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Tailoring the Cooperative Acid–Base Effects in Silica-Supported Amine Catalysts: Applications in the Continuous Gas-Phase Self-Condensation of *n*-Butanal

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A highly efficient solid-base organocatalyst for the gas-phase aldol self-condensation of *n*-butanal to 2-ethylhexenal was developed by grafting site-isolated amines on tailored silica surfaces. The catalytic activity depends largely on the nature of amine species, the surface concentration of amine and silanol groups, and the spatial separation between the silanol and amine groups. In situ FTIR measurements demonstrated that the formation of nucleophilic enamines leads to the enhanced catalytic activity of secondary amine catalysts, whereas the formation of imines (stable up to 473 K) leads to the low activity observed for silica-supported primary amines. Blocking the silanol groups on the silica support by silylation or cofeeding water into the reaction stream drastically decreased the reaction rates, demonstrating that weaker acidic silanol groups participate cooperatively with the amine groups to catalyze the condensation reaction. This work demonstrates that the spatial separation of the weakly acidic silanols and amines can be tuned by the controlled dehydration of the supporting silica and by varying the linker length of the amine organosilane precursor used to graft the amine to the support surface. A mechanism for aldol condensation was proposed and then analyzed by DFT calculations. DFT analysis of the reaction pathway suggested that the rate-limiting step in aldol condensation is carbon–carbon bond formation, which is consistent with the observed kinetics. The calculated apparent activation barrier agrees reasonably with that measured experimentally.

Introduction

Enzymes accelerate chemical reactions by the cooperative interaction between two or more functional groups accurately positioned within their active sites.[1] For example, serine protease significantly enhances ($\approx 10^{12}$ times) the hydrolysis of amides through the cooperative catalytic triad nucleophilic alcohol, basic imidazole, and acidic carboxylic acid interactions.[2] To achieve high activity, mutually incompatible groups, e.g., acids and bases, must be positioned to suppress direct proton transfer; however, the distance between the two active moieties must be close enough so that they can function synergistically.[3] This paradigm of biological transformations has inspired the synthesis of a large library of homogeneous acid–base bifunctional catalysts that exhibit excellent activity in many organic transformations.[4]

Solid-base catalysts synthesized by functionalization of organosilanes or nitrogen doping of inorganic oxides constitute a new class of heterogeneous catalysts capable of catalyzing various carbon–carbon bond formation such as the Knoevenagel, Henry, and aldol condensation reactions.[3,5] As organic amines (base sites) supported on silica surfaces (acid sites) can activate nucleophiles and electrophiles, respectively, several synthetic approaches have been reported for tailoring the spatial separation between the antagonist functional groups.[6] The later feature is crucial for cooperative catalysis because the functional groups must be close enough to each other to achieve cooperativity without mutual neutralization. For example, Kubota and co-workers have shown that higher rates of aldol condensation can be achieved if homogeneous amines are used with mesoporous silica containing weakly acidic silanol groups.[7] Katz and co-workers have shown the pivotal role of silanol groups in the acid–base cooperativity between the silanol and amines groups by demonstrating that the activity of such acid–base pairs is greatly reduced when the silanol groups are passivated.[8] The structure of the support can also influence the performance of acid–base pairs. Shimizu and co-workers have observed that amines supported on mesoporous silica (FSM-16) are nearly twice as active as amines supported on amorphous silica and five times more active than homogenous amines.[9] The superior performance of mesoporous silica was attributed to the enrichment of reactants inside the ordered channels of this support. The influence of acidity of the acid groups in acid–base pairs has been explored by Davis and co-workers.[10] These authors noted that the activity of the bifunctional materials increased with increasing pK_a of the organic acid component, and the material containing weakly acidic

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carboxylic acid and amine groups exhibited the highest activity for aldol condensation. By contrast, Jones and co-workers have recently shown that an organosilane possessing carboxylic acid and amine groups are less active than surface silanols and amines.[6,11]

The present study was focused on identifying the factors governing the catalytic activity of silica-supported primary, secondary, and tertiary amine catalysts for the gas–phase self-condensation of *n*-butanal to 2-ethylhexenal. We report here experiments conducted with the aim of establishing the roles of amine groups and their surface density, the size of the pores in the mesoporous silica support, the surface density of silanol groups on the surface of the support, and the influence of the spatial separation between the acid and base groups to the catalytic activity of silica-supported amine catalysts for aldol self-condensation of *n*-butanal. The mechanism and kinetics of *n*-butanal condensation were also investigated in detail.

Experimental Section

The preparation of silica-supported amine catalysts was performed in the following manner. One gram of silica (Silicycle, surface area: 500 $m^2 g^{-1}$, average pore diameter 6 nm) was dried in vacuum at 423 K for 24 h, or pretreated at 823 K and 973 K for 5 h, and then stored in vacuum prior to use. The silylating agents used were 3-aminopropyltrimethoxysilane (APTS), 3-(*N*-methylaminopropyl)trimethoxysilane (MAPTS) and 3-(*N*,*N*-diethylaminopropyl)trimethoxysilane (DEAPTS) and methyltrimethoxysilane (MMTS) obtained from Gelest, Inc. Typically, grafting of organoamines onto silica was done by stirring a 1 g portion of silica with the required amount of amino organosilanes in ethanol (100 mL) at 343 K for 15 h under inert atmosphere. The hot solution was then cooled to RT, filtered, washed with copious amounts of ethanol, and then dried in a vacuum oven at 373 K overnight. Silica-supported primary (SiO_2–NH_2), secondary (SiO_2–NHR) and tertiary amines (SiO_2–NR_2) were prepared with nearly identical amine loadings (≈0.4 amine nm^{-2}, according to elemental analysis). A similar synthesis procedure was used for grafting of a secondary amine onto mesoporous silicas (MCM-41, SBA-15, surface area: 800–1300 $m^2 g^{-1}$, pore diameter 2.5–12 nm).[12,13] Silylation of amine-supported silica catalysts was performed by dispersing the catalyst (1 g) in 25 mL of dry toluene followed by the addition of methyl trimethoxysilane (3.75 mmol) and stirring at 373 K for 15 h under an inert atmosphere. The final material is referred to as Sil-SiO_2–NHR.

