Consequences of Intrapore Liquids on Reactivity, Selectivity, and Stability for Aldol Condensation Reactions on Anatase TiO$_2$ Catalysts

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This study provides evidence and mechanistic interpretations for the significant consequences of intrapore non-polar liquids on acetone aldol condensation turnover rates, selectivity to primary dimer products, and catalyst stability for reactions at Lewis acid-base site pairs on TiO$_2$ surfaces. These non-polar liquids confer such benefits through the preferential stabilization of transition states (TS) for adsorption (“entry”) and desorption (“exit”) steps, which place their respective reactants or products within a solvating outer sphere environment. The extent to which non-polar fluids (n-heptane) form an intrapore liquid phase within TiO$_2$ voids was obtained from N$_2$ uptakes using established formalisms that consider the different molar volume, surface tension, and volatility between N$_2$ and n-heptane. Acetone condensation rates are limited by C–H activation, an “entry” step that forms bound prop-1-en-2-olates via a TS stabilized by intrapore liquids, leading to higher aldol condensation turnover rates as n-heptane pressure increases and active TiO$_2$ surfaces become increasingly immersed within a non-polar liquid phase. These solvates later form the late TS structures that mediate the desorption of primary C$_6$ condensation products even more effectively than those involved in prop-1-en-2-olate formation or in nucleophilic attack events that later form C–C bonds. Such preferential solvation favors desorption over C–C coupling events, thus disfavoring the formation of larger oligomers that become stranded at active sites, thus leading to much slower deactivation. Moreover, solvation by non-polar liquids also leads to C$_6$ alkanones as the sole products formed in a single surface sojourn. These effects of a non-polar dense phase circumvent the inherent stability, reactivity, and selectivity hurdles that have precluded practical aldol condensation catalysis on Lewis acid-base pairs at oxide surfaces; these consequences are demonstrated here for TiO$_2$ catalysts, acetone aldol condensation reactions, and n-heptane as the non-polar liquid but through strategies, concepts, and mechanistic features that extend to other systems. More generally, these observations and their mechanistic origins demonstrate how a contacting liquid preferentially solvates TS structures for elementary steps that involve either reactants arriving from or products entering into an outer sphere environment that contains a dense non-polar phase.

Introduction

Aldol condensation reactions convert carbonyl compounds (and related oxygenates) into products of higher value by removing O-atoms and forming new C–C bonds, thus leading to less volatile products with higher energy densities.$^\text{[1–8]}$ Such reactions are catalyzed by Lewis acid-base site pairs on TiO$_2$ and ZrO$_2$; an exposed cation (Ti$^{4+}$ or Zr$^{4+}$) acts in concert with a vicinal oxygen anion to mediate the bond cleavage and formation steps involved in aldol condensation turnovers.$^\text{[9,14,27]}$ These reactions form α,β-unsaturated alkanals and alkanones via steps that include the kinetically-relevant cleavage of the α-C–H bonds in reactants and subsequent nucleophilic attack of carbonyls by enolates and dehydration of the resulting aldol species;$^\text{[9–17]}$ these mechanistic routes resemble those that mediate C–C bond formation and O-removal in reactions of carboxylic acids (ketonization).$^\text{[9,17–25]}$ The unsaturated primary products formed in aldol condensation events can react further to form larger molecules, which bind strongly onto Ti–O and Zr–O acid-base pairs, leading to selectivity losses and fast deactivation.$^\text{[12,14–15,26–28]}$

The steps that form the primary unsaturated oxygenates can reach near-equilibrium conversions on competent catalysts,$^\text{[11]}$ but the significant bed residence times required to achieve such conversions also favor sequential chain growth.$^\text{[10,12]}$ The resulting deactivation and loss of primary products not only interfere with rigorous kinetic inquiries$^\text{[14,27]}$ required for unequivocal mechanistic conclusions, but also preclude the efficient use of these reactions in practice. Several recent studies have reached contradictory conclusions about the identity of the kinetically-relevant steps and the most abundant bound intermediates in surface-catalyzed aldol condensation reactions. Acetaldehyde condensation was proposed to occur via kinetically-relevant reactant adsorption or product desorption steps on TiO$_2$ surfaces that had become densely-covered by organic residues, thus predominantly exposing residual Ti–O centers that become isolated within such
adlayers;\textsuperscript{[11]} other studies, also conducted on catalysts after their significant deactivation, proposed that rates are limited instead by nucleophilic attack on bound acetaldehyde by bound enolates.\textsuperscript{[14]} In both instances, the evidence was based on kinetic trends observed on surfaces decorated by significant coverages of unreactive species. 

Mechanistic studies based on kinetic analysis were combined with spectroscopic, isotopic, and theoretical methods on TiO\textsubscript{2} surfaces protected from deactivation by scavenging unsaturated primary products through hydrogenation by H\textsubscript{2} on a co-mixed Cu-based catalytic function.\textsuperscript{[14,27]} These studies showed that enolate formation of Ti=O acid-base site pairs on essentially bare surfaces is the sole kinetically-relevant step for a broad range of alkanal and alkanone reactants.\textsuperscript{[14,27]} The transition states that mediate such steps involve concerted interactions with acid-base site pairs, in which O-atoms abstract the H-atom located at the \(\alpha\)-position to the carbonyl group and Ti centers stabilize enolate moieties as they incipiently form. TiO\textsubscript{2} surfaces densely-covered by unreactive residues lead to Ti=O pairs that become isolated, thus favoring the bimolecular steps that form C=C bonds, but which require accessible vicinal Ti=O pairs. As a result, the kinetic relevance shifts from monomolecular enolate formation at a single Ti=O pair on protected clean surfaces\textsuperscript{[14,27]} to bimolecular C=C bond formation steps at vicinal pairs\textsuperscript{[19]} as unreactive organic residues form on unprotected TiO\textsubscript{2} surfaces. 

This study reports an alternate strategy to inhibit secondary reactions and concomitant deactivation events without requiring another function or the presence of H\textsubscript{2}, thus leading to unsaturated primary products with high selectivity. Stability and selectivity improvements are achieved through the purposeful capillary condensation of a non-polar inert intrapore liquid phase. This liquid phase strongly influences reactivity, selectivity, and catalyst stability for monofunctional anatase TiO\textsubscript{2} surfaces by preferentially stabilizing specific transition states that mediate kinetically-relevant and selectivity-determining steps. These findings parallel the recent demonstration of TiO\textsubscript{2} surfaces that mediate kinetically-relevant and selectivity-determining steps. These concepts and their catalytic consequences are illustrated here for acetone reactants, using \(n\)-heptane as the non-polar liquid, and for anatase TiO\textsubscript{2} as the catalyst; the concepts and the mechanistic framework, however, are broadly applicable and general. To our knowledge, no previous strategies have prevented the fast deactivation of TiO\textsubscript{2}-based multifunctional catalysts, even though the competence (and impractical selectivities and deactivation rates) of such catalysts was first demonstrated nearly four decades ago.\textsuperscript{[18,24]}

