

Enolization and Aldol Reactions of Ketone with a La³⁺-Immobilized Organic Solid in Water. A Microporous Enolase Mimic

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There has recently been a renewed interest in recoverable/reusable solid catalysts.¹ Organic zeolites may be defined as catalytically active microporous materials made up mostly of organic components. A prototype of such materials with immobilized Lewis acid centers catalyzes the Diels–Alder reactions in a remarkable manner.² A La³⁺ analogue (La host), on the other hand, catalyzes typical base-promoted reactions such as Michael and aldol in benzene.³ As for the media, the “green” or ecological one is of course water.⁴ The present work is concerned about the catalytic behavior of the La host in water. We report here that it catalyzes the enolization of the ketone by the mechanism, which suggests that these types of materials can be used as microporous enzyme mimics.

As reported, treatment of anthracenebisresorcinol **1** (Chart 1) with La(OⁱPr)₃ in THF affords a 1:2 polycondensate,³ which, upon aqueous workup, gives rise to an adduct **1**⁴⁻·2(LaOH)²⁺·6(H₂O) (La host). This formulation is consistent with the network structure **2** in which the hydrogen bond (●···● = O–H···O–H) in apohost **1** is replaced by a metal coordination (●···● = O⁻···La³⁺···O⁻) with a hydroxide ion and 3 water molecules on each metal center, which is eventually hexacoordinated. The La host is microporous. The binding isotherm for N₂ at 77 K at lower guest pressures is of the Langmuir type (Figure 1A). A BET analysis⁵ of the monolayer-coverage region gives a specific surface area of A_{BET} = 230 m²/g.

The La host is completely insoluble in water but readily binds ~30 mol of H₂O with no leak of the metallic (by inductively coupled plasma (ICP) analysis) or organic component (by ¹H NMR) into the aqueous phase, the latter being kept neutral at pH 7. The aquo complex separated from the aqueous phase easily gets rid of extra water molecules at <150 °C (by thermogravimetry) to regenerate the original La host, **1**⁴⁻·2(LaOH)²⁺·6(H₂O), which can be identified by all the analytical⁶ and spectroscopic means. Thus, the La host, while readily hydrated, is stable against hydrolytic decomposition, in marked contrast to simple La³⁺ alkoxides and aryloxides.

When immersed in an aqueous solution of cyclohexanone, the La host binds the ketone as a guest. The binding isotherm of a saturation behavior (Figure 1B, open circles) is consistent with a reversible Langmuir-type host–guest complexation and is expressed as guest/host = (guest/host)_{sat} · K[guest]₀ / (1 + K[guest]₀), where (guest/host)_{sat} = 5.7 and K = 5.3 M⁻¹. The ketone adduct recovered shows a significant complexation-induced shift to lower

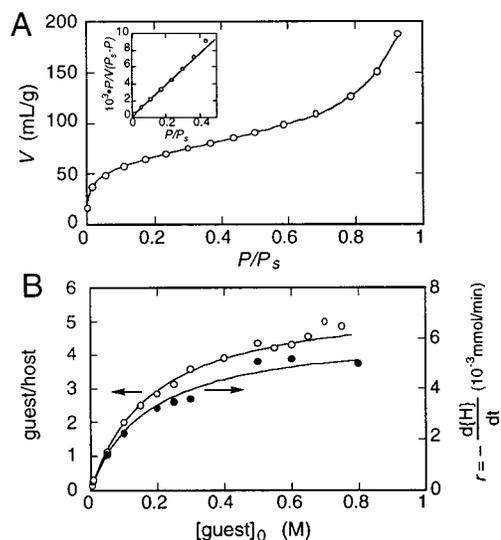
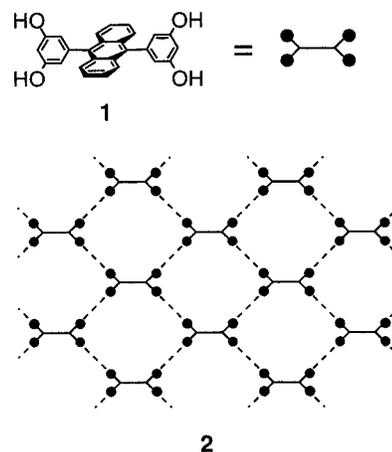


Figure 1. (A) Binding isotherm for N₂ as a guest at 77 K with the La host and BET plot (inset), where V (mL) refers to the standard state and P_s = 760 Torr. (B) Binding isotherm (O) for cyclohexanone as a guest in water (50 mL) with the La host (0.02 mmol) at 298 K and initial rates (●) of H/D exchange in cyclohexanone in D₂O (2 mL) as catalyzed by the La host (0.02 mmol) at 298 K.