Infrared spectra were acquired by using a Thermo Scientific Nicolet 6700 FTIR spectrometer equipped with a liquid-nitrogen-cooled MCT detector. Each spectrum was obtained by averaging 32 scans taken with 1 cm^{-1} resolution. A 0.05 g portion of silica-supported amine was pressed into a 20 mm-diameter pellet (<1 mm thick) and placed into a custom-built transmission cell equipped with CaF_2 windows, a K-type thermocouple for temperature control, and resistive cartridge heaters. Unless otherwise mentioned, all scans were acquired at 343 K. The spectrum of the catalyst under He was subtracted from the results reported.

Solid-state ^{13}C CP MAS NMR and ^{29}Si MAS NMR experiments were performed on a Bruker Avance I 500 MHz spectrometer equipped with a H/X double resonance magic-angle spinning probe that uses 4 mm O.D. rotors. ^{13}C cross-polarization, tuned to 125.79 MHz, MAS NMR experiments were obtained by using a ^1H 90° pulse width of 4.2 μs, 2 ms contact time, 60 kHz decoupling field and 2–5 s recycle delay at a spinning rate of 7–13 kHz. All ^{13}C spectra were referenced against the chemical shifts of adamantane at 38.48 and 29.45 ppm. The ^{29}Si with ^1H decoupling MAS NMR spectra were acquired at 99.37 MHz, by using a ^{29}Si 90° pulse width of 7.5 μs, recycle delay of 600 s, and spinning rate of 10–11 kHz. All ^{29}Si spectra were referenced against polydimethylsiloxane at −22 ppm (relative to TMS at 0 ppm). The resolution obtained in the ^{29}Si NMR spectra was sufficient for accurate peak assignments, and the relative peak area of each site was obtained by the curve-fitting, using a series of Gaussian peaks.[14]

Gas-phase self-condensation of *n*-butanal was performed in a 6.35 mm OD (≈4 mm ID) quartz tube containing an expanded section (≈12.7 mm OD, ≈20 mm length). The reactor was packed with quartz wool above and below the catalyst bed to hold the catalyst in place. The feed to the reactor consisted of *n*-butanal (0.02 $cm^3 h^{-1}$) and He. The catalysts were pretreated at 423 K before passing the feed. Experiments were performed at 343 K, total gas pressures of 1 atm, total gas flow rate of 150 $cm^3 min^{-1}$. Under these conditions, the conversion of *n*-butanal was less than 10%. Reaction products were analyzed by using an Agilent 6890N gas chromatograph containing a bonded and cross-linked (5%-phenyl)-methylpolysiloxane capillary column (Agilent, HP-1) connected to a flame ionization detector.

Results and Discussion

The successful grafting of the respective organosilanes onto the silica supports was confirmed by ^{13}C CP MAS NMR (see Supporting Information). The observed chemical shifts of the organic amine groups agree well with those of the corresponding organosilane precursors measured in solution.[15] Small peaks were also observed at $\delta = 62$ and 20 ppm and attributed to ethoxy carbon atoms formed by partial esterification of surface silanol groups by ethanol.[16] ^{29}Si MAS NMR further confirmed the presence of organic functional groups grafted on the silica support (Supporting Information). Peaks at $\delta = -110$, −100, −90, −65, and −55 ppm were assigned to the $Q^4(Si(OSi)_4)$, $Q^3(Si(OH)(OSi)_3)$, $Q^2(Si(OH)_2(OSi)_2)$, $T^3(SiR(OSi)_3)$, and $T^2(Si(OH)\ R(OSi)_2)$ sites, respectively. The presence of a sharp peak for T^3 sites confirms the formation of a strong covalent linkage between the organic amine groups and the support surface.[12]

The catalytic activity of silica-supported amines was evaluated for the self-condensation of *n*-butanal to 2-ethylhexenal. As shown in Figure 1, the catalyst prepared with secondary amine was approximately five times more active than that prepared with primary amine, whereas the catalyst prepared with tertiary amine showed negligible activity. Control experiments with silica displayed no catalytic activity, indicating that the surface-bound organic amine functional groups are responsible for the observed catalytic activity. The only products observed under the conditions investigated were the condensation product, 2-ethylhexenal. Despite the stronger basicity of alkyl-substituted tertiary amines, the poor catalytic activity observed with silica-supported tertiary amine suggests that aldol condensation does not occur according to a general base-catalyzed mechanism. Instead, the order of the activity (secondary ≫ primary > tertiary) suggests that the reaction proceeds through an enamine mechanism involving a carbinolamine intermediate.[8,17]