**Results and Discussion**

Reactions and elementary steps for acetone condensation on anatase

Reactions of acetone (0.5–2.5 kPa; 363 K) on anatase TiO\textsubscript{2} (TiO\textsubscript{2}(a)) form C\textsubscript{6} and C\textsubscript{9} alkane products as detectable products. Mesityl oxide (4-methylpent-3-en-2-one) and isomesityl oxide (4-methylpent-4-en-2-one) are the C\textsubscript{6} products; the C\textsubscript{9} products consist of skeletal and positional isomers of symmetric (e.g., 2,6-dimethyl-hepta-2,5-dien-4-one) and unsymmetric (e.g., 4,6-dimethyl-hepta-3,5-dien-2-one) C\textsubscript{9} alkanes. The canonical mechanisms for aldol condensation (Scheme 1) give symmetric C\textsubscript{9} alkanes via the cross-condensation of acetone with C\textsubscript{9} alkenes derived from mesityl oxide (e.g., 4-methylpenta-1,3-dien-2-ol; Scheme 1A). Unsymmetric C\textsubscript{9} alkenes form via cross-condensation of acetone with C\textsubscript{9} enols derived from isomesityl oxide (e.g., 4-methylpenta-2,4-dien-2-ol; Scheme 1B) or of C\textsubscript{9} alkenes with acetone-derived prop-1-en-2-ol (Scheme 1C).\textsuperscript{[26]}

Adapted from ChemCatChem with permission.

![Aldol condensation products](https://example.com/aldol-condensation-diagram.png)

**Scheme 1.** Symmetric and unsymmetric C\textsubscript{9} alkanone products of C\textsubscript{6} + C\textsubscript{9} cross-condensations.
Figure 1 shows selectivities to primary C₉ alkanone products at different acetone conversions on TiO₂(a) (2.5 kPa acetone; 363 K) in the absence of intraporous n-heptane liquids. Acetone conversions were varied through changes in residence time or via deactivation, with identical consequences for selectivity trends; this shows that Ti–O Lewis acid-base site pairs are involved in the formation of both C₉ and C₆ alkanones. The asymptotic C₉ selectivity (extrapolated to zero conversion) is smaller than unity, indicative of the formation of both C₉ and C₆ alkanones in a single surface sojourn. The zero-conversion asymptotic ratio of unsymmetric C₉ (B and C in Scheme 1) to symmetric C₉ (A in Scheme 1) products is essentially zero (Figure 1) and increases monotonically as conversion increases. These data indicate that symmetric C₉ alkanones form as primary products and that secondary reactions are responsible for the formation of symmetric and unsymmetric C₉ alkanones. The self-condensation of acetone gives mesityl and isomesityl oxide and sequential reactions of bound C₆ products before desorption give primary C₉ alkanones. The cross-condensations of acetone and primary C₉ alkanones in subsequent surface sojourns give secondary C₉ alkanones. The observed relationship between product rank (primary or secondary) and C₉ alkanones (un)symmetry (Figure 1) is consistent with accepted mechanisms for aldol condensation, which involve C₉ and C₆ enolates as intermediates (Scheme 1), suggesting that the elementary step sequences for the self- and cross-condensation of acetone on TiO₂(a) proceed through mechanisms akin to the accepted ones but instead with bound C₉ and C₆ enolates as intermediates.

These observations, taken together with the linear dependence of turnover rates on acetone pressure (vide infra), indicate that self-condensation of acetone and cross-condensation of acetone with C₆ alkanones proceed via the elementary steps depicted in Scheme 2, with prop-1-en-2-olate (C₆*) formation from acetone (C₆) reactions on bare Ti–O site pairs (*) (Step 1; Scheme 2) as the sole kinetically-relevant step in the elementary step sequences for both the self and cross-condensation reactions, as also shown previously from kinetic, isotopic, and theoretical evidence.¹⁴,²⁷ Acetone condensation turnover rates (per exposed Ti–O Lewis acid-base site pair) on TiO₂(a) are proportional to acetone pressure with rate constants for (CH₃)₂CO and (CD₃)₂CO condensation giving rise to the expected normal kinetic isotope effect.¹⁴,²⁷ The DFT-derived free energy barrier for C₆* formation is higher than those for subsequent C–C bond formation steps. This C₆* formation transition state (TS) gives kinetic isotope effects in agreement with measured values; it shows a significant elongation of the α-C–H bond in acetone (0.1103 nm) at the TS (0.1403 nm).¹⁴,²⁷

The elementary steps after the formation of C₆* enolates complete acetone self-condensation and cross-condensation turnovers; they involve a second acetone molecule reacting with C₆* to give a TiO₂(a)-bound C₆ enolate (C₆*) (Step 2; Scheme 2), which either desorbs (Step 3) to give mesityl or isomesityl oxide (lumped as C₆ products) or reacts with another acetone molecule (Step 4) to form primary C₆ products (lumped as C₆′ products). C₆ alkanones formed in a single surface sojourn can react with α-C₆* (Step 5) to form the secondary C₆ products (lumped as C₆′′ products). The catalytic sequences that form C₆, C₆′, and C₆′′ share C₆* enolate formation (Step 1) as a common

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**Figure 1.** Fractional selectivity to C₉ alkanones (left ordinate, filled circles; Equation 30) and ratio of rate of unsymmetric C₉ alkanone formation to rate of symmetric C₉ alkanone formation (right ordinate, open squares) versus fractional conversion for acetone condensation on TiO₂(a) at 363 K and 2.5 kPa acetone. The dashed and dotted lines represent trend curves.

**Scheme 2.** Elementary steps for aldol condensation of acetone on TiO₂(a).
irreversible elementary step. Thus, the rate of the kinetically-
relevant enolate formation step (Equation 1 [Eq. (1)]) is given by
the combined molar rates of formation of \( C_9 \), \( C_9^* \), and \( C_9^{**} \),
\[
  \tau_{\text{enol}} = \tau_1 = \tau_{C_9} + \tau_{C_9^*} + \tau_{C_9^{**}} \tag{1}
\]

Scheme 2 and Equation 1 provide the context used in what
follows to describe reactivity, selectivities, and deactivation
rates for acetone condensation reactions on TiO\(_2\)(a) in the
presence or absence of intrapore \( n \)-heptane condensation
within TiO\(_2\)(a) mesopores through the formalism of transition-
state theory.