Chart 1



wavenumber in $\nu_{C=O}$ for the bound guest ($\Delta\nu_{C=O} = 17 \text{ cm}^{-1}$). This, coupled with the saturation guest/host ratio of ~6, suggests that the ketone binding is actually a water/ketone exchange as metal ligands on each La³⁺ center (Scheme 1).⁷

When treated with the La host, the ketone in D₂O undergoes facile deuterium incorporation at the α -positions of the carbonyl group to give 2,2,6,6-tetradeuterated ketone. When the insoluble La host is removed by centrifugation, the supernatant liquid left shows no reaction. Thus, the La host in the solid state must catalyze the enolization of the ketone, a compelling process for the H/D exchange. Under typical substrate-excess (ketone/La³⁺ = 10) conditions ([ketone] = 1 M in 2 mL of D₂O containing 0.1 mmol (on the formula basis) of the La host), the reaction goes to completion with a half-life of $\tau = 1.8 \text{ h}$, following the first-order kinetics with respect to the ketone.⁸ Alicyclic and aromatic ketones such as acetone ($\tau \approx 5.9 \text{ h}$) and acetophenone ($\tau \approx 2.8 \text{ h}$) also undergo deuteration at the α -positions. Neither soluble LaCl₃ nor insoluble La(OH)₃ as a reference is active; no

(7) Alternatively, the ketone may be hydrogen bonded to a metal-bound water.

(1) (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985–2986. (b) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229–11230.

(2) (a) Sawaki, T.; Dewa, T.; Aoyama, Y. *J. Am. Chem. Soc.* **1998**, *120*, 8539–8540. (b) Sawaki, T.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4793–4798.

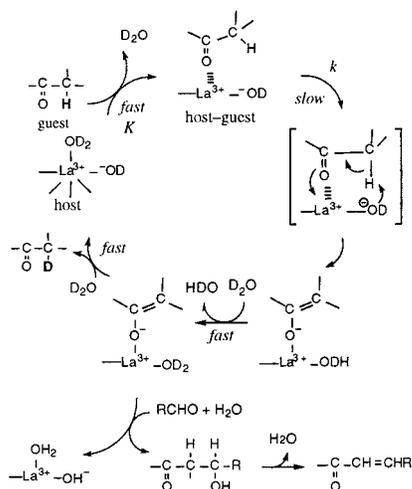
(3) Saiki, T.; Aoyama, Y. *Chem. Lett.* **1999**, 797–798.

(4) Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646–1647.

(5) Brunauer, S.; Emmett, P. H.; Teller, E. *J. Am. Chem. Soc.* **1938**, *60*, 309–319.

(6) Calcd for C₂₆H₂₆O₁₂La₂ (**1**⁴⁻·2(LaOH)²⁺·6(H₂O)): C, 38.54; H, 3.48; La, 34.3. Found: C, 38.49; H, 3.04; La (ICP), 34.3.

Scheme 1

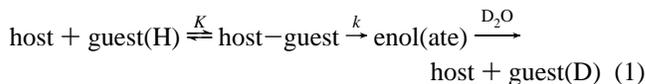


reaction can be detected even after 48 h under otherwise identical conditions. The H/D exchange of cyclohexanone does take place in the presence of Na_2CO_3 at 0.1 M (0.2 mmol in 2 mL of D_2O with a resulting pD of 12.4) with $\tau \cong 2.3$ h. Thus, as far as reaction rates are concerned, the insoluble La host in neutral pure water may be equivalent to Na_2CO_3 as a soluble base at pD $\cong 12$. As expected, however, the former system allows a much simpler workup procedure. After the reaction is complete, the La host is recovered readily by centrifugation followed by washing and can be used repeatedly with the same catalytic activity. The combined aqueous phase and washings are free from La^{3+} contamination (by ICP) and leave nothing behind other than the deuterated product upon evaporation of solvent D_2O .

