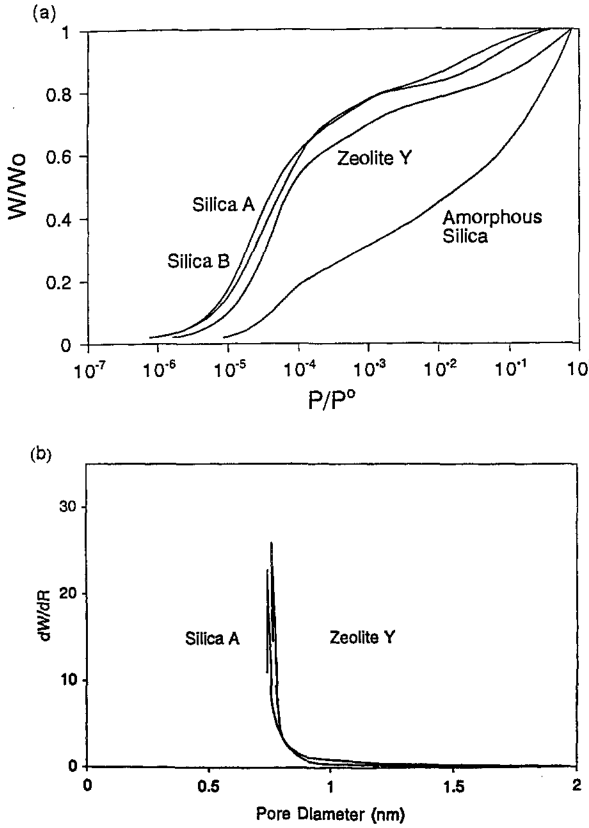


Fig. 1. (a) Nitrogen adsorption isotherms for A and B (W/Wo is the fraction of the total weight gain of N_2) and (b) pore size distributions for A and zeolite Y calculated by the method of Horvath and Kawazoe. Typical adsorption curves for amorphous silica and zeolite Y are shown for comparative purposes.

peak near 0.75 nm. There are no discernible differences in the nitrogen adsorption behavior between silicas **A** and **B**. In the synthesis of silica **A**, the ratio of TEOS/**3** is approximately 100. For comparison, the pure-silica ZSM-5 possesses a Si/organic ratio of 96/4 or approximately one-fourth that of silica **A**. Additionally, **3** is slightly larger than the organic used to prepare ZSM-5 (tetrapropylammonium cation). With ZSM-5, the space occupied by the organic is approximately 0.18 cm^3/g. Thus, by comparison to ZSM-5, a crude estimate of the volume of **3** in silica **A** should therefore be in the vicinity of 0.045 cm^3/g. Actually, our calculated value is 0.07 cm^3/g and is consistent with that obtained from the ZSM-5 model. We have previously shown that pore volumes of this magnitude are readily observable by nitrogen physical adsorption [9]. Thus, the adsorption results suggest that if cavities are left by the removal of **3** they must be the same size as the pores formed by occluded ethanol alone since the complete isotherms are the same for silicas **A** and **B**. We believe that this possibility is doubtful and a more likely scenario is that the organosiloxy linkage (Si–O–C) is lost during the synthesis process allowing the organic fragment of **3** to reside in the same space as the ethanol. To date, neither we nor HM have been able to provide any evidence to prove that the organosiloxy linkage in **3** is intact in silica **A**.

There are no significant differences in the ^{29}Si NMR spectra of silicas **A** and **B** that can provide a clue to the nature of the imprinted site. Since the silica substrate is itself catalytically inactive, HM suggest that the catalytic activity is due to the presence of phosphorous sites that remain in the solid following calcination [5–7]. These phosphorous sites act as Brønsted acid centers that catalyze the transesterification reaction. The ^{31}P MAS NMR spectrum for the as-prepared silica **A** exhibits a single peak at $\delta = -22$ ppm (close to that of the organic imprint molecule alone) suggesting that the organic fragment of the TSA remains reasonably intact within the silica **A** framework before calcination. The ^{31}P NMR spectrum for the imprinted silica following calcination treatment has a large peak at $\delta = -19$ ppm with two spinning sidebands. The presence of these sidebands suggests that the phosphorous is tightly bound to the silica framework and that there is little ion mobility. This is in contrast to analysis of the sample after exposure to ambient atmosphere for a few hours. In this case, the spectrum has four resonances at $\delta = -37, -23, -11$ and 0 ppm. The peak at $\delta = -37$ ppm is assigned to $O{=}P(OSi)_3$ units, while the $\delta = -23$ ppm peak is assigned to a silica bound phosphanol group, i.e., $O{=}P{-}(OSi)_2(OH)$ [10]. Peaks at $\delta = -11$ ppm and 0 ppm correspond to additional successive hydroxylation of the phosphanol moiety [11]. The absence of noticeable spinning sidebands and the narrowing of peak linewidth with successive hydroxylation indicates increasing ion mobility. Hence, a significant alteration in the local environment surrounding the phosphorous center is observed with exposure to moisture. Upon leaving the sample exposed to the atmosphere overnight, the silica continues to adsorb moisture and ultimately gives rise to a single peak at $\delta = 0$ ppm in the ^{31}P NMR spectrum corresponding to *o*-phosphate.

