Entropy-Driven High Reactivity of Formaldehyde in Nucleophilic Attack by Enolates on Oxide Surfaces

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ABSTRACT: CH₃OH dehydrogenation on a metal function occurs in tandem with C−C coupling of HCHO with enolates derived from alkanals or alkanones on acid−base pairs at anatase TiO₂ surfaces with very high specificity for nucleophilic attack by enolates on HCHO over larger carbonyl molecules. The measured rate constants for enolate coupling with HCHO are >10³-fold larger than for its coupling with acetone. Free energies derived from theoretical treatments of reactions between C₂−C₄ bound enolates and carbonyls show that such specificity for nucleophilic attack on HCHO reflects smaller entropy losses upon formation of the transition state (TS), instead of enthalpic effects caused by weaker steric effects or the stronger electrophilic character of HCHO compared with larger carbonyls. The easier steric access and higher electrophilicity of the carbonyl C atom of HCHO in C−C coupling with enolates are compensated by a later TS and by stronger van der Waals contacts for the corresponding reactions of the larger carbonyls. The preeminence of entropic effects over enthalpic stabilization reflects the greater structural organization imposed by surfaces on TS structures compared with similar reactions and structures in gaseous or liquid media. Such organization imposes significant entropic penalties that become least consequential for smaller electrophiles, thus enabling highly selective routes for sequential addition of C₁ groups at nucleophilic C atoms in co-reactants using HCHO, whether added or formed in situ from CH₃OH, as the monomer source. Such entropy-driven specificity is therefore a unique and unrecognized characteristic of reactions catalyzed by surfaces.

1. INTRODUCTION

Formaldehyde (HCHO) is much more reactive than other alkanals or alkanones in C−C coupling reactions with nucleophiles, such as enolates in aldol condensation¹−⁴ or alkenes in Prins condensation,⁵ making it a monomer of choice in backbone lengthening strategies.⁶−⁸ Weaker steric hindrance at C＝O centers³⁹ and the more electrophilic character of the carbonyl C atom of HCHO in C−C coupling with enolates are compensated by a later TS and by stronger van der Waals contacts for the corresponding reactions of the larger carbonyls. The preeminence of entropic effects over enthalpic stabilization reflects the greater structural organization imposed by surfaces on TS structures compared with similar reactions and structures in gaseous or liquid media. Such organization imposes significant entropic penalties that become least consequential for smaller electrophiles, thus enabling highly selective routes for sequential addition of C₁ groups at nucleophilic C atoms in co-reactants using HCHO, whether added or formed in situ from CH₃OH, as the monomer source. Such entropy-driven specificity is therefore a unique and unrecognized characteristic of reactions catalyzed by surfaces.

Scheme 1. Self Condensation and Cross Condensation Pathways for Cₙ Carbonyl Compounds (n = Number of C-Atoms) and HCHO on Anatase TiO₂ (with Ag/SiO₂ Co-Catalysts and Added H₂)
Additionally, HCHO can be formed in situ via dehydrogenation of CH₃OH on metal catalysts (Cu₆, Ag₁₅) present as mixtures with TiO₂ or ZrO₂, thus enabling the use of CH₃OH here as a C₁ monomer in carbon chain lengthening reactions that is less costly and easier-to-handle than HCHO.

Here, we combine kinetic and theoretical methods to examine the C–C coupling reactions of C₂–C₆ enolates with HCHO and with larger carbonyl reactants on anatase TiO₂ (TiO₂(a)) using Ag/SiO₂ as co-catalysts in experiments in order to convert CH₃OH to HCHO. The effects of alkyl substituents in carbonyls on C–C bond formation rates and on the enthalpy and entropy components of activation free energy barriers for self-condensation and C–C coupling with HCHO (Scheme 1) are assessed using state-of-the-art theoretical treatments, with acetone-HCHO reactions used as the experimental benchmark.

