ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

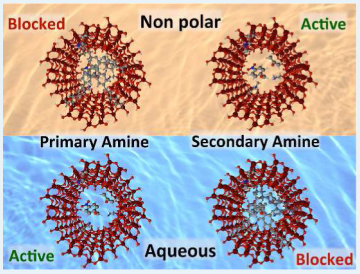
Solvent-Induced Reversal of Activities between Two Closely Related Heterogeneous Catalysts in the Aldol Reaction

Kapil Kandel,[‡] Stacey M. Althaus,[†,‡] Chorthip Peeraphatdit,[†,‡] Takeshi Kobayashi,[†] Brian G. Trewyn,[‡] Marek Pruski,[†,‡] and Igor I. Slowing*[,†]

[†]U.S. Department of Energy, Ames Laboratory and [‡]Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111, United States

Supporting Information

ABSTRACT: The relative rates of the aldol reaction catalyzed by supported primary and secondary amines can be inverted by 2 orders of magnitude, depending on the use of hexane or water as a solvent. Our analyses suggest that this dramatic shift in the catalytic behavior of the supported amines does not involve differences in reaction mechanism, but is caused by activation of imine to enamine equilibria and stabilization of iminium species. The effects of solvent polarity and acidity were found to be important to the performance of the catalytic reaction. This study highlights the critical role of solvent in multicomponent heterogeneous catalytic processes.



KEYWORDS: *mesoporous silica nanoparticles, aldol condensation, enamine catalysis, solvent effects, solid-state NMR*

INTRODUCTION

It is well-known that the selection of solvents can have an important effect on the rates of homogeneous reactions. Such an effect is commonly explained by the contribution of solvation energy to the total free energy of the systems and by stabilization of the transition states with a subsequent reduction in the free energy of activation.[1] The analysis of solvent effects may be relatively simple for single-step processes but becomes more complicated in reactions involving multiple equilibria. In such cases, the solvent effects can change preferences for various possible pathways over the potential energy surface of the reaction system.[2−4]

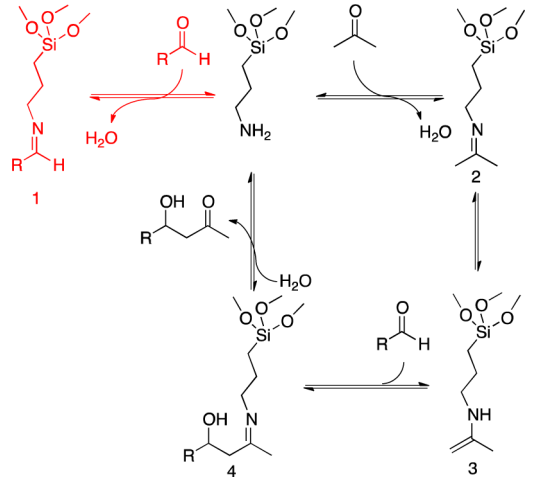
Whereas the role of solvents in homogeneous reactions has been studied thoroughly, less effort has been dedicated toward understanding their involvement in heterogeneous processes.[1] Heterogeneous reactions entail greater complexity because they involve multiple equilibria and multiple components interacting with each other. Interfacial phenomena, competitive adsorption and kinetics of mass transfer are some of the additional factors that determine the apparent rates of heterogeneous reactions and complicate their understanding. For example, Drexler and Amiridis observed increased activity of MgO as a catalyst for the synthesis of flavanone in DMSO as compared with other polar and nonpolar solvents. They attributed the increased reaction rates to the interaction between DMSO and MgO, which facilitated the adsorption of substrates onto the surface of the catalyst.[5] García and collaborators recognized that the competition between polar solvents and reactant molecules for diffusion into the pores and adsorption onto acid sites was responsible for the poor activity of Al-MCM-41 in the rearrangement of 1,2-epoxyoctane.[6] Using an acid−base bifunctional SBA-15 type mesoporous silica, Davis and co-workers showed how solvents with different polarities changed the equilibria of the acid−base pairs and how this affected the aldol reaction between *p*-nitrobenzaldehyde and acetone.[7] They concluded that the acidic and basic groups interacted more strongly with the polar solvents than with each other, thereby inhibiting cooperative catalysis. To the contrary, in nonpolar solvents, the groups associated with each other, and the cooperative effect was clearly observed. This result was later supported by Solin, using carboxylic acid and primary amine bifunctionalized mesoporous silica catalyst in hexane and nonane.[8]

We recently reported that mesoporous silica nanoparticles (MSNs) functionalized with primary amines are poor catalysts for the aldol reaction in hexane because of the formation of an imine intermediate **1** (Schiff base, Scheme 1).[9] This intermediate was clearly identified by solid-state NMR and infrared spectroscopies. We eliminated this inhibition by replacing the primary amine with a secondary amine and achieved catalytic activities comparable to those of the previously reported bifunctional materials.[9] We also showed that the imine intermediate **1** could regenerate the primary amine upon treatment with dilute aqueous HCl. This led us to consider the possibility that the catalytic activity of supported primary amines toward the aldol reaction could be improved by replacing the nonpolar solvent (hexane) with water.