**Acetone condensation rates and deactivation within liquid-free TiO\(_2\)(a) mesopores**

Enolate formation rates per exposed Ti–O site pair ([Ti–O]\(_0\)) =
3.7 nm\(^{-2}\), measured via propanoic acid titration during acetone
reactions) decreased with time-on-stream after initial contact with reactants at all acetone pressures (Figure 2). The slope of
such trends (Figure 2) gives the first-order deactivation constant
\((-k_d, Equation 2 [Eq. (2)]\)
\[
  \frac{r(t)}{r(t_0)} = e^{-k_d t} \tag{2}
\]
where \( r(t) \) and \( r(t_0) \) denote, respectively, the rates at any time \( t \)
and upon initial contact with reactants \( (t_0) \). The mean catalyst
life \((k_d^{-1})\) decreased with increasing acetone pressure, because
secondary C–C bond formation events become more prevalent
and lead to the formation of larger molecules that bind strongly
at Ti–O pairs.\(^{[35–36]}\)

Enolate formation rates extrapolated to the time of initial
contact with reactants reflect the properties of bare TiO\(_2\)(a)
surfaces before active sites are titrated by strongly-bound
products. Such initial rates are strictly proportional to acetone
pressure (Figure 3), consistent with the sole kinetic relevance
of prop-1-en-2-olate formation elementary steps (Step 1; Scheme 2) and with unoccupied Ti–O site pairs as the most
abundant surface species; enolate formation rates are then
given by Equation 3 [Eq. (3)]:
\[
  \frac{r_{\text{enol}}}{[\text{Ti–O}]_0} = k_{C_3^* (g)} P_{\text{acetone}} \tag{3}
\]
with [Ti–O]\(_0\) as the total concentration of exposed Ti–O site
pairs \((3.7 \text{ nm}^{-2}\)). This first-order rate constant, \( k_{C_3^* (g)} \)^{(*)}, denotes their value at conditions leading to gas-filled TiO\(_2\)(a)
holes in contrast to liquid-filled pores; \textit{vide infra}, reflects the
free energy of the prop-1-en-2-olate \((C_3^*)\) formation TS
referenced to those of a bare Ti–O site pair and gaseous acetone
reactants.

The stability of bound molecular species and transition
states species depends on outer sphere environments beyond
the point of binding, as in the case of voids of molecular
dimensions\(^{[37]}\) or a liquid phase;\(^{[29,30]}\) such interactions comple-

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**Figure 2.** Rates of enolate formation per exposed Ti–O site pair (3.7 nm\(^{-2}\))
versus time-on-stream for acetone condensation on TiO\(_2\)(a) at 363 K and
0.4 kPa (\(\blacktriangleleft\)), 0.7 kPa (\(\blacksquare\)), 1.4 kPa (\(\blacklozenge\)), and 2.5 kPa (\(\bullet\)) acetone. The solid lines
are lines of best fit obtained upon regression of data to Equation 2.

**Figure 3.** Rates of enolate formation per exposed Ti–O site pair (3.7 nm\(^{-2}\))
extrapolated to the time of initial contact of acetone reactants versus
acetone pressure on TiO\(_2\)(a) at 363 K. The solid line is the line of best fit
obtained upon linear regression of data to Equation 3; the slope,
\( k_{C_3^* (g)} = 0.14 \text{ (kPa Ti–O ks)}^{-1}\), is the first-order rate constant.
extent those conferred upon such species by direct binding at catalyst surfaces. The consequences of such interactions for reactivity are most evident when kinetically-relevant steps involve adsorption (entry) or desorption (exit) steps, because the bonds with the surface are incomplete at their respective transition states. These entry and exit steps are invariably exothermic and endothermic, respectively, leading to TS structures that occur either early or late along the reaction coordinate, thus exhibiting significant reactant or product character because they reside, in part, within the outer sphere environment; as a result, they sense outer sphere solvation effects by inorganic or organic moieties located beyond the binding point.

These outer sphere solvation effects are evident in previous work from the contrasting effects of liquids on rates of methylcyclohexene hydrogenation on Pt and Pd catalysts. Rates of methylcyclohexene hydrogenation on Pt are higher when a liquid is present because they reflect the rate of an entry step: the (dissociative) adsorption of H. The outer sphere environment stabilizes the early TS for this entry step, thus increasing turnover rates on Pt. In contrast, neither the presence nor the identity of the liquid solvent influences rates of methylcyclohexene hydrogenation on Pd because the kinetically-relevant step occurs neither early nor late along its reaction coordinate; it involves a bimolecular surface reaction between two Pd-bound intermediates. The TS for this step is predominantly stabilized by direct binding at the Pd surface: the inner sphere environment.

In the case of acetone condensation, the kinetically-relevant enolate formation is an entry step (Step 1; Scheme 2) and the desorption of the bound C$_2$ enolates formed as primary products (Step 3) allows the “exit” of such species before subsequent C–C bond formation steps, which form C$_6$ alkanones (Step 4) and deactivating residues in a single surface sojourn. Thus, rates of enolate formation, primary selectivities, and deactivation constants are expected to sense the presence of a surrounding liquid phase that can interact with the relevant entry and exit transition states. n-Heptane is used here as the liquid because of its inert character, high mutual solubility with acetone, and a vapor pressure at 300–400 K (7–218 kPa) that allows intrapore condensation at modest prevalent n-heptane pressures.

**Extent of intrapore n-heptane condensation within TiO$_2$(a) voids**

TiO$_2$(a) voids consist of interstices of non-uniform cross-section formed by the packing of non-porous TiO$_2$(a) crystallites; these voids fill with a liquid phase at pressures below the saturation point of a contacting gas phase through capillary effects. The fraction of the pore volume that becomes liquid-filled can be accurately assessed using Barrett-Joyner-Halenda (BJH) treatments, the accepted construct to describe multilayer formation and capillary condensation within nanometer-sized voids. The extent of pore filling depends on temperature, the pressure of the contacting gas, the molecular properties of the fluid, and the size of the voids. This fraction, or more precisely, in this case, the extent to which the active surface area becomes immersed within a liquid, determines the concomitant effects on rates, selectivities, and deactivation in acetone condensation on TiO$_2$(a). Here, N$_2$ uptakes at its normal boiling point (Figure S1a; Supporting Information (SI)) are used to determine the pore size distribution of TiO$_2$(a) (Figure S1b); this distribution is then used to estimate the fraction of surface area immersed within n-heptane liquids at each n-heptane pressure at reaction temperatures.

The shape of the measured N$_2$ isotherm at 77 K (Figure S1a) reflects the sequential formation of adsorbed layers and a bulk intrapore liquid phase as the relative pressure increases to its saturation point ($P/P_{sat} \geq 1$). BJH formalisms enable deconvolution of uptakes to distinguish between guest molecules involved in multilayer adsorption and those involved in capillary condensation, thus enabling, in turn, the determination of the distribution of (cylindrical) pore sizes (Figure S1b). The void size distribution can then be used to calculate equilibrium uptakes of any molecule at any temperature and pressure provided that the molecular properties of the fluid are known; the fidelity of this calculation relies on the adsorbate conforming to Langmuir idealizations, as expected here for the uptake of inert, non-polar n-heptane on TiO$_2$(a) at 363 K.

The calculated n-heptane uptakes at 363 K (Figure 4; filled symbols) together with the pore size distribution of TiO$_2$(a) (Figure S1b) can be used to estimate, through geometric

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Calculated n-heptane (n-C$_7$) uptakes on TiO$_2$(a) (175 m$^3$ g$^{-1}$) versus relative n-heptane pressure ($P/P_{sat}$) at 363 K. These n-C$_7$ uptakes were calculated from measured N$_2$ uptakes at 77 K (Figure S1a), the BJH pore size distribution of TiO$_2$(a) (Figure S1b), and n-heptane properties (molar volume of 1.54 x 10$^{-3}$ m$^3$ mol$^{-1}$ and surface tension of 0.0134 J m$^{-2}$). The filled circles show uptakes as a fraction of the total pore volume occupied by n-heptane fluids on the left ordinate, and the open squares show uptakes as a fraction of total surface area immersed within n-heptane liquids on the right ordinate. The dash-dotted and dotted lines are guides for the eye.
arguments based on cylindrical capillary models,29,30,31 the fraction of the TiO\(_2\) (a) surface area immersed within n-heptane liquids at each relative n-heptane pressure; Figure 4 (open symbols) shows how this fraction increases as the relative n-heptane pressure increases and the interstices form a liquid phase. In the next sections, the consequences of increased contact between the active TiO\(_2\) (a) surface and the intraporous non-polar liquid phase on rates, selectivities, and deactivation for acetone condensation reactions are described and interpreted to show how a solvating outer sphere environment preferentially stabilizes transition states that occur either “early” or “late” along their respective reaction coordinates.