The uniquely high reactivity of HCHO (relative to larger alkanals or alkanones) with a given enolate does not reflect a greater enthalpic stabilization of transition states (TS), typically expected for HCHO, which is the stronger electrophile and has a sterically less hindered C atom; these expected enthalpic effects are offset by stronger van der Waals and covalent stabilization of the larger carbonyl molecules by the enolates at the bimolecular C–C coupling TS. They reflect instead the much smaller entropy loss upon formation of the TS with the smaller electrophiles and the preeminent role of entropy on activation free energies at the relatively high reaction temperatures required for these reactions on oxide surfaces. These entropic effects become more preeminent at surfaces which impose a greater degree of organization at TS than homogeneous gaseous or liquid media.

2. EXPERIMENTAL METHODS

2.1. Catalyst Synthesis and Characterization. Ag/SiO₂ co-catalysts (ca. 20% wt. Ag) were prepared using homogeneous deposition–precipitation methods. AgNO₃ (≥99.5%, Sigma-Aldrich; 5 mmol) and urea (99%, Aldrich; 25 mmol) were dissolved in 50 cm³ deionized water at ambient temperature. Fumed SiO₂ (Cab-O-Sil, Sigma-Aldrich; 395 m² g⁻¹; 2.0 g) was then added into this solution, and the pH value of the suspension was adjusted to 2–3 using HNO₃ solutions (0.5 mmol cm⁻³; 99%, Sigma-Aldrich). This suspension was heated to 353 K (at 0.167 K s⁻¹) for 3 h in flowing dry air (1.67 cm³ g⁻¹ s⁻¹) at ambient temperature, then treated in ambient stagnant air at 383 K for 24 h and in flowing dry air (1.67 cm³ g⁻¹ s⁻¹; Praxair) at 1073 K (at 0.033 K s⁻¹) for 2 h. These samples were finally treated in flowing 10% H₂/He (5.56 cm³ g⁻¹ s⁻¹; Praxair) by heating to 803 K (at 0.033 K s⁻¹; held for 2 h) and then in flowing 1% O₂/He mixtures (0.83 cm³ g⁻¹ s⁻¹; Praxair) at ambient temperature for 1 h to passivate the samples before exposure to ambient air. Cu/SiO₂ co-catalysts (ca. 20% wt. Cu) were also prepared using homogeneous deposition–precipitation methods that are described elsewhere in detail. These Ag/SiO₂ and Cu/SiO₂ samples were characterized by powder X-ray diffraction (XRD) (Cu Kα radiation, λ = 0.15418 nm, 40 kV, 40 mA, Bruker D8 Advance). The mean crystallite size of metal particles in these samples was determined from the breadth of their most intense (111) reflections in XRD diffractionograms (2θ: 38.1° for Ag; 43.3° for Cu) using the Scherrer equation. The mean Ag crystallite size of the Ag/SiO₂ catalysts was 15.5 nm, and that for the Cu particles in the Cu/SiO₂ catalysts was 7.9 nm.

Anatase TiO₂ (TiO₂(a), 99.7%, 240 m² g⁻¹, Alfa Aesar) was used here as the condensation catalyst. It was treated at 673 K (0.167 K s⁻¹) for 3 h in flowing dry air (1.67 cm³ g⁻¹ s⁻¹; 99.999%; Praxair) before use. The crystalline phase of TiO₂(a) was confirmed by XRD.

2.2. Rates of Acetone-HCHO Condensation Reactions. TiO₂(a) and Ag/SiO₂ (or Cu/SiO₂) co-catalysts were mixed together using a mortar and pestle with a mass ratio that ranged from 1/2–1/8. Aggregates of these mixtures (125–180 μm), obtained via pressing, crushing, and sieving, were loaded into a quartz tubular flow reactor (1.0 cm I.D.), treated in flowing 10% H₂/He (5.56 cm³ g⁻¹ s⁻¹, 99.999%, Praxair) at 803 K (0.0833 K s⁻¹ from ambient temperature) for 2 h, and then cooled to desired reaction temperature (723–773 K). Liquid acetone (99.9%, Fisher Scientific) and methanol (HCHO precursor, 99.9%, Fisher Scientific) were introduced into the reactor via vaporizing into H₂ (99.999%, Praxair) and He (99.999%; Praxair) flows, and the liquid and gas flow rates were metered via syringe pumps (Cole Parmer, 74900 series) and electronic mass flow controllers (Porter, Inc.), respectively. All transfer lines were kept above 430 K in order to avoid reactant or product condensation.