Since water is either a reactant or a byproduct in various steps of the aldol reaction, it is difficult to predict whether its inclusion in the mixture would improve or inhibit the reaction.

Received: July 30, 2012
Revised: January 9, 2013
Published: January 11, 2013

Scheme 1. Proposed Cycle for an Aldol Reaction Catalyzed by Primary Amines Supported on Mesoporous Silica (black) and the Formation of a Product of Inhibition (red)[9]



However, the beneficial contribution of water to the proline-catalyzed aldol condensation has been observed in homogeneous media.[10−12] A recent study by Blackmond and collaborators showed that the addition of water to the homogeneous proline-catalyzed aldol reaction regenerates the active amine group at the expense of the inactive iminium form, leading to higher rates. They concluded that the reaction rate is highly dependent on the relative stabilities of the inactive imine of the acceptor aldehyde and the active enamine of the donor ketone and that water shifts the equilibrium toward the active enamine intermediate.[13] These reports suggested that using water as a solvent could improve the performance of our MSN-based catalysts.

EXPERIMENTAL SECTION

Materials. Cetyltrimethylammonium bromide (CTAB) ($CH_3(CH_2)_{15}N(CH_3)_3Br$), mesitylene, *p*-nitrobenzaldehyde (PNB), hexamethyldisilazane (HMDS), and dimethyl sulfone were purchased from Sigma-Aldrich. Tetraethoxysilane (TEOS), 3-aminopropyl trimethoxysilane and [3-(methylamino)propyl] trimethoxysilane were purchased from Gelest. All reagents were used as received without further purification.

Synthesis of Functionalized Mesoporous Silica Nanoparticles. The synthesis and characterization of the materials has been described in a previous article.[9] In brief, CTAB, (1.0 g, 2.7 mmol) was dissolved in water (480 g, 26.7 mol), followed by the addition of NaOH solution (2.0 M, 3.5 mL, 7.0 mmol) and mesitylene (1.73 g, 14.4 mmol). The mixture was heated at 80 °C for 1 h. To this clear solution, TEOS (4.7 g, 23 mmol) was added dropwise, followed by immediate addition of 3-aminopropyl trimethoxysilane (for AP-MSN) (1.0 mL, 5.7 mmol) or [3-(methylamino)propyl]trimethoxysilane (for MAP-MSN) (1.0 mL, 5.0 mmol). The solution was stirred vigorously at 80 °C for 2 h and then filtered to yield a white functionalized MSN solid. The as-synthesized material was washed with copious amounts of water and methanol, then dried under vacuum. The CTAB surfactant was removed by Soxhlet extraction with methanol for 24 h, and the resulting surfactant-removed functionalized MSN was dried overnight under vacuum.

Blocking of Silanol Groups of AP-MSN. AP-MSN (1.0 g) was suspended in 100 mL of hexane. Hexamethyldisilazane (HMDS) (10 mmol) was then added to the suspension.[14,15] The suspension was heated to reflux for 24 h; the solid was then recovered by filtration, washed with hexane, and dried overnight under vacuum.

Characterization of Catalysts. Surface properties of the functionalized MSNs were measured by nitrogen sorption analysis in a Micromeritics Tristar 3000 using the Brunauer−Emmett−Teller method for surface area and the Barrett−Joyner−Halenda method for pore size distribution. Small-angle X-ray diffractometry was performed on a Rigaku Ultima IV diffractometer using a Cu target at 40 kV and 44 mA. Loading of the catalysts was determined by elemental analysis in a Perkin-Elmer 2100 Series II CHN/S analyzer using acetanilide as a standard and combustion and reduction at 925 and 640 °C. To measure the pH of the suspensions, the materials were dispersed in water/acetone mixtures at the same concentration as the ones used in the reaction. The pH of the suspension was measured with a pH meter at room temperature until a stable reading was obtained. The characterization information for each material is provided in ref 9, where AP-MSN is denoted AP-MSN-3.6 and MAP-MSN is denoted MAP-MSN-3.5.

General Procedure for Aldol Reaction. Catalytic processes were performed in screw-cap vials. *p*-Nitrobenzaldehyde (PNB, 0.39 mmol) was dissolved in acetone (1.5 mL). A suspension containing 3 mol % of catalyst (0.012 mmol) in the selected solvent (1.5 mL) was then added to the PNB solution. The reaction kinetics were studied by stirring the mixture at 60 °C and quenching the reaction at desired times by setting the vials on ice. The catalysts were then separated by centrifugation, and the supernatants were concentrated under reduced pressure. Reaction yields were measured by ^{1}H NMR using dimethyl sulfone as the internal standard. Resonances of the substrate and products were observed as follows: PNB (**5**), ^{1}H NMR (300 MHz, $CDCl_3$) 10.16 (s, 1H), 8.41 (d, J = 9.0 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H); aldol product (**6**), ^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 9.0 Hz, 2H), 5.26 (t, J = 6.0 Hz, 1 H), 2.86 (d, J = 6.0 Hz, 2H), 2.21 (s, 3H); enone product (**7**), ^{1}H NMR (300 MHz, $CDCl_3$) 8.29 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 15 Hz, 1H), 6.84 7.56 (d, J = 15 Hz, 1H), 2.42 (s, 3H).