Effects of intrapore n-heptane liquids on acetone condensation rates and deactivation

Figure 5 shows deactivation constants (\(k_d\), Eq. 2) determined from regression of rate versus time data to the functional form of Equation 2 [Eq. (2)] (details in Section S2; SI) for acetone condensation reactions in the absence (\(P/P_{\text{sat}}\)\(_{\text{C}_7}\) = 0) – and presence (\(P/P_{\text{sat}}\)\(_{\text{C}_7}\) > 0.1) of intrapore n-heptane liquids; acetone and its \(C_6\) and \(C_7\) condensation products cannot condense to any measurable extent within the anatase pores at the conditions of this study (363 K, 0–3 kPa acetone, <0.06 fractional acetone conversion) since the prevailing relative pressures are all smaller than 0.01. These \(k_d\) values monotonically decreased as n-heptane liquids increasingly filled TiO\(_2\) (a) voids (Figure 5). The mean catalyst life (\(k_d^{-1}\)) exceeds 120 ks when ~0.6 of the TiO\(_2\) (a) surfaces reside within liquid-filled voids. Such stable aldol condensation rates were previously attained only through bifunctional strategies using H\(_2\) co-reactants to scavenge unsaturated products on a physically-mixed Cu-based hydrogenation function.\(^{14,25}\) Intrapore non-polar liquids inhibit secondary C–C bond formation events and subsequent chain growth, not through chemical reactions that saturate C–O bonds in products (and reactants), but by stabilizing the TS for desorption of primary products (Step 3; Scheme 2) preferentially over those that form C–C bonds (as shown below in the context of selectivity). Such preferential stabilization of the late desorption TS that mediates an exit step is reminiscent of the effects of intrapore liquids on deactivation and selectivity for alkene dimerization on Ni-exchanged aluminosilicates.\(^{29,30}\)

Enolate formation rates remained strictly proportional to acetone pressure as TiO\(_2\) (a) voids filled with liquid n-heptane (Figure 6), consistent with the mechanistic conclusions for reactions in gas-filled voids (vide supra); the sole kinetically-relevant step is still the cleavage of an \(\alpha\)-C–H bond within acetone for \(C_7^\alpha\) formation (Step 1; Scheme 2) and the most abundant surface intermediates are still vacant Ti–O site pairs. Enolate formation rates in the presence of intrapore n-heptane liquids are then given by Equation 4 [Eq. (4)]:

\[
\frac{d[\text{enolate}]}{dt} = k_d \times \frac{d[\text{Ti–O}]}{dt}
\]

where \(k_d\) is the deactivation constant for acetone reactions on TiO\(_2\) (a) at 363 K in the absence (gray circles, \(P/P_{\text{sat}}\)\(_{\text{C}_7}\) = 0) and presence (black diamonds, \(P/P_{\text{sat}}\)\(_{\text{C}_7}\) = 0.5) of intrapore liquid n-heptane; relative n-heptane pressure of 0.5 corresponds to 66% of the total TiO\(_2\) (a) surface area immersed within liquid n-heptane (Figure 4). The gray and black solid lines are the lines of best fit obtained upon linear regression of data to Equations 3 and 4, respectively.

Figure 5. Deactivation constants (Eq. 2) versus fraction of TiO\(_2\) (a) surface area immersed in intrapore n-heptane liquids (Figure 4) for acetone condensation on TiO\(_2\) (a) at 363 K, 2.5 kPa acetone, and 0–0.63 relative n-heptane pressure (\(P/P_{\text{sat}}\)). The dashed line is a guide for the eye.

Figure 6. Rates of enolate formation per exposed Ti–O site pair (3.7 nm\(^2\)) for acetone reactions on TiO\(_2\) (a) at 363 K in the absence (gray circles, \(P/P_{\text{sat}}\)\(_{\text{C}_7}\) = 0) and presence (black diamonds, \(P/P_{\text{sat}}\)\(_{\text{C}_7}\) = 0.5) of intrapore liquid n-heptane; relative n-heptane pressure of 0.5 corresponds to 66% of the total TiO\(_2\) (a) surface area immersed within liquid n-heptane (Figure 4). The gray and black solid lines are the lines of best fit obtained upon linear regression of data to Equations 3 and 4, respectively.
First-order rate constants for C₃* formation (k₃"(g); \( ^* \) denotes liquid-filled TiO₂(a) pores) increased monotonically as voids filled with liquid with increasing n-heptane pressure. The data in Figure 7 (filled symbols, left ordinate) show the ratio of first-order rate constants for acetone condensation in the presence and absence of intrapore n-heptane liquids (\( \chi \)) (Equation 5 [Eq. (5)]):

\[
\chi = \frac{k_{3*}(g)}{k_{3*}(l)}
\]  

The tenets of transition state theory invoke a quasi-equilibrium between an activated complex and the reactants in an elementary step, thus requiring that the sum of chemical potentials (\( \mu_i \)) for each species i times their stoichiometric coefficients (\( \nu_i \)) be zero. The kinetically-relevant step (Step 1; Scheme 2) in acetone condensation within liquid-filled TiO₂ voids involves the reaction of dissolved acetone (C₃(l)) at a Ti–O site pair on TiO₂(a) surfaces in contact with liquid n-heptane (\( ^*l \)) to form a bound prop-1-en-2-olate also in contact with the liquid (C₃^"(l)) (Equation 6 [Eq. (6)]),

\[
C_3(l) + ^*l \rightleftharpoons TS_{enal}(l) \rightarrow C_3^*l
\]

where TS_{enal}(l) represents the TS for the formation of the C₃* enolate within liquid-filled voids. The equilibrated nature of the TS dictates that (Equation 7 [Eq. (7)]):

\[
\mu_{TS_{enal}}(l) - \mu_{C_3^*}(l) = 0
\]

For liquid-filled voids. In the absence of liquids, the kinetically-relevant step is (Equation 8 [Eq. (8)]):

\[
C_3(g) + ^*g \rightleftharpoons TS_{enal}(g) \rightarrow C_3^*g
\]

where C₃(g) represents acetone in the gas phase and \(^*g\), C₃^*(g), and TS_{enal}(g) are the bare Ti–O site pair, bound prop-1-en-2-olate, and TS for C₃* formation, respectively, within TiO₂(a) voids without a liquid phase, thus requiring that (Equation 9 [Eq. (9)]):

\[
\mu_{TS_{enal}}(g) - \mu_{C_3^*}(g) = 0
\]