The concentrations of the effluent components were measured by gas chromatography (Agilent 6890) using a capillary column (Agilent, HP-1, methyl silicone, 50 m, 0.32 mm I.D. × 1.05 um) connected to a flame ionization detector and also a packed column (Porapak Q, 4.8 m, 80–100 mesh) connected to a thermal conductivity detector. Conversions and selectivities were reported on a carbon basis. Reaction rates were measured periodically at a reference condition (1.0 kPa acetone, 5.0 kPa methanol, 10 kPa H₂, 773 K) to correct rates for some slow deactivation detected at the reaction conditions used in this study.

2.3. Computational Methods. TiO₂H₈₁₈ clusters (Scheme 2) were extracted from TiO₂(a) (101) surfaces as described elsewhere. These TiO₂H₈₁₈ clusters have been shown to represent adequate models in assessing the elementary steps and their kinetic relevance in aldol condensations on TiO₂(a). Geometry optimizations of reactants, products, and TS involved in enolate-carbonyl C–C coupling reactions on TiO₂H₈₁₈ clusters were carried out using the B3LYP geometry algorithm as implemented in the Gaussian 09 program. During optimizations, the five Ti atoms and the three internal O atoms in TiO₂H₈₁₈ clusters were allowed to relax, while all remaining atoms were held fixed in order to preserve the structure of the extended parent anatase surfaces. All calculations were carried out at the hybrid B3LYP functional level of theory with the Gaussian-type 6-311G(d,p) basis set for the C, O, and H atoms and the effective core potential LANL2DZ basis set for the Ti atoms. Wave functions were converged to 10⁻⁸ Ha with an ultrafine grid of 99,590 points for the numerical integration; structures were optimized until the root-mean-square force was <1.5 × 10⁻³ Ha Bohr⁻¹. The van der Waals contributions to electronic energies were calculated for all structures using Grimme’s D3BJ dispersion correction in each step of the geometry optimization. The overestimation of binding energies brought forth by the basis-function overlaps when finite basis sets are used, known as the basis set superposition error, was eliminated using the counterpoise correction.
method. These optimized structures were further examined by frequency calculations at the same computational level.

Zero-point energies and thermal corrections used to calculate the enthalpy and entropy of each structure were determined using DFT-derived frequencies with the rigid rotor harmonic oscillator (RRHO) approximation. A factor of 0.9682 was used to scale these frequencies to compensate anharmonicity effects excluded in RRHO treatments. In addition, the vibrational entropies corresponding to the low-frequency modes of weakly bound adsorbates (<100 cm$^{-1}$; listed in Table S1, Supporting Information (SI)) were calculated using a free-rotor model, as proposed by Grimme, because of the significant errors in the vibrational entropies derived from RRHO treatments of such modes. The charges of each atom in all reactants, products, and TS structures were calculated using the natural bond orbital (NBO) analysis that provided the most likely Lewis electronic structure for each molecule or coordination complex, and the properties of chemical bonds in these structures were analyzed using the Wiberg bond indices.