Solid-State NMR. Solid-state ^{13}C and ^{29}Si NMR experiments were performed to determine the structure and loading of the surface groups on the MSNs.

The identification of the catalytic groups and intermediates was accomplished by measuring the ^{13}C cross-polarization spectra under magic angle spinning (CPMAS). These experiments were performed at 14.1 T on a Varian System 600 spectrometer equipped with a 1.6-mm FastMAS probe operated at 599.6 MHz (^{1}H) and 150.8 MHz (^{13}C).

To accurately determine the loading of both functional groups and silanols on the MSN surface, the ^{29}Si NMR measurements were performed using direct polarization under MAS (DPMAS) with Carr−Purcell−Meiboom−Gill (CPMG) refocusing.[16,17] The spectra were acquired on a Chemagnetics Infinity 400 spectrometer equipped with a 5-mm MAS probe operated at 400.0 MHz (^{1}H) and 79.4 MHz (^{29}Si).

The experimental parameters are given using the following notation: ν_R denotes the MAS rate, $\nu_{RF}(X)$ is the magnitude of the RF magnetic field at the frequency of X nuclei, τ_{CP} is the mixing time during CP, N_{CPMG} is the number of echoes acquired in CPMG experiment, τ_{CPMG} is the corresponding

dx.doi.org/10.1021/cs300748g | ACS Catal. 2013, 3, 265−271

time interval between π pulses, τ_{RD} is the recycle delay, NS is the number of scans, and AT is the total acquisition time.

^{13}C CPMAS (Figure 2: AP-MSN and intermediate 2): ν_R = 40 kHz, $\nu_{RF}(^{13}C)$ = 62 kHz, $\nu_{RF}(^{1}H)$ during CP = 102 kHz, $\nu_{RF}(^{1}H)$ during SPINAL-64 decoupling = 12 kHz, τ_{CP} = 2 ms, τ_{RD} = 3 s, NS = 10240, and AT = 8.7 h.

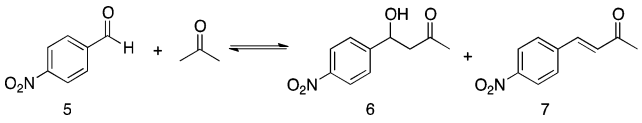
^{13}C CPMAS (Figure 2: intermediate 1): ν_R = 40 kHz, $\nu_{RF}(^{13}C)$ = 140 kHz, $\nu_{RF}(^{1}H)$ during CP = 60 kHz, $\nu_{RF}(^{1}H)$ during SPINAL-64 decoupling = 12 kHz, τ_{CP} = 3 ms, τ_{RD} = 2 s, NS = 26400, and AT = 15 h.

^{29}Si DPMAS with CPMG: ν_R = 10 kHz, $\nu_{RF}(^{29}Si)$ = 50 kHz, $\nu_{RF}(^{1}H)$ = 45 kHz, N_{CPMG} = 10, τ_{CPMG} = 10 ms, τ_{RD} = 300 s, NS = 296, and AT = 25 h.

RESULTS AND DISCUSSION

To evaluate the effects of replacing hexane with water on the activity of supported amines toward the aldol reaction, two MSN materials, AP-MSN and MAP-MSN, were tested for the cross aldol reaction between **5** and excess acetone (Scheme 2).

Scheme 2. Cross Aldol Reaction between *p*-Nitrobenzaldehyde and Acetone



The catalytic activity was determined by measuring the amounts of the substrate, **5**, and products (aldol **6** and enone **7**) using NMR. In a previous report, we measured the apparent pseudo-first-order rate constant of AP-MSN in hexane, which was $k_{AP\text{-}MSN\ hex}$ = 0.37 h^{-1} (Figure 1a).[9] This low activity of AP-

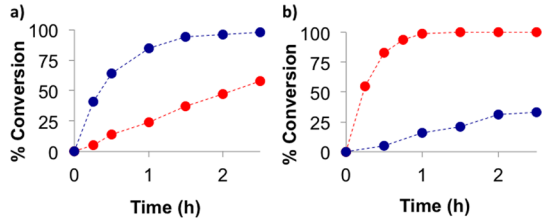


Figure 1. Kinetics of aldol reaction between **5** and acetone catalyzed by AP-MSN (red) and MAP-MSN (blue) in (a) hexane (from ref 9) and (b) water at 60 °C with 3 mol % catalyst.

MSNs was overcome by using a secondary amine-functionalized material (MAP-MSN), which was unable to form the imine intermediate and gave a 3-fold increase in the apparent rate constant in hexane ($k_{MAP\text{-}MSN\ hex}$ = 1.35 h^{-1}, Figure 1a).[9]

Replacing hexane with water had a dramatic effect on the activity of AP-MSN: the apparent rate constant increased more than 10-fold ($k_{AP\text{-}MSN\ w}$ = 4.98 h^{-1}, Figures 1b and Supporting Information S1a), yielding an almost quantitative conversion after only 1 h of reaction. However, the effect of replacing hexane with water on the activity of MAP-MSN was completely unexpected: instead of becoming more active, like AP-MSN, the apparent rate constant of the reaction dropped more than 10-fold to $k_{MAP\text{-}MSN\ w}$ = 0.127 h^{-1} (Figures 1b and Supporting Information S1a). These results correspond to a change in the relative activities of the two catalysts by 2 orders of magnitude (in hexane: $k_{AP\text{-}MSN}/k_{MAP\text{-}MSN}$ = 0.27, in water: $k_{AP\text{-}MSN}/k_{MAP\text{-}MSN}$ = 39).