Equations 7 and 9 can be combined with that for vapor-liquid equilibrium between the extrapore gas phase and the intrapore liquids (Equation 10 [Eq. (10)]):

\[
C_3(g) \rightleftharpoons C_3(l)
\]

and the consequent equality of their chemical potentials (Equation 11 [Eq. (11)]):

\[
\mu_i(l) = \mu_i(g)
\]

to give (Equation 12 [Eq. (12)]):

\[
\left( \mu_{TS_{enal}}(l) - \mu_{TS_{enal}(g)} \right) - \left( \mu_{C_3^*}(l) - \mu_{C_3^*(g)} \right) = 0
\]

The rate of an elementary step is proportional to the number of transition states. Consequently, the ratio of enolate formation rates with \( r_{enal(l)} \), Eq. 4) and without \( r_{enal(g)} \), Eq. 3) the presence of a liquid (Equation 13 [Eq. (13)]):

\[
\frac{r_{enal(l)}}{r_{enal(g)}} = \frac{TS_{enal}(l)}{TS_{enal}(g)} = \chi
\]

equals the ratio of first-order rate constants for enolate formation, defined as \( \chi \) in Equation 5. Equation 13 can be expressed in terms of free energy differences between transition states (TS_{enal}) and bare Ti–O site pairs (\(^*l\)) by:

(i) expressing the chemical potential of each species i in Equation 12 as [Eq. (14)]
\[ \mu_i = \mu^*_i + RT \ln \frac{\alpha_i}{\alpha'_i} \]  

(14)

where \( \alpha_i \) is the activity of species \( i \) and \( \alpha'_i \) and \( \mu^*_i \) are the activity and the chemical potential of species \( i \) at some specified standard state;

(ii) choosing identical standard states for \( T \Delta S_{\text{mol}}(T) \) and \( T \Delta S_{\text{mol}}(g) \) and identical standard states for \( T \Delta S_i(T) \) and \( T \Delta S_i(g) \) such that the \( \alpha_i \) and \( \mu_i^* \) terms for \( T \Delta S_{\text{mol}} \) and \( T \Delta S \) cancel upon incorporating Equation 14 into Equation 12;

(iii) denoting \( a_i \) as the product of an activity coefficient \( (\gamma_i) \) and a concentration \( \left( \frac{[i]}{[i]} \right) \) [Eq. (15)]

\[ a_i = \gamma_i \left[ \frac{[i]}{[i]} \right] \]  

(15)

and

(iv) taking bare Ti–O site pairs as the most abundant surface intermediates, as shown by the forms of the rate equations with (Eq. 4) and without (Eq. 3) intrapore liquids, such that [Eq. (16)]

\[ \left[ \frac{\Delta S_i(T)}{\Delta S_i(g)} \right] = \left[ \frac{T - O}{O} \right] \]  

(16)

Equations 12–16 then lead to an expression for \( \chi \) [Eq. (17)]

\[ \chi = \exp \left( \frac{\Delta \Delta G_{\text{C}}^*}{RT} \right) \]  

(17)

in terms of \( \Delta \Delta G_{\text{C}}^* \), which represents a difference in excess Gibbs free energies, defined for a given species \( i \) (\( \bar{G}_i \)) as (Equation 18 [Eq. (18)])

\[ \bar{G}_i = RT \ln \gamma_i \]  

(18)

\( \Delta \Delta G_{\text{C}}^* \) values reflect the difference in \( \bar{G}_i \) values for \( C_i^* \) formation transition states with and without a liquid phase (\( G_{\text{mol}}(T) - G_{\text{mol}}(g) \)) and that for Ti–O site pairs with and without a liquid phase (\( G_{\text{C}}(T) - G_{\text{C}}(g) \)) (Equation 19 [Eq. (19)]),

\[ \Delta \Delta G_{\text{C}}^* = \left( G_{\text{mol}}(T) - G_{\text{mol}}(g) \right) - \left( G_{\text{C}}(T) - G_{\text{C}}(g) \right) \]  

(19)

These \( \chi \) values increase and \( \Delta \Delta G_{\text{C}}^* \) becomes more negative as TiO\(_2\)(a) voids become increasingly filled with liquid with increasing \( n \)-heptane pressure (Figure 7). These trends indicate that a non-polar liquid stabilizes the \( C_i^* \) formation TS to a greater extent than it stabilizes an unoccupied Ti–O site pair and that a greater fraction of the TiO\(_2\) surface benefits from such solvation effects as liquids increasingly fill its void space.

These outer sphere solvation effects influence rates because an entry step (Step 1; Scheme 2) limits aldol condensation rates. This step involves a TS that retains some reactant-like character as it forms along the reaction coordinate; thus, it is able to sense the presence and nature of the contacting fluid phase. These significant effects of non-polar intrapore liquids on acetone condensation turnover rates on TiO\(_2\)(a) stand in contrast with the much weaker effects for ethene, propene, and butene dimerization rates observed on Ni-exchanged MCM-41, in reactions that are limited by kinetically-relevant C–C bond formation steps.\(^{29,30}\) These C–C coupling steps involve bond reactants, transition states, and products that are predominantly stabilized by direct interactions with (Ni–OH\(^+\)) active sites and to a lesser extent by the contacting fluid phase. In the case of acetone condensation on TiO\(_2\)(a), the C–C bond formation steps (Steps 2, 4, and 5) that occur after the kinetically-relevant entry step (Step 1) are also expected to be influenced less strongly by the nature of the outer sphere environment because, as in the case of C–C coupling on Ni-MCM-41, such steps involve bound species as reactants (\( C_i^* \) in Steps 2 and 5 or \( C_i^* \) in Step 4) and products (\( C_i^* \), (\( C_i^* \)), and \( C^* \) in Steps 2, 4, and 5, respectively). The transition states involved in these C–C bond formation steps do not exhibit significant reactant or product character, especially in comparison with those for entry (enolate formation) or exit (product desorption) steps that occur early or late along their respective reaction coordinates.

The bound alkene dimers formed upon kinetically-relevant C–C coupling steps on Ni-MCM-41 desorb in endothermic steps through late product-like transition states; such TS structures detect the nature of the contacting phase that accepts such species upon desorption, thus allowing them to sense the solvating properties of the intrapore phase. Consequently, the presence of a liquid makes the desorption of bound dimers favored over their sequential C–C coupling reactions, thus favoring the desorption of the initial product formed before additional C–C coupling events that lead to strongly-bound larger alkene oligomers. Consistent with such interpretations, intrapore liquids favor higher dimer selectivities and suppress deactivation to nearly undetectable extents. Similar effects of an intrapore non-polar liquid phase (\( n \)-heptane) on selectivity are observed here for acetone condensation on TiO\(_2\)(a) together with slower deactivation (Figure 5). These trends also reflect a preferential enhancement of desorption rates of primary \( C_i^* \) enolate products (Step 3; Scheme 2) over those of subsequent C–C bond formation events during the initial reactive surface sojourn. These effects of outer sphere environments on the relative rates of exit steps and C–C bond formation events also influence selectivities to primary dimers in acetone condensation at Lewis acid-base pairs on TiO\(_2\)(a), as shown in the next section.