3.2. Catalysis: reactions of type I

Maier reports that the transesterification of **1** with hexanol proceeds at a rate of 27 mmol/(h g) in the presence of sulfuric acid and silica **A** and at a rate of 18 mmol/(h g) in the absence of silica **A** [7, example 1d]. Additionally, Maier shows that this transesterification reaction occurs at a rate of 10 mmol/(h g) with silica **B** and sulfuric acid [7, example 1d]. Our experiments conducted in the absence of sulfuric acid reveal no noticeable reaction even after 2 days, which is consistent with Heilmann's observation [6, p. 45]. Fig. 2 shows results for the transesterification reaction conducted using 1 g of silica and 100 mg sulfuric acid vs. sulfuric acid alone (background rate). It is clear from the data that the control material **B** has no effect on the reaction rate. At the conditions studied, the reaction appears to be pseudo-first order in ethyl phenylacetate with an enhancement by silica **A** of about 40% over the background rate (10.3 mmol/(h g) for silica **A** vs. 7.0 mmol/(h g) for silica **B**). Silica catalyst **C** is synthesized identically to **A** except that **5** is used as a "non-transition-state" imprint in place of the transition state analogue **3**. The transesterification reaction is then conducted using **C** and 100 mg sulfuric acid. As with silica **A**, there is similar enhancement in the reactivity over background when using silica **C** thus demonstrating the lack of specific activity associated with an imprinted site. While it may be argued that silicas **A** and **C** are not appreciably different to observe altering

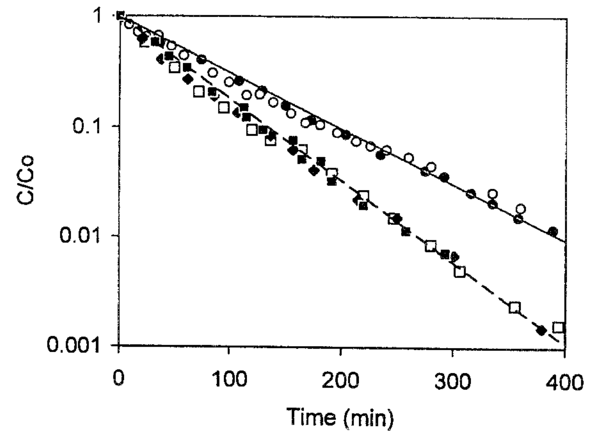
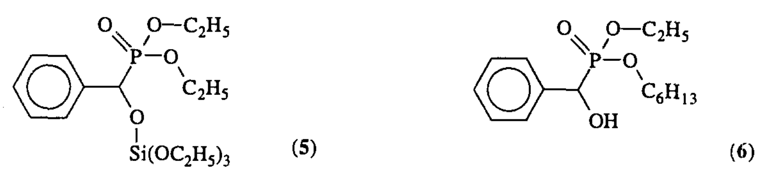


Fig. 2. Normalized ethyl phenylacetate concentration for the transesterification reaction to hexyl phenylacetate at a 10 : 1 molar excess of hexanol in toluene at 386 K with 100 mg of sulfuric acid. The background rate (sulfuric acid alone) is shown as the upper solid line. Data points correspond to: 1 g **B** (○), reused catalyst **A** (●), 1 g **A** (□), 1 g **C** (◆) and 1 g **A** + compound **6** (■). The lower dashed line indicates a rate enhancement of 40% over the background rate.



Scheme 2.

of the catalytic activity, a system based on true imprinting should in principle be capable of distinguishing between the ethyl and hexyl side chains of TSAs **3** and **5**.

Spent catalyst **A** is recovered by filtering the reaction mixture and washing the solid with toluene. On reuse of this catalyst, the catalytic activity is essentially that of the background. Additionally, no inhibition of the reaction is observed when compound **6** is added in a five-fold molar excess to the maximum number of imprinted sites possibly produced by **3**. Since **6** should adsorb into an imprinted catalytic site, the lack of inhibition raises serious questions as to whether the enhancement in activity is due to these sites (see scheme 2).