This remarkable inversion of the relative activities could result from the solvents directing each catalytic reaction through different pathways. However, the inversion of activities could also result from water stabilizing to a different extent the intermediates associated with each catalyst, without necessarily altering the reaction mechanism. Thus, the solvent could have multiple effects on the reactions, with each effect having variable magnitudes, depending on the structural constraints of each catalyst, and still preserve the same mechanistic pathway. Although solvent polarity may be the most obvious parameter, the protic nature of water could also play a role in the mechanism of the reaction. In addition, according to Scheme 1, water participates directly as a reagent and product in different steps of the reaction. Therefore, it is possible that water affects the reaction by modifying its equilibrium. To better understand the reason for this inversion in the relative activities of the catalysts in water and hexane, we evaluated each of these factors separately by testing the rate of the reaction in additional solvents.

Effects of Solvent Polarity. The effect of polarity on the activity of both materials was studied by comparing the kinetics of the reactions in hexane and water with those in low-polarity dichloromethane and polar aprotic acetonitrile. Figure 2 shows

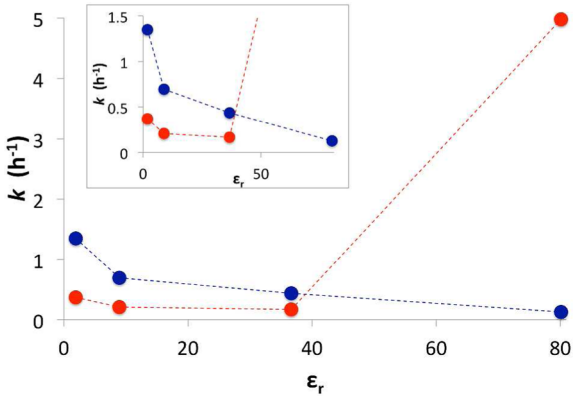


Figure 2. Rates of aldol reaction catalyzed by AP-MSN (red) and MAP-MSN (blue) in solvents of increasing dielectric constants: hexane (ε_r = 1.89), dichloromethane (ε_r = 8.93), acetonitrile (ε_r = 36.64), and water (ε_r = 80.1).[20] Inset: same graph with the *x*-axis cut at 1.5 h^{-1} to show the details of the lower reaction rates.

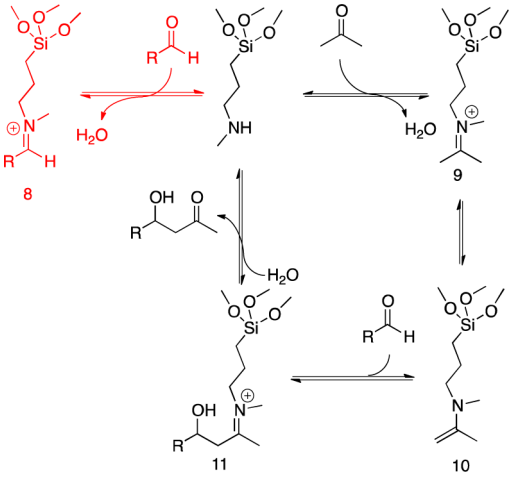
that increasing the polarity leads to a small decrease in activity for AP-MSN (with the exception of the rate in water) and a more significant decrease in MAP-MSN. This trend is consistent with the previous findings by Davis and co-workers on the negative effect of polarity on the activity of bifunctionalized materials toward the cross aldol reaction. They suggested that sulfonates and amines could undergo acid–base neutralization in polar solvents and lose their activities.[7] In the case of AP-MSN in nonpolar solvents, aminopropyl groups and acidic silanols have mild noncovalent interactions with each other.[18,19] However, as polarity increases, proton transfer between the acidic silanols and the basic amine can take place, reducing the availability of the deprotonated amine required to perform enamine catalysis.

As mentioned above, the drop in the activity of MAP-MSN with polarity was larger than that of AP-MSN: as the polarities of nonaqueous solvents increase, the differences between the activities of the two catalysts lessen. We previously reported that the higher activity of MAP-MSN in hexane was caused by

dx.doi.org/10.1021/cs300748g | ACS Catal. 2013, 3, 265–271

the formation of substrate-inhibiting imine **1** in AP-MSN, whereas the methyl group in MAP-MSN prevented the formation of imine.[9] Our new observation on the effect of polarity suggests that this deficit of AP-MSN is compensated as polarity increases. Although MAP-MSN cannot form the inhibitory imine in hexane, it could form the cationic iminium intermediate **8** in a polar solvent, leading to reduced activity (Scheme 3). Being ionic, this intermediate would be further

Scheme 3. Possible Reaction Pathways of *p*-Nitrobenzaldehyde 5 and Acetone in the Presence of MAP-MSN and Water[a]



[a]R = *p*-nitrophenyl.

stabilized by increased solvent polarity, explaining the decrease in the difference between the two catalysts' activities with increasing polarity.