**Effects of intrapore \( n \)-heptane liquids on acetone condensation selectivities**

This section examines the effects of intrapore \( n \)-heptane liquids on selectivity and deactivation rates in the context of the stability of transition states for desorption and subsequent reactions of bound \( C_i \) products.

Figure 8 shows the selectivity to \( C_6 \) products (\( S_{C_6} \), Eq. 30) at different levels of acetone conversion (\( X \)), varied by changes in
residence time or extent of deactivation, with \((P/P_{\text{water}})_{C_6} = 0.5\); filled symbols) and without \((P/P_{\text{water}})_{C_6} = 0\); open symbols) intrapore liquids on TiO\(_2\)(a) at 0.5 kPa (triangles), 1.5 kPa (squares), and 2.5 kPa acetone (circles). \(C_6\) selectivities extrapolated to zero conversion reflect the extent to which \(C_6\) enolates formed in a primary \(C-C\) coupling event desorb before forming \(C_9\) and larger chains. These asymptotic selectivities are less than one without intrapore liquids and decrease with increasing acetone pressure, indicative of rates of \(C_6^*\) reactions with acetone (to form \(C_7^*\); Step 4; Scheme 2) that increase relative to those of \(C_6^*\) desorption (Step 3) as acetone pressures increase. The presence of intrapore liquids leads to asymptotic \(C_6\) selectivities near unity at all acetone pressures, consistent with the prevalence of longer chains as reactants in such events when the magnitude of the ratio of quadratic term to \(\Omega\) (details in Section S3.4; SI). Equation 20 accurately describes such systems when the magnitude of the ratio of the quadratic term to \(X^2\) is much smaller than unity. This ratio (which is directly proportional to both \(X\) and \(\Phi\); details in Section S3.5; SI) is calculated to be between 0.02 and 0.2 when using the best-fit \(\Omega\) and \(\Phi\) values obtained upon regression of data in Figure 8 to the functional form of Equation 20 (Table 1). These small values for estimates of the absolute relative errors combined with the absence of any systematic deviation from linearity in the \(S_{C_6}\) versus \(X\) to form \(C_9^*\) molecules. \(C_6\) selectivities were lower at higher acetone pressures for all conversions (Figure 8; open symbols). These trends reflect higher rates of \(C-C\) bond formation events and the prevalence of longer chains as reactants in such events as acetone pressures and conversions increase. The slopes of these selectivity-conversion trends \(S_{C_6}\) (Figure 8) reflect the extent to which \(C_6\) enolates, formed in the sole kinetically-relevant step, are consumed by acetone (Step 2) to ultimately form primary products \(C_6\) and \(C_7^*\) versus the extent to which they are consumed by \(C_9\) enolates (Step 5) to ultimately form secondary products \(C_9^*\).

The rate constants for Steps 2–5 (Scheme 2) account for the slope and intercept of the selectivities \(S_{C_6}(X)\) in Figure 8 in a manner that becomes evident from plug-flow reactor descriptions of the rates of primary and secondary events along the bed. The resulting coupled differential equations account for the rates of \(C_6 \rightarrow C_9^*\), and \(C_9^*\) formation and include rate equations derived from the elementary steps in Scheme 2 (details in Section S3.1–3.3; SI).

Table 1 reports \(\Omega\) and \(\Phi\) parameters for the best-fit models (Equations 21 and 22) for acetone conversion \(X\) when \(P_{\text{acetone}}\) is increased. The linear trends of \(S_{C_6}\) with acetone conversion \(X\) (Figure 8) are consistent with the predictions of these analysis protocols when only terms linear in \(X\) are retained (Equation 20 [Eq. (20)]):

\[
S_{C_6}(X) = \frac{1}{1 + \frac{3}{2} \Phi} \left( 1 + \Omega \frac{1}{1 + \Omega} X \right) \tag{20}
\]

The \(\Omega\) and \(\Phi\) terms in Equation 20 represent dimensionless groups that combine kinetic parameters for Steps 2–5 in Scheme 2 [Eq. (21) and (22)].

\[
\Omega = \frac{\bar{\Phi} P_{\text{acetone}}}{k_{C-C} P_{\text{acetone}}} \quad \text{and} \quad \Phi = \frac{k_{C-C}}{k_{C-C}} \tag{21} \quad \Phi = \frac{k_{C-C}}{k_{C-C}} \tag{22}
\]

These equations are derived using an asymptotic treatment of the net rates of \(C_6\) formation and \(C_6\) consumption (details in Section S3.4; SI). Equation 20 accurately describes such systems when the magnitude of the ratio of the quadratic term to \(X^2\) is much smaller than unity. This ratio (which is directly proportional to both \(X\) and \(\Phi\); details in Section S3.5; SI) is calculated to be between 0.02 and 0.2 when using the best-fit \(\Omega\) and \(\Phi\) values obtained upon regression of data in Figure 8 to the functional form of Equation 20 (Table 1). These small values for estimates of the absolute relative errors combined with the absence of any systematic deviation from linearity in the \(S_{C_6}\) versus \(X\)
trends (Figure 8) show that the asymptotic linear expansion in Equation 20 is appropriate to accurately describe the data.

The \( \Omega \) term accounts for the asymptotic \( C_6 \) selectivity \((X \to 0)\) and is equal to the ratio of the rate of \( C_6^* \) enolates reacting with acetone molecules to ultimately form \( C_6 \) (Step 4; Scheme 2) and desorbing to form \( C_6 \) (Step 3); the \( \Omega \) term in Equation 21 is the ratio of the respective rate constants: \( k_{\text{C-C}} \) (Step 4) and \( k_{\text{des}} \) (Step 3). The \( \Phi \) term accounts for the selectivity to secondary \( C_6'' \) products; it contains kinetic parameters for reactions of \( C_6^* \) enolates derived from acetone with previously desorbed \( C_6 \) alkanones to form \( C_6'' \) products \( (k_{\text{C-C}} \cdot \text{Step 5}) \) or with acetone to form \( C_6^* \) species \((k_{\text{C-C}} \cdot \text{Step 2})\) that ultimately desorb as \( C_6 \) or \( C_6' \) primary products.

The solid and dashed lines in Figure 8 are derived from a regression of the selectivity data with or without intrapore liquids, respectively, to the form Equation 20, and the corresponding values of \( \Omega \) and \( \Phi \) are shown in Table 1. The \( \Omega \) value is \((3.5 \pm 0.8) \times 10^{-3}\) kPa \(^{-1}\) when intrapore liquids are present \((P/ P_{\text{atm}} C_6 = 0.5)\); this small \( \Omega \) value renders the denominator of the intercept in Equation 20 approximately equal to unity, consistent with asymptotic \( C_6 \) selectivities near unity (Figure 8). In contrast, the \( \Omega \) value is much larger \((1.5 \pm 0.2) \times 10^{-2}\) kPa \(^{-1}\) in the absence of a liquid phase, consistent with the formation of \( C_6' \) primary products during initial surface sojourns in gas-filled TiO\(_2\) (a) pores. The \( \Phi \) values, unlike the disparate \( \Omega \) values, are similar for reactions with \((2.6 \pm 0.4)\) and without \((3.3 \pm 1.1)\) intrapore \( n \)-heptane liquids, suggesting that the outer sphere environment affects similarly the transition states mediating the initial \( C-C \) bond formation steps in both the self-condensation of acetone (Step 2; Scheme 2) and the cross-condensation of acetone with \( C_6 \) alkanones (Step 5).