3. RESULTS AND DISCUSSION

3.1. Formation of HCHO via CH$_3$OH Dehydrogenation on Cu/SiO$_2$ and Ag/SiO$_2$ Catalysts. Use of CH$_3$OH as a precursor to HCHO is favorable over direct introduction of HCHO because of the chemical instability, volatility, and toxicity of HCHO reactants and the fact that HCHO is available only as dilute aqueous solutions (≈60% H$_2$O by volume). HCHO can form in situ from CH$_3$OH on a dehydrogenation function (e.g., Cu$^{16}$ and Ag$^{37}$) and then be scavenged by condensation reactions with C$_2$, alkanals/alkanes in the presence of an acid–base function (e.g., anatase TiO$_2$ (TiO$_2$(a)), as shown below, thus minimizing HCHO decomposition to CO and H$_2$. These tandem dehydrogenation–condensation processes would also lead to a novel and practical approach to using methanol as a C$_1$ growth monomer with the condensation events account for most of the products formed with acetone pressure than with either acetone (to form 4-hydroxy-4-methyl-pentan-2-one; self-condensation) or HCHO (to form 4-hydroxy-butan-2-one; cross-condensation) on TiO$_2$(a). These coupling steps lead to the formation of aldols that subsequently dehydrate and hydrogenate to form methyl isobutyl ketone (C$_{2+1}$) and butan-2-one (C$_{1+1}$), respectively (Scheme 3). These larger alkane

Figure 1. CH$_3$OH reaction selectivity on Ag/SiO$_2$ as a function of CH$_3$OH conversion (varied through changes in reactor residence time; 20% wt. Ag/SiO$_2$, 773 K, 5 kPa methanol, 10 kPa H$_2$). Dashed lines indicate trends.

products can also react further with acetone or HCHO, leading to primary product selectivities that ultimately decrease with increasing residence time. For instance, secondary condensations between butan-2-one and HCHO produced pentan-3-one (C$_{3+1}$), 3-methylbutan-2-one (C$_{3+1+2}$), and 2-methylpentan-3-one (C$_{3+1+3}$) (Scheme 3). The selectivity to the primary butan-2-one product decreased from 99% to 83% as the acetone conversion increased from 1% to 38% (773 K, 1 kPa acetone, 5 kPa methanol, 10 kPa H$_2$), while the selectivities to all secondary cross-condensation products increased (Figure 2). The selectivity to methyl isobutyl ketone (C$_{2+1}$) remained nearly constant at 1% throughout this acetone conversion range (Figure 2), indicating methyl isobutyl ketone is less reactive than butan-2-one in subsequent coupling reactions with HCHO.

The combined rates of self-condensation ($r_{self}$) and cross-condensation ($r_{cross}$) increased linearly with acetone pressure, but did not depend on the HCHO pressure, set in these experiments by the CH$_3$OH dehydrogenation function (Figure 3). These data indicate that condensation rates are limited by α-C–H activation steps that form propen-2-olates from acetone on essentially bare TiO$_2$(a) surfaces. HCHO (or CH$_3$OH) did not influence enolate formation rates, because of their low prevalent coverages at Ti–O site pairs. Propen-2-olates react with either acetone or HCHO to form C$_6$ or C$_4$ alkanones via competitive reactions that cause $r_{self}$ to increase more strongly with acetone pressure than $r_{cross}$ at all conditions, cross-condensation events account for most of the products formed from these enolates (Figure 3a). Faster scavenging of propen-2-olates at higher HCHO pressures renders them unavailable for self-condensation, leading to $r_{self}$ values that consequently decrease as the HCHO pressure increases (Figure 3b).

The $r_{cross}/r_{self}$ Ratios increased linearly with HCHO/acetone ratios and were much larger than unity at all conditions and even
at very low HCHO/acetone ratios (Figure 4). The slope of the data in Figure 4 reflects the ratio of rate constants for nucleophilic attack at HCHO and acetone by the bound propen-2-olates; this ratio is 1110 ± 40 (773 K), consistent with the high reactivity of HCHO relative to acetone. Heuristic constructs would typically assign such high reactivity to the less crowded nature and the more electrophilic character of the C atom in HCHO compared with the carbonyl C atom in larger alkanals or alkanones. Kinetic data and DFT-derived free energies are used here to provide these heuristic descriptions with a more rigorous mechanistic basis and to show that entropic effects, instead of the enthalpic considerations implicit in steric and electrophilicity, make HCHO the preferred electrophile in nucleophilic attack by enolates on catalytic surfaces that impose a level of organization at TS absent in reactions occurring in homogeneous gaseous or liquid media.