The ^{31}P NMR spectrum of recovered **A** following reaction shows three resonances that are assigned to the non-, mono-, and di-hydroxylated phosphosilicate species as discussed previously. Since there is no noticeable reaction without addition of sulfuric acid to fresh catalyst **A**, it is conceivable that partial hydroxylation of the phosphate is necessary for activation. To test this hypothesis, a used silica **A** catalyst exposed to sulfuric acid and then recovered is employed in a reaction experiment without further addition of sulfuric acid. The results show greatly reduced catalytic activity (less than 1% of the fresh silica **A**+ sulfuric acid).

Fig. 3 shows results from the transesterification of ethyl naphthylacetate using 100 mg sulfuric acid and 1 g **A** vs. sulfuric acid alone. As in the previous case, the reaction appears to be pseudo-first order in ester concentration. Although the reaction rates are much lower than those observed using ethyl phenylacetate, an enhancement of the reaction rate with the use of silica **A** is observed. This result contradicts the findings of Maier, who reported no acceleration in reaction rate with the naphthyl ester, *n*-hexanol and silica **A** [7, example 1d]. Since only a statement regarding the result (no data) is provided by Maier, we are unable to ascertain plausible explanations for this discrepancy.

The apparent lack of selectivity of the imprinted site could be due to several reasons. For example, it could be argued that in the pulverization of the catalyst, numerous fracture planes are created causing imprinted sites to lose their structural integrity. However, the evidence presented thus far, particularly the catalyst deactivation, leads us to a more likely possibility: leaching of active phosphorous species from the solid leading to a higher effective acid concentration in the liquid solvent. This may be a significant contribution since the ratio of maximum possible phosphorous sites to sulfuric acid is 3.1 for the co-catalyzed reaction with silica **A**.

As a definitive test to check whether the leached species contribute to the catalytic activity, a reaction is conducted in the usual manner with silica **A** (co-catalyzed with 100 mg sulfuric acid). After 1 h, the silica is filtered off and the reaction allowed to continue. Several minutes are necessary for the reaction solution to return to the reaction temperature following filtration. The results shown in fig. 4 demonstrate that the reaction kinetics are not significantly altered by removal of silica **A**. Although the very slight drop in the reaction rate does not completely rule out activity from the silica **A** sites, the variations from the 40% enhancement curve are well within experimental error. Evidently, the bulk enhancement of reactivity is simply due to the leached phosphorous species. This result explains the lack of selectivity observed between the phenyl and naphthyl ester catalysis. The ^{31}P NMR spectrum of the filtered reaction reveals that phosphorous is present ($\delta = -10.5$ ppm). Hence, our findings indicate that the activity in type I transesterifications of the "imprinted" silica of the type first synthesized by HM can be largely due to phosphorous species that have leached out of the silica **A** catalyst and not to an imprinted catalytic site and that the leaching of phosphorous is stimulated by the presence of sulfuric acid.

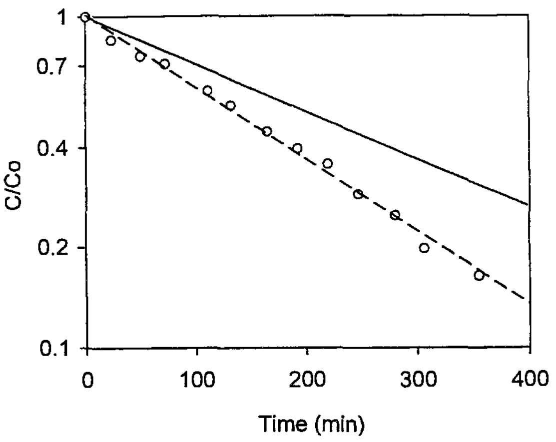


Fig. 3. Normalized ethyl naphthylacetate concentration for the transesterification reaction to hexyl naphthylacetate at a 10 : 1 molar excess of hexanol in toluene at 386 K with 100 mg sulfuric acid. The background rate (sulfuric acid alone) is shown as the upper solid line. Data points are for 1 g A (○). The lower dashed line indicates a rate enhancement of 40% over the background rate.

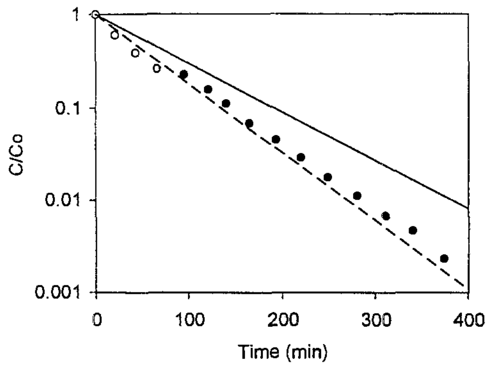


Fig. 4. Normalized ethyl phenylacetate concentration for the transesterification reaction to hexyl phenylacetate at a 10 : 1 molar excess of hexanol in toluene at 386 K with 100 mg sulfuric acid. The upper solid line corresponds to the background rate (sulfuric acid alone). The lower dashed line illustrates a 40% enhancement in activity characteristic of a reaction permitted to run uninterrupted with 1 g A. The first four data points (○) are for a reaction run with 1 g A. The remaining data points (●) correspond to the same reaction after removal of A by filtration.