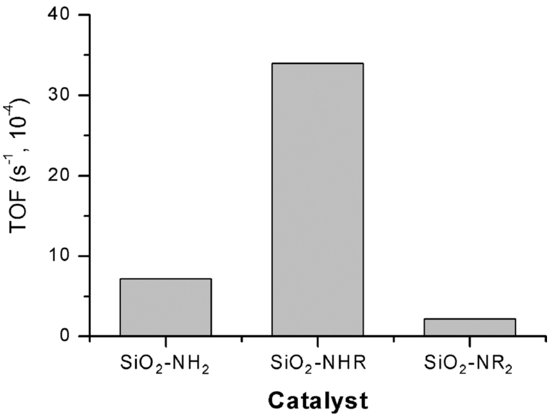


Figure 1. The effect of amine composition on the rate of 2-ethylhexenal synthesis over silica-supported amine catalysts $P_{total} = 1$ atm; $P_{n\text{-butanal}} = 0.2$ kPa, balance He; total gas flow rate = 150 cm^3 min^{-1}; $T = 343$ K; amine loading = 0.4 –amine nm^{-2}, TOF = turnover frequency.

The apparent activation energies calculated from Arrhenius plots for primary, secondary and tertiary amines in the temperature interval 333–353 K are 97, 82, and 115 kJ mol^{-1}, respectively. The partial pressure dependence on the rate of formation of 2-ethylhexenal was measured by varying the partial pressure of *n*-butanal while keeping the total gas flow rate and pressure constant at 150 cm^3 min^{-1} and 1 atm. The order of reaction rate with respect to the partial pressures of *n*-butanal for primary and secondary amine catalysts was 0.40 and 0.43, respectively. By contrast, a first-order dependence in *n*-butanal was noted for the silica-supported tertiary amine catalysts (see Supporting Information).

In situ IR spectroscopy was used to obtain information about the mechanism of *n*-butanal self-condensation on silica-supported amine catalysts and to identify differences in the chemistry of primary, secondary and tertiary amine catalysts. In Figure 2 the spectra of the catalysts exposed to *n*-butanal and recorded at 343 K are shown. SiO$_2$–NHR (spectrum b) exhibits bands at 1705, 1650, and 1630 cm^{-1}. The first of these peaks is attributable to carbonyl vibrations of *n*-butanal adsorbed on the silanol groups, whereas the second two peaks are attributable to the C=O and C=C vibrations of the product, 2-ethylhexenal.[18] The shoulder at 1680 cm^{-1} is tentatively assigned to iminium species, the formation of which is frequently reported for homogenous secondary amine catalysts.[17] By contrast, the spectrum of SiO$_2$–NH$_2$ (spectrum c) during contact with *n*-butanal exhibits sharp peaks at 1705 and 1670 cm^{-1}. The first of these peaks is assigned to carbonyl vibrations of *n*-butanal adsorbed on the silanol groups, whereas the second peak is assigned to the formation of imine (–HC=N–) species.[19] This species was found to be stable up to 473 K. The formation of stable imines was further confirmed using UV/Vis spectroscopy and solid-state ^{13}C CP MAS NMR of the spent catalysts (see Supporting Information). The only feature observed in the spectrum of SiO$_2$–NR$_2$ (spectrum a) was a band at 1705 cm^{-1}, attributable to interactions of *n*-butanal with the silanol groups of the support.

The low catalytic activity observed for SiO$_2$–NH$_2$ is attributed to the formation of stable imines, which are known to be inhibitors for enamine catalysis.[5,19] The absence of imines or enamines in the spectrum of SiO$_2$–NR$_2$ suggests that the reaction proceeds through an ion-pair mechanism, with the formation of enolate species in the rate-determining step. The ion-pair mechanism involves the abstraction of a proton from the methylene carbon by a base, forming a carbanion, which then attacks the carbonyl carbon of another aldehyde to form the C–C bond-forming step with the release of a proton from the base to form the product (see Supporting Information). Corma and co-workers have shown that the ion-pair mechanism give rise to kinetics that are first order in aldehyde if proton abstraction is assumed to be the rate-limiting step.[20] This finding is consistent with the first-order partial pressure dependency on *n*-butanal observed with the tertiary amine catalysts and suggests that aldol condensation on the tertiary amine catalysts proceeds through a general base-catalyzed mechanism.

Having established that silica-supported secondary amines exhibit the highest activity for self-condensation reaction of *n*-butanal, the density of secondary amine groups on the silica surfaces was varied to investigate the effect of amine loading on the catalytic activity. As seen from Figure 3, increasing the amine surface density on the silica surface progressively decreased the catalytic activity. Even though an increase in the amine surface density leads to a decrease in the silanol surface density, the least active amine catalyst, which contains 0.6 –NHR nm^{-2} still possess a ten-fold excess of silanol relative to

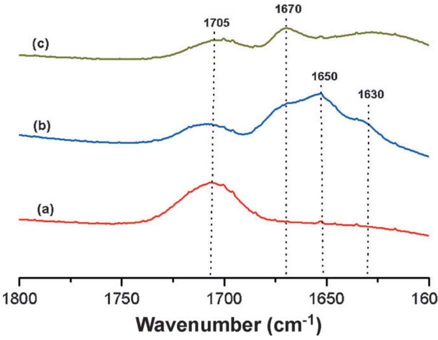


Figure 2. In situ FTIR spectra of *n*-butanal adsorbed at 343 K on silica-supported amine catalysts: (a) SiO$_2$–NR$_2$; (b) SiO$_2$–NHR, and (c) SiO$_2$–NH$_2$.