3.3. Kinetic Assessment of the Reactivity of Acetone and HCHO in Nucleophilic Attack by Enolates on TiO2 Surfaces. Aldol condensation on TiO2 involves C–C coupling of bound enolates, formed in rate-limiting steps, with carbonyl molecules bound weakly at vicinal Lewis acid centers (Scheme 4). The rate of C–C bond formation between a bound enolate (EN*), derived from reactant i, with a carbonyl C atom in species j (rij) is given by

\[ r_{ij} = k_{ij}K_i(EN_i^*)(P_j)/(L) \]  

where (*) is the number of unoccupied Ti–O site pairs, (L) is the total number of such pairs at oxide surfaces, Pj and Ki are the respective pressure and adsorption constant of species j, and kij is the rate constant for EN*–j coupling. For each i-derived enolate, the rate ratio for self (j = i) to cross (j ≠ i) C–C coupling is then given by

\[ \frac{r_{ij}}{r_{ii}} = \left( \frac{k_{ij}K_i}{k_{ii}K_j} \right) \left( \frac{P_j}{P_i} \right) \]  

Eqs 1 and 2 provide general kinetic descriptions for competitive reactions of enolates with carbonyl molecules at Lewis acid–base site pairs prevalent on oxide surfaces and specifically on TiO2(a) and monoclinic ZrO2 systems that are particularly proficient catalysts for aldol condensations.

The slope in Figure 4 gives the ki,kj/kii,Kj ratio when i is acetone and j is HCHO. This ratio reflects the magnitude of ΔG\text{TS,i,j}0, the difference between the free energy barriers to form a C–C bond between propen-2-olate and acetone (ΔG\text{TS,i,j}0) from the bound i-derived enolate (EN*,i) and a gaseous electrophile j) and to form a C–C bond with HCHO (ΔG\text{TS,i,j}0) from the same bound EN*,i and a gaseous electrophile j):

\[ k_{ii}K_i = \frac{\exp\left(\frac{-\Delta G_{ij-i,i}^{TS}}{RT}\right)}{k_{ij}K_j} \]  

\[ \Delta G_{ij-i,i}^{TS} = \Delta G_{ij}^{TS} - \Delta G_{ij}^{TS} \]  

Measured ki,kj/kii,Kj ratios (1110 ± 40, Figure 4) correspond to ΔG\text{TS,i,j}0 values of −45 ± 1 kJ mol−1 for acetone-HCHO reactions on TiO2(a) at 773 K; these values are similar to the DFT-derived free energies reported below (Section 3.4).

3.4. Theoretical Treatments of Nucleophilic Attack at Carbonyl Compounds by Enolates on TiO2 Surfaces.
condensation of the carbonyl compounds\(^{9,11}\) but the C–C bond order (BO\(_{C-C}\)) a measure of the extent to which the C–C bond has formed\(^{33}\) at the TS is smaller for HCHO than for larger electrophiles for all the C\(_x\)–C\(_y\) enolates examined (e.g., 0.29 and 0.37 for propen-2-olate couplings with HCHO and acetone, respectively; Table 1); such trends in bond orders are consistent with an earlier TS when HCHO acts as the electrophile. These trends in the location of the TS along the reaction coordinate reflect the stronger electrophilic character of the C atom in HCHO compared with the carbonyl C atom in the other reactants. Such trends in electrophilic character are consistent with the more exothermic nature of the reactions of F\(^{-}\) or CH\(_3\)\(^{-}\) anions with HCHO compared to those with the carbonyl C atoms in larger reactants (DFT-derived energies for the reactions of these anions with C\(_1\)–C\(_4\) carbonyl molecules in gas phase shown in Table S2). Such reaction energies are essentially unaffected by steric effects for these carbonyl species because of the small sizes of the F\(^{-}\) and CH\(_3\)\(^{-}\) nucleophiles.