Although we have been able to observe the formation of **1** in hexane by infrared and solid-state NMR,[9] the detection of **8** by infrared was not straightforward because the C=N$^+$ stretching band is shifted to higher frequencies compared with those of C=N[21] so that it is likely to overlap with the C=O stretching frequency of the unbound starting material **5**. Similarly, solid-state NMR spectroscopy did not show any clear evidence of the expected iminium **8**. However, iminium intermediates are not unusual in aldol and related reactions when secondary amines are used as catalysts.[22−26] In fact, iminium intermediates are central in reactions that undergo Mannich-type pathways with secondary amines.[19,27−30]

Since the reaction catalyzed by AP-MSN in water is off the trend followed by the other solvents, the enhanced activity of the catalyst in this solvent cannot be due to polarity. Another effect must be responsible for increasing the activity of the catalyst, despite the negative effect that the polarity of water should have on the reaction.

Effects of Solvent Acidity. A second possible effect of water that might influence the reaction is its protic character. Being a weak acid, water could assist the reaction by protonating or hydrogen-binding the oxygen on carbonyls, thereby activating the molecules for nucleophilic attack. To evaluate this possibility, we tested the activity of the catalysts in methanol, whose pK_a (15.5) is very close to that of water (15.7).[20]

Figure 3 shows that the two catalysts gave similar reaction kinetics in methanol. In addition, the reactions in methanol were slower than the corresponding reactions in water and in

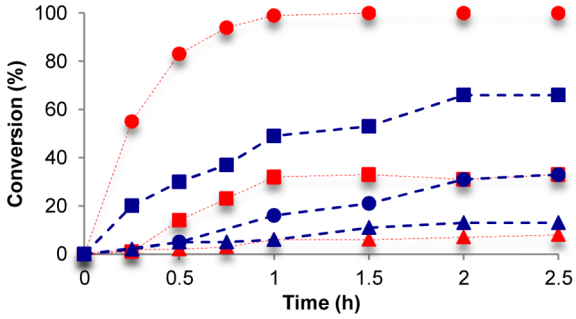


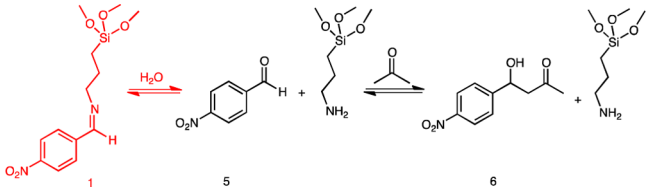
Figure 3. Effect of protic solvents on the rates of aldol reaction catalyzed by AP-MSN (red) and MAP-MSN (blue): water (circles) and methanol (triangles). The rate in polar aprotic acetonitrile (squares) is shown as a reference.

aprotic acetonitrile. Therefore, rather than improving catalysis, the acidity of the solvent is detrimental to the activity of the silica-supported amines. Furthermore, since the rate of the reaction catalyzed by MAP-MSN is greater in water than in methanol, it is likely that water has an additional effect on the catalysis by MAP-MSN, similar to the reactions catalyzed by AP-MSN.

Effects of the Solvent on Equilibrium. The anomalous effect of water on the catalysis by these materials could also arise from the different equilibria involved in the reaction. According to Scheme 1, the addition of water to the reaction catalyzed by AP-MSN should lower the concentration of the product of inhibition, **1**. The same consideration, however, would also predict an inhibition of the formation of the active imine and the subsequent enamine intermediates **2** and **3**.

The observed increase in the activity of AP-MSN in water may then be the result of two factors: (1) the relative values of the equilibrium constants leading to imine **2** versus imine **1** and (2) the fact that water is also a reagent in the last step of the process, where it combines with intermediate **4** to give the final product. Thus, in the overall conversion (Scheme 4), water is a

Scheme 4. Overall Reaction Pathways for *p*-nitrobenzaldehyde and Acetone in the Presence of AP-MSN: Inhibition (red) and Aldol (black)



product only in the inhibition route (red) but is not part of the net reactants or products of the aldol route (black). Therefore, the excess of water shifts the overall equilibrium toward the formation of the aldol product and minimizes the inhibition pathway. The excess of acetone also contributes to shift the equilibrium toward the aldol product, making the impact of water on the dissociation of **1** even larger.

These same considerations can apply to the reaction catalyzed by MAP-MSN. If MAP-MSN is less active in polar solvents due to the formation of **8**, this inhibition could be disrupted by the addition of water, which would hydrolyze this intermediate (**8**). Thus, the catalytic activity of both materials in water should be a balance between the inhibitory effects of polarity and the promoting effect of the solvent on equilibria.

dx.doi.org/10.1021/cs300748g | *ACS Catal.* 2013, 3, 265−271

Using $^{1}H-^{13}C$ CPMAS solid-state NMR, imines **1** and **2** could be identified only in samples prepared in the hexane solution of **5** and hexane−acetone mixtures, respectively (Figure 4). However, detection of the enamine intermediates was not possible, most likely because of their short lifetimes.