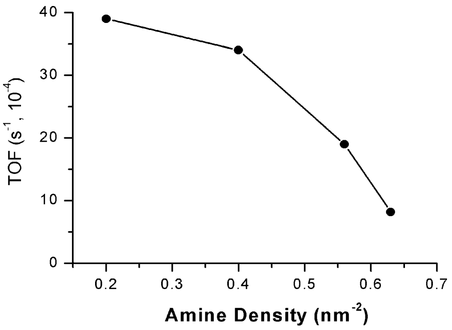


Figure 3. The effect of secondary amine loading on the rate of 2-ethylhexenal synthesis: $P_{total} = 1$ atm; SiO$_2$-423K; $P_{n\text{-butanal}} = 0.2$ kPa, balance He; total gas flow rate = 150 cm^3 min^{-1}; $T = 343$ K.

amine groups. This suggests that at low amine loadings, efficient amine–silanol catalytic cooperativity exists because the amine groups are isolated from one another and cannot interact through hydrogen bonding as a consequence of clustering of the amine groups near the pore mouth in the silica support.[6]

To determine how the spatial confinement of amine groups enhances the catalytic activity, secondary amines were supported on high-surface-area mesoporous silicas having pore diameters of 2.5 nm to 12 nm. The catalytic activity increased for mesoporous silicas up to a pore diameter of approximately 6 nm, after which the activity remained nearly constant (Figure 4). Remarkably, a three-fold increase in catalytic activity was noted if the pore size of the support was changed from 2.5 nm to 6 nm. These results suggest that the rate of reaction is limited by molecular diffusion of the products if the reaction is conducted with mesopores of less than 6 nm. Comparison of the activities of secondary amines (0.4 –NHR nm^{-2}) supported mesoporous SBA-15 and amorphous silica (average pore diameter ≈ 6 nm) revealed that the mesoporous SBA-15 has a two-fold higher catalytic activity than the amorphous silica. The higher activity obtained with SBA-15 may be attributed to the (a) higher silanol content of SBA-15 (5 –OH nm^{-2}) than of amorphous silica (3.8 –OH nm^{-2}) and/or (b) to the difference in acidity of silanols between mesoporous and amorphous silicas.[21] To better understand whether the high density of the silanol groups or the acidity of these groups contributes to the high activity of the secondary amine supported SBA-15, each of these factors was evaluated separately.

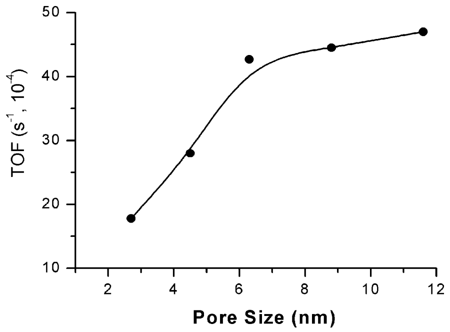


Figure 4. The effect of the pore size of mesoporous-silica-supported secondary amine catalysts on the rate of 2-ethylhexenal synthesis: P_{total} = 1 atm; $P_{n\text{-butanal}}$ = 0.2 kPa, balance He; total gas flow rate = 150 cm^3 min^{-1}; T = 343 K; amine loading ≈ 0.4 –amine nm^{-2}.

To assess the influence of silanol group concentration, the surface concentration of silanol groups was reduced by grafting methyltrimethoxysilane onto the amine-supported silica. Irrespective of the support material (SBA-15 or amorphous silica), blocking the silanol groups by silylation decreased the rate seven-fold, confirming that silanols act cooperatively with amines in the aldol condensation of *n*-butanal. ^{29}Si MAS NMR spectroscopy corroborated that silylation decreased the total concentration of silanol groups by approximately 35 %. To further ascertain the role of silanol groups, an experiment was performed by cofeeding water with *n*-butanal into the reaction stream. A 20-fold decrease in the rate of aldol condensation was noted after 6 h time on stream relative to that observed without the addition of water. IR spectra of SiO$_2$–NHR catalysts in the presence of co-fed water with *n*-butanal confirmed that water interferes with the adsorption of *n*-butanal on the silanol group. The loss in catalytic activity with co-fed water can thus be related to the passivation of silanols with water molecules, where the aldehyde need to adsorb and get activated during the C—C bond forming step (see Supporting Information).

The role of silanol groups on the amorphous silica support surface was further probed by changing the surface density of silanol groups by varying the temperature at which dehydration of the silica support was performed, prior to grafting the secondary amines. Dehydration temperatures of 423 K, 823 K and 973 K were used. The apparent surface concentration of the silanols determined from ^{29}Si MAS NMR spectroscopy and the BET surface areas reveal that the concentration of silanol groups decreases from 4 OH nm^{-2} for SiO$_2$-423K to 2.8 OH nm^{-2} for SiO$_2$-823K and to 1.6 OH nm^{-2} for SiO$_2$-973K.[14] As shown in Figure 5, the catalytic activity passed through a maximum as the concentration of silanol groups decreased. Secondary amine supported on silica pretreated at 823 K was nearly two times more active than that supported on silica pretreated at 423 K, and four times more active than that supported on silica pretreated at 973 K.

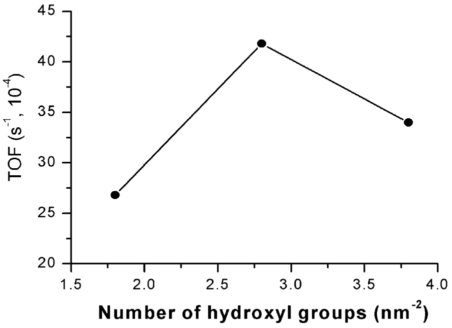


Figure 5. The effect of silanol density on the rate of 2-ethylhexenal synthesis over silica-supported silica secondary amine catalysts: P_{total} = 1 atm; $P_{n\text{-butanal}}$ = 0.2 kPa, balance He; total gas flow rate = 150 cm^3 min^{-1}; T = 343 K; amine loading = 0.4 –amine nm^{-2}.