The effects of alkyl substituents on the enthalpy components \((\Delta H_{TS}^f)\) of the activation free energy barriers for C–C coupling between gaseous carbonyl molecules and enolates bound at Ti\(_2\)O\(_3\)(a) surfaces \((\Delta G_{ij}^D)\) were examined first. Changes in \(\Delta H_{TS}^f\) brought forth by steric and electronic effects of alkyl substituents in carbonyl reactants, have been proposed to determine relative reactivity and thus changes in the relative values of \(\Delta G_{ij}^f\). A Born–Haber thermochemical cycle (Scheme 4) is used to dissect \(\Delta H_{TS}^f\) into enthalpy changes upon structural distortion of bound enolates and carbonyls in forming the TS \((\Delta H_{ij}^{TS})\), covalent \((\Delta H_{ij}^{cov})\), and electrostatic \((\Delta H_{ij}^{elec})\) forces:

\[
\Delta H_{ij}^{TS} = \Delta H_{ij}^{dist} + \Delta H_{ij}^{vdW} + \Delta H_{ij}^{cov} + \Delta H_{ij}^{elec}
\]

(5)

The \(\Delta H_{ij}^{TS}\) term in \(\Delta G_{ij}^{TS}\) \((\text{eq 4})\) can then be expressed as

\[
\Delta H_{ij}^{TS} = \Delta H_{ij}^{dist} + \Delta H_{ij}^{vdW} + \Delta H_{ij}^{cov} + \Delta H_{ij}^{elec}
\]

(6)

where each \(\Delta H_{ij}^{X}\) term \((X = \text{dist}, \text{vdW}, \text{cov}, \text{or elec})\) is given by

\[
\Delta H_{ij}^{X} = \Delta H_{ij}^{X} - \Delta H_{ij}^{X}(0)
\]

(7)

\(\Delta H_{ij}^{dist}\) values depend weakly on temperature\(^{29}\) and are approximated here by the corresponding electronic energies:

\[
\Delta H_{ij}^{dist} = E_{TS}^{carbonyl} - E_{carbonyl} + E_{EN}^{TS} - E_{EN}
\]

(8)

Here \(E_{carbonyl}^{TS}\) and \(E_{EN}\) are the electronic energies for the bound carbonyl and enolate moieties at the TS, respectively, calculated separately for the gaseous carbonyl compound and the bound enolate using their respective structures at the TS, and \(E_{carbonyl}\) and \(E_{EN}\) are those for the fully relaxed gaseous carbonyl compounds and the fully relaxed bound enolates as described in Section 2.3. \(\Delta H_{ij}^{vdW}\) values were derived from classical Coulomb interactions that assume each atom in the TS structure is a point charge of a magnitude determined using the NBO analysis\(^{34}\) (Section 2.3):

\[
\Delta H_{ij}^{elec} = \frac{1}{4\pi\varepsilon_0} \sum_{y=1}^{N} \sum_{x=1}^{M} \frac{C_x C_y}{r_{xy}}
\]

(9)

where \(C_x\) and \(C_y\) represent the charge at the \(x\) atom in a bound carbonyl moiety with M C atoms and that at the \(y\) atom in a bound enolate with N C atoms, respectively, \(r_{xy}\) is the distance between the \(x\) and \(y\) atoms, and \(\varepsilon_0\) is the permittivity of free space. Similar to the treatments used for \(\Delta H_{ij}^{vdW}\), \(\Delta H_{ij}^{cov}\) values
were determined using the two-body interaction potentials implemented in the D3BJ functionals.26 ∆H_{corr} values were given by the difference between ∆H_{TS} and the sum of ∆H_{corr,T}, ∆H_{corr,elec}, and ∆H_{corr,vdW} (eq 5). These DFT-derived individual ∆H_{TS} values (X = TS, dist, vDW, cov, or elec) for condensations of HCHO-C_{2-4} carbonyl mixtures on TiO_{2}(a) are included in Table S3 and used here to calculate ∆H_{TS}^X values (eq 7) for each i-j carbonyl reactant pair, as described next.