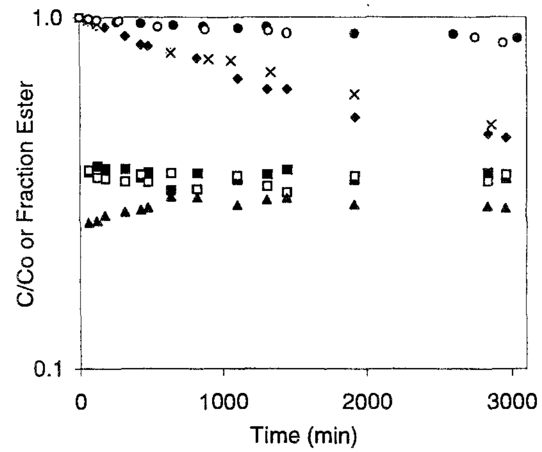


Fig. 5. The upper half of the figure represents normalized ethyl phenylacetate concentration for the transesterification reaction of type II. The data points correspond to homogeneous reaction (○), 1 g B (●), 1 g A (◆) and 1 g A that is removed by filtration at 895 min (×). The lower half of the figure represents a product distribution for silica A that is typical of all type II experiments. The data points correspond to hexyl ester (■), octyl ester (□) and phenyl ester (▲).

3.3. *Catalysis: reactions of type II*

HM report that a mixture of 10 mmol of **1**, 100 mmol of *n*-hexanol, 100 mmol of *n*-octanol and 100 mmol of 2-phenylethanol (no toluene solvent) do not reveal any reaction products until greater than 2 h of contact after which autocatalysis is oberved giving three esters in 1 : 1 : 1 ratios [5, 7 example 1]. In the presence of silica **B**, no reaction is reported for 48 h. With the addition of silica **A**, the reaction is immediate at a rate of 0.07 mmol/(h g) [7, example 1a] (the rate of 7 mmol/(h g) in ref. [5] we believe is misreported). At the initiation of the reaction with silica **A**, a 1 : 1 mixture of hexyl and octyl phenylacetate is obtained with no formation of phenyl ethyl ester. Only later is the phenyl ethyl ester detected and ascribed to autocatalysis [5] with 9 : 9 : 1 ratios of hexyl : octyl : phenyl esters up to 50% conversion [6, pp. 46,47]. These experiments and others led HM to conclude that substrate-specific cavities with catalytic activity exist in silica **A**.

Two factors complicate our attempts to reproduce the experimental results for the type II reactions of HM. First, we are unable to reproduce the inhibition of autocatalysis for type II reactions by silica **B** as reported by HM [5–7], vide infra. Second, the rates in type II reactions are very low and render analysis of product distributions at early reaction times, i.e., low conversion, susceptible to large errors. Despite these complications, our results are shown in fig. 5. The reaction rates are much lower than those for the type I experiments. For silica **A**, the reaction rate is 0.1 mmol/(h g), which is close to the value of 0.07 mmol/(h g) reported by Maier [7, example 1a]. Removal of silica **A** at $t = 895$ min does not significantly alter the reaction kinetics, which is consistent with our observations for type I experiments. For silica **B**, the reaction rate is 0.065 mmol/(h g) and the kinetics are similar to the autocatalysis observed here (no inhibition of autocatalysis).

At a conversion level of 5% for silica **A** (time ≈ 2 h), the product distribution of esters (hexyl : octyl : phenyl) is 0.38 : 0.35 : 0.27, whereas for silica **B** at the same conversion level (time ≈ 11 h) the ratio is 0.36 : 0.33 : 0.31. Comparison of silica **B** at the same time as **A** (2 h) reveals a similar product distribution of 0.39 : 0.35 : 0.26 for **B** (although the conversion level for **B** is only 1.7%). The product distribution at longer times is not significantly altered for either silica **A** or silica **B** and we do not observe selectivities approaching those reported by Heilmann [6, pp. 46,47]. Hence, our data indicate that silica **A** is essentially non-selective for type II esterification reactions and that the marginal enhancement in activity could be due to the same effect as observed with type I reactions. However, since we cannot reproduce the exact results of HM, we can not conclusively rule out the presence of selective sites in silica **A** whose behavior could be masked by the large background observed here in type II experiments.

Acknowledgement

We thank Dr. H. Koller for assistance with the NMR work and Hoechst-Celanese for partial funding.

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