It is known that an increase in the calcination temperature of silica not only reduce the concentration of silanol groups on the silica surface but also increase the acidity of the remaining silanol groups. For instance, the pK_a of isolated silanols is reported to be approximately 2–4 (Q^3 sites) whereas the pK_a of geminal silanols (Q^2 sites) is approximately 6–8.[22] To ascertain whether the acidity of the silanol groups enhances the rate, ^{13}C CP MAS NMR spectra were taken of secondary amine groups supported on silica pretreated at different temperatures. As shown in Figure 6, ^{13}C CP MAS NMR spectra did not display an upfield shift in the terminal carbon peak position indicating that amines do not interact with the acidic silanol groups. This result was corroborated by the adsorption of ho-

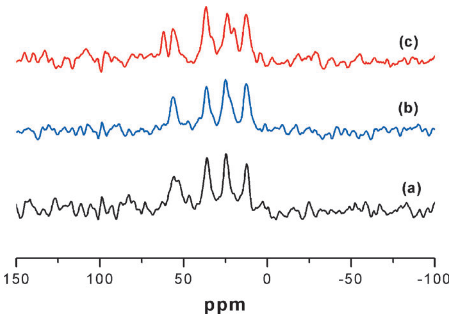


Figure 6. Effect of pretreatment temperature on the solid-state ^{13}C CP MAS NMR spectrum of silica-supported secondary amine catalysts: (a) SiO_2-423K; (b) SiO_2-823K; and (c) SiO_2-973K.

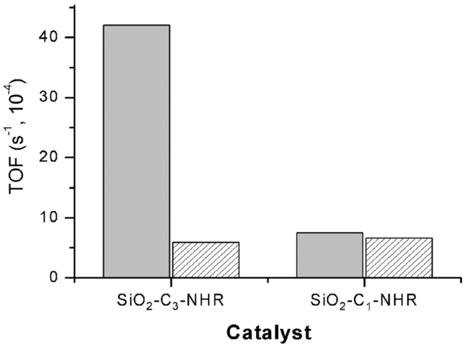


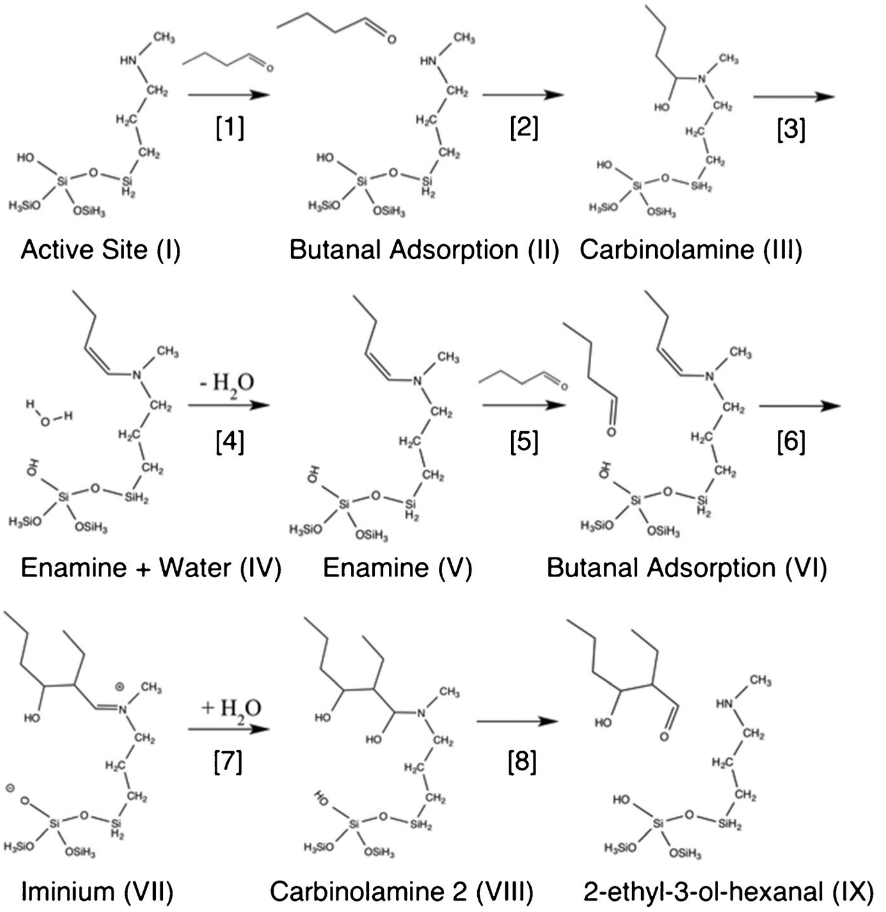
Figure 7. Effect of linker length on the catalytic activity of silica-supported secondary amine catalysts (solid bars) and comparison with their silylated analogs (striped bars). $P_{total} = 1$ atm; $P_{n\text{-butanal}} = 0.2$ kPa, balance He; total gas flow rate = 150 cm^3 min^{-1}; $T = 343$ K; SiO_2-823K; amine loading = 0.4 –amine nm^{-2}.

mogenous triethylamine (NEt_3) on silica. Irrespective of the pretreatment procedures, an upfield shift of the terminal carbon atoms of organic amine catalysts did not occur confirming that acidity of the silanol groups does not contribute to the enhanced catalytic activity of the catalyst prepared on silica dehydrated at 823 K (see Supporting Information).[23] Further indication that the dehydration temperature has no effect on the acidity of the silanols was obtained from the absence of a shift in the position of the 1705 cm^{-1} peak for *n*-butanal adsorbed on silanol groups. All these results taken together indicate that the temperature of silica dehydration does not alter the acidity of the silanol groups for the conditions used in this study.