Table 1 shows DFT-derived ∆H_{TS}^X values for HCHO (i) and C_{2-4} carbonyls (j) on TiO_{2}(a). ∆H_{corr,elec} values are negative for all HCHO-(j) pairs (−43 to −115 kJ mol\(^{-1}\)) and become more negative as the number of C atoms in the molecule i increases. Such trends reflect the greater distortion required to form the C–C coupling TS for larger carbonyl nucleophiles in order to minimize steric effects upon interaction with a given enolate. ∆H_{corr,vdW} values are positive (+9 to +37 kJ mol\(^{-1}\)), however, because larger carbonyls establish more effective van der Waals contacts with a given enolate. Covalent bonding at the TS is also weaker for HCHO than for larger carbonyls (−33 to +24 to +51 kJ mol\(^{-1}\)) for each enolate, even though HCHO is a stronger electrophile. This reflects the weaker σ-electron orbital overlap at a C–C coupling TS structure that occurs significantly earlier along the reaction coordinate for the HCHO-enolate-coupling pairs than for C–C coupling of enolates with larger carbonyl molecules. Such differences in σ-electron orbital overlap are evident from their different C–C bond order at the TS (BO_{C-C} Table 1), which correlates linearly with the corresponding ∆H_{corr,vdW} value for each reactant pair (Figure S3).

Electrostatic interactions between the enolate and the carbonyl co-reactant depend weakly on the electrophile (2 to 14 kJ mol\(^{-1}\), Table 1), in contrast with van der Waals and covalent interactions (−2 to −14 kJ mol\(^{-1}\)) due to a decrease in the carbon atom of the carbonyl, because carbonyl moieties are nearly neutral at the TS (Table S3). The overall ∆H_{TS}^X values resulting from the combined effects of distortion and of covalent, electrostatic, and van der Waals interactions vary only slightly (from −3 to −14 kJ mol\(^{-1}\)) for these i-j reactant pairs (Table 1), showing that the steric repulsion inherent in forming C–C coupling TS is almost fully compensated by stronger van der Waals and covalent interactions of enolates with the larger carbonyls. As a consequence, the enthalpic components in ∆G_{TS}^f typically associated with steric and electrophilicity, are, in fact, not responsible for the very high reactivity of HCHO in nucleophilic attack by enolates at Lewis acid–base pairs on oxide surfaces.

These weak effects of alkyl substituents on ∆H_{TS} show above render the entropy component (∆G_{TS}^S) in ∆G_{TS} critical in determining the relative values of ∆G_{TS} for each i-j carbonyl reactant pair at temperatures relevant for catalysis. DFT-derived ∆G_{TS}^S values for HCHO-C_{2-4} condensation vary between +12 and +53 J mol\(^{-1}\) K\(^{-1}\) (Table 1), indicating that activation entropies are less negative when HCHO acts as the electrophile and that they become increasingly negative for larger electrophiles (C_{2-4} carbonyls). ∆G_{TS}^S values for C–C coupling with enolates derived from alkanals are nearly identical to the difference in entropies for species i and j (HCHO) upon their respective adsorption at a Ti center in the absence of any coadsorbed species (∆G_{ads}^S Table 1):

\[
\Delta G_{ads}^{S,j-i} = S_j - S_i - S_{(g)} + S_{(g)}
\]

(10)

where S_{(g)} are the entropies for bound i and j, respectively, and S_{(g)} and S_{(g)} are those for their gaseous precursors. The ∆G_{TS}^S values for alkanone-derived enolates are much larger than their ∆G_{ads}^S components (e.g., +28 and +51 J mol\(^{-1}\) K\(^{-1}\) for the respective ∆G_{ads}^S,j-i values of acetone-derived propen-2-olate, Table 1), because of rotational modes that become increasingly hindered as larger alkanones interact with the enolate at the C–C coupling TS.