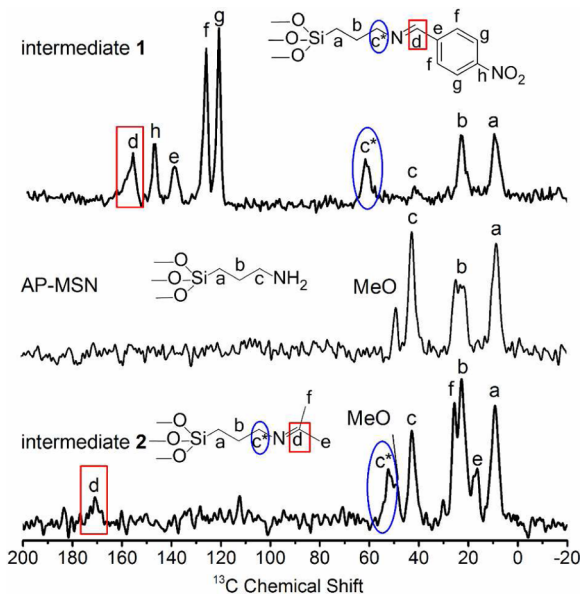


Figure 4. ^{13}C CPMAS solid-state NMR spectra of intermediate 1, AP-MSN, and intermediate 2 obtained from samples prepared in hexane. The spectra of AP-MSN and intermediate **1** were assigned according to our previous study,[9] whereas resonances c*, d, e, and f in the bottom spectrum are consistent with the existence of intermediate **2**, on the basis of the solution NMR data reported for similar functionalities.[31,32].

Product Distribution and Mechanistic Considerations. The above interpretation of the effect of water on equilibrium assumes that the main product of the reaction is **6**, which would be obtained directly if the reaction proceeded through an enamine pathway (Schemes 1 and 3). However, if the most abundant product were **7**, water would be formed as a byproduct of the reaction and would therefore play no role at all in shifting the equilibrium. Product **7** can be formed by dehydration of **6**, following enamine catalysis, or it can be produced via a Mannich type mechanism following the production of intermediate **1** (or **8** for MAP-MSN). Intermediate **1** is an inhibitor in hexane, demonstrating that the Mannich mechanism does not take place in this solvent; however, this does not indicate that this mechanism cannot take place in water.

Analysis of our product distribution revealed that aldol **6** was the major product for the reactions catalyzed by each material in all of the solvents tested (Supporting Information Figures S2 and S3). The selectivities for **6** ranged from 75 to 90% with AP-MSN and from 70% to 85% with MAP-MSN, with the only exception being the reaction with MAP-MSN in water, where no enone **7** was observed at all. Not only was enone **7** the minor product, but it also appeared, in most cases, after longer reaction times than the aldol product **6**. The observation of constant ratios for aldol and enal in the homogeneously catalyzed self-condensation of aldehydes has been associated with the competition between enamine and Mannich type mechanisms throughout the reaction.[33] In contrast to these observations, in most of our experiments, an increase in the amount of enone **7** seemed to correspond to a decrease in the rate of formation of aldol **6**. When the AP-MSN-catalyzed reaction was carried out in water, the concentration of enone **7** increased at the later stages of the reaction and was concurrent with a measurable decrease in the concentration of aldol **6** (Figure 5). These observations suggest that the products are

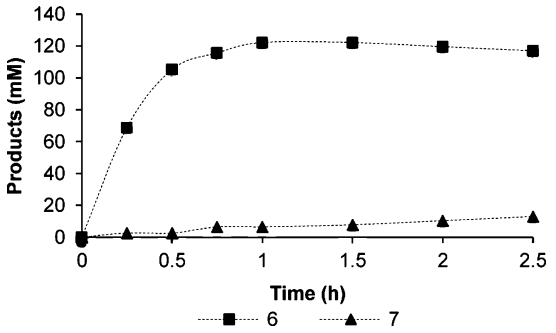


Figure 5. Formation of addition (squares) versus condensation (triangles) products in the aldol reaction between **5** and acetone catalyzed by AP-MSN in water.

formed sequentially, rather than via competing pathways, that is, it shows that the reaction does *not* involve a Mannich type mechanism, but more likely, the enone is formed via dehydration of the aldol.

Although the formation of enamines in water may be deemed as counterintuitive, these intermediates have been observed in homogeneous aqueous media.[34−37] The other mechanism that could account for the formation of the aldol product in water involves general-base catalysis, which tends to occur at high pH values (>10). Other research groups have shown that buffering the aqueous media at pH 8 directs the reaction through an enamine rather than a general base pathway because too little of the acetone enolate could form because of its high pK_a (10.83).[37−39] Since the surface of the mesoporous silica support is rich in weakly acidic silanol groups (pK_a 2−4 for isolated and 8 for geminal silanols), it is possible for it to play the role of a buffer in the reaction system.[40,41] Indeed, DPMAS ^{29}Si NMR measurements of AP-MSN and MAP-MSN indicated that the materials have a large quantity of acidic silanol groups. The ratios $(T^2 + T^3)/(T^2 + 2Q^2 + Q^3)$ of the materials suggest there are considerably more silanol groups than amine groups at the surface (loadings of 4.3 SiOH/nm^2 and 4.8 SiOH/nm^2, and 0.8 AP/nm^2 and 0.73 MAP/nm^2, respectively).[9] The presence of these silanol groups prevented the aqueous suspensions of AP-MSN and MAP-MSN from reaching high pH values, stabilizing them at 8.1 and 8.3, respectively, as opposed to the pH > 11 observed for the free amines at the same concentrations in water. The lower activity of MAP-MSN than AP-MSN, despite their similar basicities, also supports the notion that general base catalysis does not take place in our aqueous system.