The influence of the spatial separation between the amine and silanol groups was examined to determine its effect on the activity of acid–base pairs. The average distance between silanols on silica pretreated at 423 K is approximately 0.3–0.4 nm and the propylamine linker has a chain length of approximately 0.5 nm.[24] This means that amines can reach over the silanols in SiO_2-423K, making all the amine groups unavailable for the catalysis. By contrast, for the SiO_2-823K support, the silanols are separated by an average distance of approximately 0.6–0.7 nm, which means that the amine groups cannot interact strongly with silanol groups, leading to an enhanced catalytic activity. Consequently, for secondary amine supported SiO_2-973K catalysts, moving the silanols farther apart lead to an inactive catalyst, because the high catalytic efficiency depends on the cooperative activation of reactants by the amines and the silanols. These studies clearly demonstrate how the spatial separation between acid and base groups influences their catalytic activity. In an alternate way to confirm that an accurate spatial separation between the amines and the silanols leads to an enhanced catalytic activity, secondary amine catalyst having a methyl linker (SiO_2–C_1–NHR) were grafted onto SiO_2-823K support, instead of the propyl linker (SiO_2–C_3–NHR).[25] Remarkably, constrained methyl linker showed a ten-fold decrease in activity relative to that for the propyl linker demonstrating that an accurate distance between the silanols and propyl amine groups, on SiO_2-823K support leads to an active and stable catalyst for the self-condensation of *n*-butanal (Figure 7). These results are consistent with those reported recently by Jones and co-workers in which it was shown that the activity of acid–base-pairs catalysts can be tuned by altering the linker length of the amine.

The acid-base cooperativity was further demonstrated by silylating the silanol groups on the SiO_2–C_3–NHR and SiO_2–C_1–NHR. Interestingly, silylation decreased the catalytic activity of the SiO_2–C_3–NHR by ten times, whereas the activity of silylated SiO_2–C_1–NHR remained similar to that of nonsilylated SiO_2–C_1–NHR (Figure 7). These results suggest that silica-supported propylamines exhibit cooperative interactions with the silanol groups for rate enhancements whereas the constrained methylamine lacks the acid–base cooperativity. Alternatively, the low activity observed with SiO_2–C_1–NHR suggests that the reaction does not proceed through a silanol-assisted acid–base bifunctional mechanism, rather this may proceed through the general base-catalyzed mechanism. A first-order dependence on *n*-butanal partial pressure and a higher activation barrier (122 kJ mol^{-1}) support the proposal that aldol condensation on SiO_2–C_1–NHR proceeds through a general base-catalyzed mechanism (see Supporting Information). Thus, short alkyl linkers like methyl inhibits the beneficial amine–silanol cooperativity on silica surfaces resulting in lower catalytic activity.

The accumulated data suggest that the self-condensation of *n*-butanal over SiO_2–C_3–NHR proceeds through a concerted mechanism involving the basic amine groups and the weakly acidic silanol groups, as shown in Scheme 1. A theoretical analysis of the aldol condensation reaction pathway was performed to test the plausibility of this mechanism and to determine the rate-limiting step. The active-site model for these steps contains both a grafted amine group ($C_3H_6NHCH_3$) and a silanol group (Si–OH), as represented by the cluster shown in Figure 8. A model of amorphous silica containing four tetrahedral silicon atoms (T4) was obtained from the crystal structure of the zeolite H-MOR [S1], with all silicon atoms terminated in oxygen. The cleaved structure gives an O–O silanol separation of 0.5 nm, consistent with the experimental measurement from the most active SiO_2–C_3–NHR catalyst. To create the dual-site model containing the grafted amine adjacent to a silanol group, two terminal Si–O fragments were substituted for Si–OH and Si–$C_3H_6NHCH_3$, respectively. The remaining terminal



Scheme 1. Proposed mechanism for aldol self-condensation of *n*-butanal over silica-supported secondary amine catalysts.

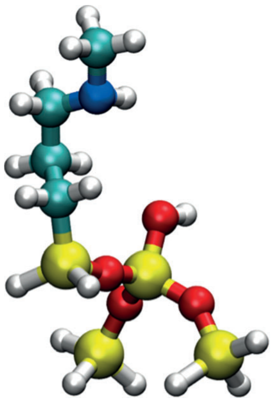


Figure 8. Model active site for the SiO_2–C_3–NHR catalyst. ●: Si, ●: O, ●: H, ●: C; ●: N.

O atoms were replaced by H and fixed in their crystallographic positions during subsequent optimization. The resulting cluster model has the stoichiometry of $C_4H_{19}NO_4Si_4$. (Further details concerning the computational method are provided in the Supporting Information).