As for \( C_6^* \) formation rate constants \((v\text{ide supra})\), transition state formalisms can be used to interpret the effects of a liquid phase on \( \Omega \) and \( \Phi \) in terms of the extent to which the relevant transition states are able to sense such outer sphere environments as a result of “lateness”.

The \( \Omega \) term is equal to the ratio of the rate of the elementary step for \( C_6^* \) consumption by acetone \((r_{\text{C-C}} \cdot \text{Step 4}; \text{Scheme 2})\) to that by desorption \((r_{\text{des}} \cdot \text{Step 3})\), which, in turn, corresponds to the ratio of concentrations of the respective transition states (Equation 23 [Eq. (23)]):

\[
\Omega = \frac{r_{\text{C-C}}}{r_{\text{des}}} = \frac{[TS_{\text{C-C}}]}{[TS_{\text{des}}]} \tag{23}
\]

where \( TS_{\text{C-C}} \) and \( TS_{\text{des}} \) are the transition states for Steps 4 and 3 (Scheme 2), respectively. The ratio of \( \Omega \) values for reactions with and without \( n \)-heptane liquids is then given by (Equation 24 [Eq. (24)]):

\[
\frac{\Omega_{(i)}}{\Omega_{(g)}} = \frac{[TS_{\text{C-C}}(i)]}{[TS_{\text{des}}(i)]} / \frac{[TS_{\text{C-C}}(g)]}{[TS_{\text{des}}(g)]} \tag{24}
\]

This ratio depends on differences in excess Gibbs free energies \((\Delta \Delta G^f)\) (Equation 25 [Eq. (25)]):

\[
\Omega_{(i)} = \exp \left( -\frac{\Delta \Delta G^f_{(i)}}{RT} \right) \tag{25}
\]

for the formation of transition states for \( C-C \) coupling to form \( C_6' \) (Step 4) \((G_{\text{TS}_{\text{C-C}}(i)} - G_{\text{TS}_{\text{C-C}}(g)})\) and \( C_6'' \) desorption to form \( C_6 \) (Step 3) \((G_{\text{TS}_{\text{des}}(i)} - G_{\text{TS}_{\text{des}}(g)})\) (Equation 26 [Eq. (26)]),

\[
\Delta \Delta G^f_{(i)} = \left( G_{\text{TS}_{\text{C-C}}(i)} - G_{\text{TS}_{\text{C-C}}(g)} \right) - \left( G_{\text{TS}_{\text{des}}(i)} - G_{\text{TS}_{\text{des}}(g)} \right) \tag{26}
\]

The best-fit \( \Phi \) values in Table 1 show that \( \Omega_{(i)} / \Omega_{(g)} \) is much smaller than unity \((2.3 \pm 0.6) \times 10^{-5}\) for \( n \)-heptane pressures leading to \( \sim 70\% \) of the TiO\(_2\) (a) surfaces immersed within \( n \)-heptane liquids; this corresponds to a \( \Delta \Delta G^f \) value of \(+ (18 \pm 5) \) kJ mol\(^{-1}\).

The estimated value of \( \Delta \Delta G^f \) being positive indicates that non-polar \( n \)-heptane liquids preferentially stabilize the TS for \( C_6^* \) desorption \((G_{\text{TS}_{\text{des}}(i)} - G_{\text{TS}_{\text{des}}(g)})\) to a much greater extent than that for \( C_6^* \)-acetone \( C-C \) coupling reactions \((G_{\text{TS}_{\text{C-C}}(i)} - G_{\text{TS}_{\text{C-C}}(g)})\); Step 4). This reflects, in turn, a desorption TS that occurs late along the endothermic reaction coordinate and senses the outer sphere environment to a greater extent than the TS for the reaction between a bound \( C_6^* \) and acetone, which is preferentially stabilized by coordination at Ti–O site pairs. These preferential solvation effects on selectivity also underpin the observed effects in intrapore liquids on deactivation rates (Figure 5) by enhancing desorption rates not only of \( C_6^* \) species but also of larger oligomers, thus inhibiting their further growth.

The rates of \( C_6^* \) reactions with \( C_6 \) alkanones to form \( C_6'' \) \((r_{\text{C-C}} \cdot \text{Step 5}; \text{Scheme 2})\) and with acetone to form \( C_6^* \) or \( C_6' \) \((r_{\text{C-C}} \cdot \text{Step 2})\) give an expression analogous to Equation 25 but for the parameter \( \Phi \) (Equation 27 [Eq. (27)]):

\[
\frac{\Phi_{(i)}}{\Phi_{(g)}} = \exp \left( -\frac{\Delta \Delta G^f_{(i)}}{RT} \right) \tag{27}
\]

where \( \Delta \Delta G^f \) is the difference in excess Gibbs free energies for the formation of the TS for Step 5 \((G_{\text{TS}_{\text{C-C}}(i)} - G_{\text{TS}_{\text{C-C}}(g)})\) and Step 2 \((G_{\text{TS}_{\text{des}}(i)} - G_{\text{TS}_{\text{des}}(g)})\) (Equation 28 [Eq. (28)]):
The stability and reactivity conferred by such a liquid phase occurrence of the rare events that form stranded larger unsaturated alkanones enabled by the presence of $H_2$ and a physically-mixed Cu function$^{[14,27]}$ at these higher temperatures, desorption becomes quasi-equilibrated, thus allowing the conversion of these initial products to less reactive ones at a remote hydrogenation function. The effects of intrapore $n$-heptane liquids on turnover rates, deactivation rates, and primary selectivities reported here for acetone condensation on TiO$_2$(a) share mechanistic underpinnings with those observed previously for alkene dimerization on Ni-exchanged aluminosilicates$^{[29,30]}$. These solvation effects reflect, in both cases, the preferential stabilization of the late product-like transition state. The distortions required to benefit from outer sphere stabilization incur a much lower enthalpic penalty in the latter that titrate TiO$_2$-bound C$_3$ enolates, formed upon initial C–C bond formation between acetone and TiO$_2$-bound prop-1-en-2-olate, over the transition states mediating subsequent C–C bond formation steps that lead to the formation of strongly bound C$_9$ inhibitors or unselective primary C$_6$ alkanone products. Such protection against deactivation was achieved previously only through bifunctional strategies that terminate aldol condensation cascades by hydrogenating alkenone products on a physically mixed Cu function prior to subsequent C–C bond formation events$^{[14,27]}$. The consequences of non-polar intrapore liquids shown here for acetone condensation on TiO$_2$ demonstrate that the versatility of this approach to affect deactivation rates and selectivity extends beyond alkene dimerization on Ni-exchanged aluminosilicates$^{[29,30]}$ suggesting apposite this approach to other complex reaction networks that suffer from low rates, short catalyst lifetimes, and poor selectivity or those in which rapid deactivation hinders mechanistic inquiries.