Role of the Silanol Groups in Water. The difference between the activities of both catalysts in water is consistent with previous reports of homogeneous primary amines being more efficient catalysts than secondary amines for this reaction.[38] This difference could be attributed to steric hindrance by the methyl in MAP-MSN during the C−C bond formation step. Such hindrance would lead to a higher barrier than that of the less impeded AP-MSN.

dx.doi.org/10.1021/cs300748g | ACS Catal. 2013, 3, 265−271

Although silanol groups are known to actively participate in the aldol reaction in organic solvents,[9,19,42−46] it is uncertain whether they do play a role when the reaction is performed in water. To evaluate if silanols assist the reaction in water, they were blocked with HMDS. Silanol blocking was confirmed by ^{29}Si NMR, where the decrease in signal of T^2, Q^2, and Q^3 sites was concurrent with the appearance of M sites (Figure 6).

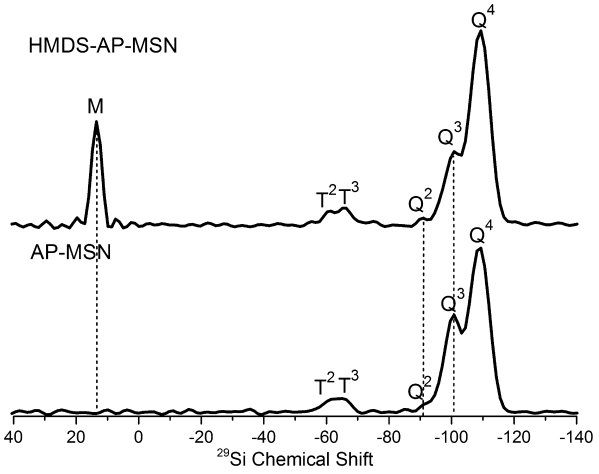


Figure 6. ^{29}Si DPMAS spectra of AP-MSN before (bottom) and after (top) blocking silanol groups with HMDS. Appearance of M site due to the attached silane matches the conversion of the Q^2 and Q^3 sites of the blocked groups to Q^3 and Q^4, respectively. The sites are denoted following as follows: Q^4: $(\equiv SiO)_4Si$, Q^3: $(\equiv SiO)_3SiOH$, Q^2: $(\equiv SiO)_2Si(OH)_2$, T^3: $(\equiv SiO)_3SiR$, and T^2: $(\equiv SiO)_2Si(OH)R$

Integration of the signals indicated that in the resulting HMDS-AP-MSN, ∼30% of the original silanol groups were blocked. This material was 10 times less active than the original AP-MSN ($k_{HMDS\text{-}AP\text{-}MSNw}$ = 0.43, Supporting Information Figure S4). This result suggests that the silanol groups play an important role in the reaction. They likely assist the reaction by hydrogen-binding the PNB substrate **5** and acetone, which not only brings the reactants into close proximity with the catalytic sites but also activates them for nucleophilic attack.

CONCLUSIONS

Switching the reaction media between hexane and water led to a reversal in the activities of two closely related catalytic species: although AP-MSN has a lower activity in hexane but a higher activity in water, MAP-MSN has a higher activity in hexane but a lower activity in water. Remarkably, these large differences in behavior are not associated with the change in reaction mechanism, but with the stability of inhibition products and with water inducing shifts in the reaction equilibria.

Far from being beneficial, increasing the polarity of the solvent tended to reduce the catalytic activity of both materials, presumably by enabling proton transfer from silanols to amines, thus blocking their nucleophilicity. Similarly, performing the reaction in a protic solvent, other than water, decreased the activity of both catalysts, likely due to the protonation or strong hydrogen binding of the nucleophilic amines.

When the reaction is performed in water, the equilibrium between formation and hydrolysis of inhibited states takes place for both catalysts. Therefore, the behavior observed in water suggests that AP-MSN is intrinsically a more active catalyst for the aldol reaction than MAP-MSN.

Silanol groups indirectly participate in the reaction in water by acting as a buffer to allow the enamine pathway rather than general base catalysis and directly by binding the carbonyl groups of the reactants. This binding of the reactants brings them close to the active sites and activates the carbonyls for nucleophilic attack.

The unusual behavior observed in this work confirms and stresses the notion that the proper choice of catalyst depends not only on its intrinsic activity but also on the environment in its specific application.