The changes in enthalpy (343.15 K) along the reaction pathway calculated at the ωB97X-D/6-311++G(3df,3pd) level of theory are shown in Figure 9 and the corresponding free-energy (343.15 K) changes are shown in Figure 10. The adsorption of *n*-butanal to the bare catalyst surface is exothermic ($\Delta H = -25\,kJ\,mol^{-1}$) and is characterized by a weak hydrogen bonding interaction between *n*-butanal and the grafted amine. The formation of a carbinolamine species proceeds through a concerted C–N bond formation and proton transfer reaction. The transition-state structure for carbinolamine formation is similar to one found for proline-catalyzed aldol condensation.[26] The enamine state is produced by intramolecular water elimination. The iminium state can be formed by the protonation of the enamine by the silanol group, but is omitted from this diagram because of its instability relative to the enamine state ($\Delta H = +35\,kJ\,mol^{-1}$). The desorption of water exhibits a favorable free-energy change attributable to the additional gain in entropy. The adsorption of *n*-butanal in the presence of the enamine resting state is exothermic ($\Delta H = -32\,kJ\,mol^{-1}$) and is promoted by hydrogen bonding between the silanol group and the carbonyl group of *n*-butanal. The formation of the C–C bond ($\Delta H^{\ddagger} = +116\,kJ\,mol^{-1}$) proceeds by the protonation of the *n*-butanal carbonyl group by the silanol group and C–C bond formation between the enamine and the alpha-carbon of *n*-butanal in a concerted fashion, and produces a second iminium species. The hydrolysis proceeds from the second iminium by the attack of water on the complex. This process leads to a concerted proton transfer from the water molecule to the deprotonated silanol group, leaving the final product, 2-ethyl-3-ol-hexenal, in the chemisorbed state. The product then desorbs to reform the catalyst (SiO_2–C_3–NHR) and leave 2-ethyl-3-ol-hexenal in the physisorbed state. The final step of the reaction pathway is desorption of 2-ethyl-3-ol-hexenal into the gas phase followed by its dehydration to form the final product, 2-ethylhexenal.[18] The theoretical analysis of the *n*-butanal self-condensation pathway leads to the conclusion that the transition state for C–C bond formation is the rate-limiting step along the free energy pathway.[26–28] The resting state of the catalyst during reaction is the enamine state, since it is the lowest-lying intermediate on the free energy surface, consistent with the characterization of the spent SiO_2-NHR catalysts. The apparent activation barrier is calculated as the difference in enthalpy between the rate-limiting

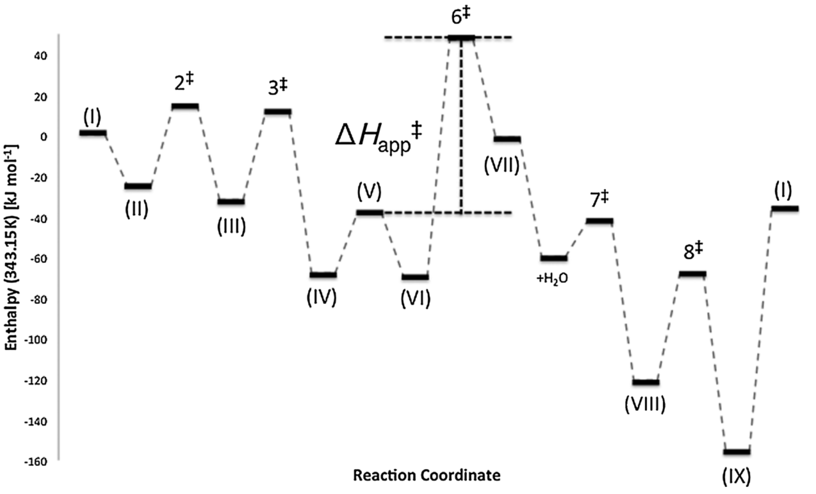


Figure 9. Enthalpy (343.15 K) diagram for aldol condensation of *n*-butanal over a SiO_2–C_3–NHR catalyst calculated at the ωB97X-D/6-311++G(3df,3pd) level of theory (kJ mol^{-1}). The elementary steps are labeled according to the reaction mechanism in Scheme 1. The calculated apparent activation energy ($\Delta H_{app}^{\ddagger}$) is 85 kJ mol^{-1}.

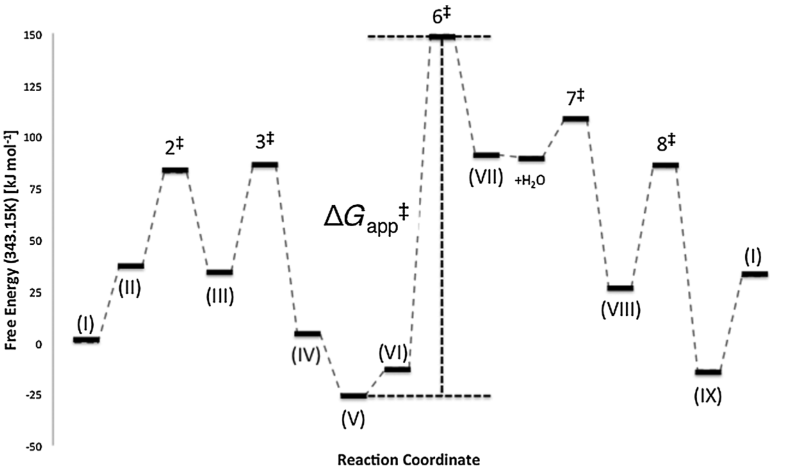


Figure 10. Free-energy (343.15 K) diagram for aldol condensation of *n*-butanal over a SiO_2–C_3–NHR catalyst calculated at the ωB97X-D/6-311++G(3df,3pd) level of theory (kJ mol^{-1}). The elementary steps are labeled according to the reaction mechanism in Scheme 1. The difference in free energy between the resting state (IV, $-H_2O$) and the rate limiting transition state ($5^{\ddagger}$) is denoted as $\Delta G_{app}^{\ddagger}$.

step and the resting state of the catalyst. The calculated apparent activation energy for this process is 85 kJ mol^{-1}, in good agreement with the value of 82 kJ mol^{-1} determined experimentally.