**Experimental Methods**

**Catalyst treatment and characterization**

The anatase phase of TiO$_2$ (TiO$_2$(a)) was chosen for study because aldol condensation turnover rates are much higher than on its rutile form, a consequence of the formation of stable proton adducts on the latter that titrate Ti–O pairs.$^{[14]}$ TiO$_2$(a) powders (Alfa Aesar, 99.7% ; 175 m$^2$g$^{-1}$) were treated in flowing air (1.7 cm$^3$g$^{-1}$ s$^{-1}$) at 673 K (0.17 K s$^{-1}$) for 3 h. TiO$_2$(a) aggregates (180–250 μm) were prepared by pressing, crushing, and sieving fine TiO$_2$(a) powders. $N_2$ physisorption uptakes were measured at its normal boiling point (after evacuating samples by heating to 573 K at 0.083 K s$^{-1}$ and holding for 3 h) using a volumetric adsorption unit (Micromeritics, ASAP 2020). The mathematical formalisms used to determine pore size distributions and $n$-heptane uptakes at 363 K from measured $N_2$ uptakes at 77 K are described in Results and Discussion.

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**Conclusions**

$n$-Heptane liquids formed within the interstices between exposed anatase surfaces accelerate turnover rates, attenuate deactivation, and increase selectivity to primary products during acetone condensation on Ti–O Lewis acid-base site pairs. These solvation effects are all consequences of the preferential stabilization afforded by the dense non-polar fluid phase to the transition states that mediate entry and exit steps within the closed and open elementary step sequences for the formation of alkanone products and deactivating residues. First-order rate constants for acetone condensation reflect the free energy of formation of the transition state mediating the entry step of dissociative adsorption of a free acetone molecule onto a bare Ti–O site pair to form a bound prop-1-en-2-olate. The intraporous $n$-heptane liquids solvate this early reactant-like transition state via stabilizing van der Waals contacts between solvent molecules and the organic moieties at the transition state of this entry step, thereby accelerating rates of acetone condensation. These liquids also effect decreased deactivation rates and increased selectivities to primary C$_6$ products by stabilizing preferentially the late product-like transition state mediating the exit step of desorption of TiO$_2$-bound C$_9$ enolates, formed upon initial C–C bond formation between acetone and TiO$_2$-bound prop-1-en-2-olate, over the transition states mediating subsequent C–C bond formation steps that lead to the formation of strongly bound C$_9$ inhibitors or unselective primary C$_6$ alkanone products. Such protection against deactivation was achieved previously only through bifunctional strategies that terminate aldol condensation cascades by hydrogenating alkenone products on a physically mixed Cu function prior to subsequent C–C bond formation events.$^{[14,27]}$ The consequences of non-polar intraporal liquids shown here for acetone condensation on TiO$_2$ demonstrate that the versatility of this approach to affect deactivation rates and selectivity extends beyond alkene dimerization on Ni-exchanged aluminosilicates$^{[29,30]}$ suggesting apposite this approach to other complex reaction networks that suffer from low rates, short catalyst lifetimes, and poor selectivity or those in which rapid deactivation hinders mechanistic inquiries.

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Catalytic rate measurements

Titanium dioxide (TiO$_2$) aggregates were held on a porous quartz disc within a tubular quartz reactor (7.0 mm i.d.) with plug-flow hydrodynamics. The reactor was placed within a three-zone resistively-heated furnace (Applied Test Systems Inc.); temperatures were controlled using electronic temperature controllers (Watlow) and measured using a K-type thermocouple (Omega) affixed to the outer wall of the quartz reactor near the axial bed midpoint. Catalysts were treated in flowing He (5.6 cm$^3$ g$^{-1} \cdot$ h$^{-1}$; Praxair, 99.999%) by heating to 543 K (at 0.083 K s$^{-1}$) and holding for 3 h before cooling to reaction temperatures. Helium flow rates were metered using mass flow controllers (Porter, Inc.). Acetone (Sigma-Aldrich, ≥ 99.9%) and n-heptane (Sigma-Aldrich, ≥ 99%) were introduced as liquids using syringe pumps (KD Scientific) and vaporized into heated transfer lines (≥ 403 K). The identity and concentration of reactants and products in reactor inlet and effluent streams were determined using a gas chromatograph (Agilent 6890 A) with a methyl silicone column (Agilent HP-1, 50 m × 0.32 mm × 1.05 μm) and a flame ionization detector. Retention times and response factors were determined from acetone (Sigma-Aldrich, ≥ 99.9%), mesityl oxide (Spectrum Chemicals, 98%), 2,6-dimethyl-hepta-2,5-dien-4-one (Sigma-Aldrich, 95%), 4,6-dimethyl-hepta-3,5-dien-2-one (Sigma-Aldrich, 95%), and n-heptane (Sigma-Aldrich, ≥ 99%) standards.

Acetone reactions on TiO$_2$ aggregates were observed at conditions given by six ($C_2H_2O$) and nine ($C_3H_3O$) carbon atoms as products. The C$_n$ alkane isomers are mesityl oxide (4-methylpent-3-en-2-one) and isosmethyl oxide (4-methylpent-4-en-2-one), and the C$_n$ alkane isomers comprise dienes with C=C double bonds at various positions along five- and seven-carbon backbones (Scheme 1). Thermodynamic data[18,38] were used to determine approach to equilibrium values ($\eta_{\text{eq}}$) for acetone conversion to primary products, defined here as Equation 29 (Eq. [29]):

$$\eta_{\text{eq}} = \frac{P_{\text{eq}, 0}}{\sum_{n=2}^{3} P_{\text{eq}, \text{n}}^{2}}$$

where $P_{\text{eq}, n}$ and $P_{\text{eq}, \text{0}}$ are the pressures of acetone, C$_n$ (n = 2) or C$_3$ (n = 3) acetone condensation products, and water, respectively (in units of bar), and $K_{\text{eq}}$ is the equilibrium constant for acetone condensation to the $f^0$ isomer of aldol condensation products with 3n C-atoms. These $\eta_{\text{eq}}$ values were smaller than $10^{-2}$ at all conditions and for all C$_n$ and C$_3$ product isomers, indicating that measured rates accurately reflect the forward rates of each reaction.

Acetone condensation rates are reported based on the number of Ti–O Lewis acid-base site pairs, determined by titration of such pairs with propanoic acid during acetone reactions (3.7 Ti–O centers mm$^{-2}$).[18] Selectivities to C$_n$ and C$_3$ alkanes ($S_{\text{air}, n}$, n = 2 or 3) are reported on a carbon basis (Equation 30 [Eq. (30)]):

$$S_{\text{air}, n} = \frac{\sum_{n=2}^{3} \sum_{\text{isomers}} (n \cdot f_{\text{air}, \text{n}}^{\text{c}})}{\sum_{n=2}^{3} \sum_{\text{isomers}} (n \cdot f_{\text{air}, \text{n}}^{\text{c}})}$$

where $f_{\text{air}, \text{n}}^{\text{c}}$ is the molar rate of formation of the $f^0$ isomer of alkane product with 3n C-atoms. Regressions of rate and selectivity data to Equations 2, 3, 4, and 20 (vide supra) were performed using known and established methods implemented either in MATLAB or Athena Visual Studio[14] codes.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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