ASSOCIATED CONTENT

Supporting Information

Additional kinetic plots and product distribution graphs. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: islowing@iastate.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported at the Ames Laboratory by the U.S. Department of Energy, Office of Basic Energy Sciences. Ames Laboratory is operated for the U.S. Department of Energy by Iowa State University under Contract No. DE-AC02-07CH11358.

REFERENCES

(1) Reichardt, C.; Welton, T. In *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010, p 165−357.
(2) Nguyen Minh, T.; Ha, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 599−602.
(3) Acevedo, O.; Jorgensen, W. L. In *Annual Reports in Computational Chemistry*; David, C. S., Ed.; Elsevier: Amsterdam, Boston, 2006; Vol. 2, p 263−278.
(4) Reichardt, C. *Org. Process Res. Dev.* **2006**, *11*, 105−113.
(5) Drexler, M. T.; Amiridis, M. D. *J. Catal.* **2003**, *214*, 136−145.
(6) van Grieken, R.; Serrano, D. P.; Melero, J. A.; García, A. *J. Mol. Catal. A: Chem.* **2004**, *222*, 167−174.
(7) Zeidan, R. K.; Hwang, S.-J.; Davis, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6332−6335.
(8) Solin, N.; Han, L.; Che, S.; Terasaki, O. *Catal. Commun.* **2009**, *10*, 1386−1389.
(9) Kandel, K.; Althaus, S. M.; Peeraphatdit, C.; Kobayashi, T.; Trewyn, B. G.; Pruski, M.; Slowing, I. I. *J. Catal.* **2012**, *291*, 63−68.
(10) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891−1896.
(11) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317−328.
(12) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986.
(13) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100−15101.
(14) Yang, H.; Zhang, G.; Hong, X.; Zhu, Y. *Microporous Mesoporous Mater.* **2004**, *68*, 119−125.
(15) Kim, D. J.; Dunn, B. C.; Cole, P.; Turpin, G.; Ernst, R. D.; Pugmire, R. J.; Kang, M.; Kim, J. M.; Eyring, E. M. *Chem. Commun.* **2005**, 1462−1464.
(16) Meiboom, S.; Gill, D. *Rev. Sci. Instrum.* **1958**, *29*, 688−691.
(17) Wiench, J. W.; Lin, V. S.-Y.; Pruski, M. *J. Magn. Reson.* **2008**, *193*, 233−242.

(18) Nedd, S.; Kobayashi, T.; Tsai, C.-H.; Slowing, I. I.; Pruski, M.; Gordon, M. S. *J. Phys. Chem. C* **2011**, *115*, 16333−16339.
(19) Bass, J. D.; Solovyov, A.; Pascall, A. J.; Katz, A. *J. Am. Chem. Soc.* **2006**, *128*, 3737−3747.
(20) *CRC Handbook of Chemistry and Physics*; 93 ed.; CRC Press: Boca Raton, FL, 2012.
(21) Paukstelis, J. V.; Cook, A. G. In *Enamines: Synthesis, Structure and Reactions*; 2 ed.; Cook, A. G., Ed.; Marcel Dekker, Inc.: New York, 1988, p 275−346.
(22) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416−5470.
(23) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557.
(24) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569.
(25) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580−591.
(26) Brazier, J.; Tomkinson, N. *Top. Curr. Chem.* **2009**, *291*, 281−347.
(27) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
(28) List, B. *Chem. Commun.* **2006**, 819−824.
(29) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425−471.
(30) Guillena, G.; Hita, M. d. C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933−5943.
(31) Naulet, N.; Filleux, M. L.; Martin, G. J.; Pornet, J. *Org. Magn. Reson.* **1975**, *7*, 326−330.
(32) Naulet, N.; Martin, G. J. *Tetrahedron Lett.* **1979**, *20*, 1493−1496.
(33) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, *2007*, 4205−4216.
(34) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100−8102.
(35) Rogers, C. J.; Dickerson, T. J.; Janda, K. D. *Tetrahedron* **2006**, *62*, 352−356.
(36) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4997−5003.
(37) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220−3221.
(38) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970−6979.
(39) Reymond, J.-L.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 2575−2578.
(40) Rosenholm, J. M.; Czuryszkiewicz, T.; Kleitz, F.; Rosenholm, J. B.; Linden, M. *Langmuir* **2007**, *23*, 4315−4323.
(41) Ong, S.; Zhao, X.; Eisenthal, K. B. *Chem. Phys. Lett.* **1992**, *191*, 327−335.
(42) Wang, Q.; Shantz, D. F. *J. Catal.* **2010**, *271*, 170−177.
(43) Kubota, Y.; Yamaguchi, H.; Yamada, T.; Inagaki, S.; Sugi, Y.; Tatsumi, T. *Top. Catal.* **2010**, *53*, 492−499.
(44) Brunelli, N. A.; Venkatasubbaiah, K.; Jones, C. W. *Chem. Mater.* **2012**, *24*, 2433−2442.
(45) Kubota, Y.; Goto, K.; Miyata, S.; Goto, Y.; Fukushima, Y.; Sugi, Y. *Chem. Lett.* **2003**, *32*, 234−235.
(46) Hruby, S. L.; Shanks, B. H. *J. Catal.* **2009**, *263*, 181−188.