Based upon the proposed reaction mechanism and considering that reactions prior to the rate-limiting C–C bond-forming step are quasi-equilibrated, the rate of 2-ethylhexenal formation can be expressed as follows:

$$r_P = \frac{\alpha P_{\text{butanal}}^2 L L_1/(L_1+L)}{P_{H_2O} + \beta P_{\text{butanal}} + \gamma P_{H_2O} P_{\text{butanal}} + K_4 P_{H_2O}^2 + \delta P_{\text{butanal}}^2 + \varepsilon P_{H_2O}^2 P_{\text{butanal}} + \lambda P_{H_2O} P_{\text{butanal}}^2} \quad (1)$$

where α, β, γ, δ, ε, and λ represent lumped equilibrium and rate parameters, K_4 is the equilibrium constant for reaction 4, P_j is the partial pressure of species j, and L and L_1 represent the total number of surface silanol and amine groups, respectively. A detailed derivation of Equation (1) is provided in the Supporting Information.

Equation (1) can be used to rationalize the experimental results. Under the experimental conditions used in this study, the partial pressure of H_2O was negligible because the conversion was less than 10%. Therefore, Equation (1) simplifies to Equation (2).

$$r_P = \frac{K_5 k_6 P_{\text{butanal}} L L_1/(L_1+L)}{1 + K_5 P_{\text{butanal}}} \quad (2)$$

The form of Equation (2) is consistent with the observation that the rate of 2-ethylhexenal formation is 0.4 order in *n*-butanal, suggesting that both terms in the denominator contribute to the overall rate.

The P_{H_2O} terms of Equation (1) in the denominator describe the inhibitory effect of water observed experimentally. Water vapor inhibits the catalytic reaction by hydrolyzing the carbon–carbon double bond of the enamine, thereby decreasing concentration of the enamine intermediate by shifting equilibrium of reaction 3 to the left. Additionally, water vapor competes with aldehyde for vacant silanol groups (see Supporting Information).

The proposed mechanism for *n*-butanal condensation demonstrates that for efficient catalysis, the basic amine groups must work in concert with the acidic silanol groups. Strong acids are undesirable because they can protonate the amine group, thereby lowering their nucleophilicity, which is essential for formation of enamine species. It is thus essential that the distance between the acid and base sites should be large enough to avoid mutual neutralization but close enough so that the acid and base groups can interact with the reactant molecule for cooperative catalysis to occur. This effect is accurately modeled by the two-site rate equation indicating that a lone silanol or amine site cannot exclusively catalyze the reaction. By increasing the density of amine, the value of the

$L' = LL_1/(L+L_1)$ term rises to a maximum and then decreases. This trend qualitatively explains the effect of amine site density on the rate of aldol condensation reaction (see Supporting Information).

Conclusions

The results presented in this study provide a comprehensive understanding of the factors influencing the acid–base cooperativity of amine-supported silica catalysts for carbon–carbon bond formation during the self-condensation of *n*-butanal. Secondary amine functionalized silica is nearly five times more active than that functionalized with primary amines; tertiary amine functionalized silica exhibits negligible catalytic activity. Formation of nucleophilic enamines leads to enhanced catalytic activity of secondary amine catalysts, whereas formation of stable imines (up to 473 K) leads to the low activity of primary amine supported silica catalysts. Secondary amines in combination with the isolated silanol groups provide the best acid–base pair and the spatial separation between acid–base groups can be tailored by simple calcination treatment of the silica support or by varying the linker length of the organosilane for catalytic enhancements. Detailed experimental as well as theoretical analysis of the *n*-butanal self-condensation pathway leads to the conclusion that carbon–carbon bond formation is the rate-limiting step in the aldol condensation of *n*-butanal over silica-supported secondary amines.

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Keywords: acidity · aldol reaction · amines · organocatalysis · silica

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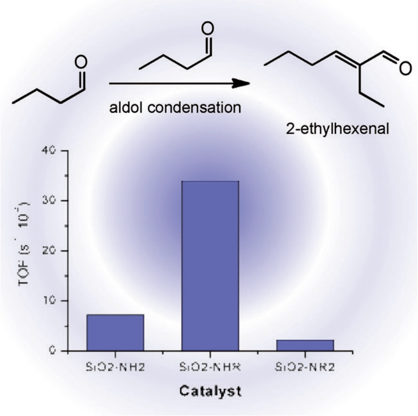
Secondary amines come first: A solid-base organocatalyst achieved by grafting amines onto silica surfaces is applied to the gas-phase aldol self-condensation of *n*-butanal to 2-ethylhexenal. Silica-supported secondary amine catalysts demonstrate a much higher catalytic activity than the primary amine analogues, owing to the respective formation of enamines as shown by in situ FTIR analysis. The reaction pathway is analyzed by DFT calculations.



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*A. T. Bell**

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Tailoring the Cooperative Acid–Base Effects in Silica-Supported Amine Catalysts: Applications in the Continuous Gas-Phase Self-Condensation of *n*-Butanal