These negative ∆H_{corr,vdW} values and positive ∆S_{TS}^S values for reactions of HCHO and C_{2-4} alkanones/alkanols with a given enolate lead to negative ∆G_{TS}^S values at all relevant catalytic temperatures. For instance, the ∆G_{TS}^S,j-i value for HCHO-acetone reactants is −43 kJ mol\(^{-1}\) (773 K, Table 1) corresponding to k_{i-K}/k_{j-K} ratios of about 800, in essential agreement with measurements (1110 ± 40, Figure 4). The kinetic preference for HCHO (as the electrophile) becomes stronger as temperature increases (Figure S5), because entropy benefits, brought forth by the strong effects of the size and structure of the carbonyl reactants on ∆G_{TS}^S become more consequential for the magnitude of the activation free energies at higher temperatures.
SELECTIVITY OF METHANOL DECOMPOSITION ON Cu/SiO₂; DERIVATION OF CONDENSATION RATE EQUATIONS; DFT-DERIVED STRUCTURES FOR REACTANTS, PRODUCTS, AND TS OF C−C COUPLING REACTIONS; DFT-DERIVED FREQUENCIES FOR VIBRATIONAL MODES OF CARBONYL MOLECULES ADSORBED ON TiO₂; DESCRIPTORS FOR THE ELECTROPHILICITY OF CARBONYL COMPOUNDS; DFT-DERIVED CHARGES AND ACTIVATION ENTHALPIES AND ENTROPIES FOR C−C COUPLING TS; DESCRIPTORS FOR THE COVALENT INTERACTIONS AT C−C COUPLING TS (PDF)

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b11749.

The higher reactivity with HCHO is evident for all enulates, but the kinetic preference for HCHO becomes stronger for larger enulates, as shown by ∆G_{TS}^{i,j} values that become more negative as the number of C atoms or the extent of substitution in the enulates increases (Figure 5). These trends predominantly reflect the lower activation entropies when HCHO is the electrophile instead of enthalpic effects associated with steric repulsion or electrophilicity, which are balanced by van der Waals and covalent interactions for the larger electrophiles. Such entropy-driven high reactivity is unique for very small electrophiles, such as HCHO, because enthalpic effects prevail in determining the relative reactivities of C₂⁺ carbonyl reactants, because the easier steric access and stronger electrophilic character of the carbonyl C atom in smaller reactants are compensated by their weaker van der Waals and covalent interactions with the enolate moieties at TS. Consequently, the relative free energy barriers for the C−C coupling of enulates with different carbonyl molecules are determined by the entropic losses upon formation of the bound TS from their gaseous reactant states. These findings elucidate the preeminent role of entropy underpinning the much higher reactivity of HCHO than larger carbonyl molecules in the nucleophilic attack by enulates on oxide surfaces at catalytically relevant temperatures.

CONCLUSIONS

Bifunctional mixtures of anatase TiO₂ and Ag/SiO₂ are used to show the unique reactivity of HCHO (derived in situ from CH₃OH) in cross-condensations with enulates derived from larger carbonyl molecules. The latter contribute reactants form enulates by kinetically relevant cleavage of their α-C−H bonds at Ti−O acid−base pairs on TiO₂ surfaces that remain essentially bare during catalysis. The preference for HCHO over large carbonyls as electrophiles in nucleophilic attack by a given enolate reflects a lower activation free energy barrier for the C−C coupling step on TiO₂ surfaces, evidenced from both experiments and theoretical treatments that account for van der Waals forces. DFT treatments also show that the more electrophilic nature of HCHO compared with larger carbonyl molecules leads to earlier TS for C−C coupling of bound enulates with HCHO, making the stability of these TS benefit less from the corresponding stronger C−C bond ultimately formed in the products compared with those for larger carbonyl reactants. The enthalpic contribution to the stability of such C−C coupling TS, however, is essentially unaffected by the size or electrophilicity of the carbonyl reactants, because the easier steric access and stronger electrophilic character of the carbonyl C atom in smaller reactants are compensated by their weaker van der Waals and covalent interactions with the enolate moiety at TS. Consequently, the relative free energy barriers for the C−C coupling of enulates with different carbonyl molecules are determined by the entropic losses upon formation of the bound TS from their gaseous reactant states. These findings elucidate the preeminent role of entropy underpinning the much higher reactivity of HCHO than larger carbonyl molecules in the nucleophilic attack by enulates on oxide surfaces at catalytically relevant temperatures.