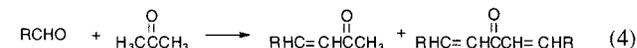
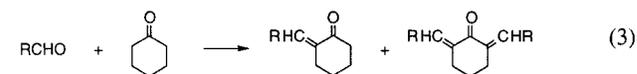
The initial rates ($r = -d\{\text{H}\}/dt$, where $\{\text{H}\}$ represents the amount of exchangeable H atoms in the $\text{O}=\text{C}-\text{CH}$ moieties) of the reaction exhibits saturation with increasing substrate concentrations (Figure 1B, closed circles). Such a Michaelis–Menten-type kinetic behavior leaves little doubt that the ketone reversibly bound to the La host undergoes rate-determining enolization and the resulting enol(ate) is rapidly captured by solvent D_2O (eq 1 for the general scheme where host represents the unit-binding site of the La host and eq 2 for the rate expression where $(\text{guest}/\text{host})_{\text{sat}} = 5.7$ and $\{\text{La host}\} = 0.02$ mmol).⁸ Double-reciprocal plots of $1/r$ vs $1/[\text{guest}]_0$ reveals that $K = 5.8 \text{ M}^{-1}$ in an excellent agreement with that ($K = 5.3 \text{ M}^{-1}$) obtained from the binding assay and $k = 0.01 \text{ min}^{-1}$. Owing to the weak Lewis acidity of the La^{3+} ion, soluble $\text{La}(\text{OR})_3$ complexes ($\text{R} = \text{alkyl}$ or aryl) often act as a Brønsted base⁹ and catalyze a number of carbonyl reactions involving essential enol(ate) intermediates.¹⁰ This may also be the case here with the metal-ligated aryl- O^- or more

(8) The strict rate expression is $r = -d\{\text{H}\}/dt = \{\text{La host}\} \cdot (\text{guest}/\text{host})_{\text{sat}} \cdot K[\text{guest}]_0 / (1 + K[\text{guest}]_0) \cdot 4k \cdot \{\text{H}\} / \{\text{H}\}_0$, where the amount of bound guest is corrected for the number of exchangeable H/D atoms (4) and then for the fraction of unexchanged H's ($\{\text{H}\} / \{\text{H}\}_0$) to give the amount of H atoms in the bound substrate in the right-hand side. Thus, the reaction is first-order with respect to $\{\text{H}\}$ and hence $[\text{H}]$. At an early stage of the reaction, $\{\text{H}\} \cong \{\text{H}\}_0$ and eq 2 results as a consequence.

plausibly the OD^- anion as the base. In addition, IR evidence for the $\text{C}=\text{O} \cdots \text{La}^{3+}$ coordination suggests that the La^{3+} center cooperates in the enolization as a Lewis acid.¹¹ A mechanism along this line is shown in Scheme 1.



$$r = -\frac{d\{\text{H}\}}{dt} = \{\text{La host}\} \cdot \left(\frac{\text{guest}}{\text{host}}\right)_{\text{sat}} \cdot \left(\frac{K[\text{guest}]_0}{1 + K[\text{guest}]_0}\right) \cdot 4k \quad (2)$$



An immediate concern may be whether the present system can be applied to aldol reactions. Cyclohexanone alone hardly (<1%) undergoes homocondensation. However, the aldol reactions with concomitant dehydration take place catalytically in the presence of an aldehyde (furfural or benzaldehyde) as a better enolate acceptor (eq 3 and Scheme 1), ultimately giving rise to a 1:1 ($\text{R} = 2\text{-furyl}$) or 1:0.8 ($\text{R} = \text{phenyl}$) mixture of the enone and dienone products in a quantitative (>95%) total yield (with respect to the limiting aldehyde substrate) under the conditions of $(\text{La host}/\text{aldehyde}/\text{ketone}) = 1/10/33$ and $[\text{ketone}] = 0.8 \text{ M}$ in H_2O at 298 K in 85 h ($\text{R} = 2\text{-furyl}$) or 20 h ($\text{R} = \text{phenyl}$).¹² Acetone in place of cyclohexanone also reacts similarly to give a 1:2 ($\text{R} = 2\text{-furyl}$) or 1:1.5 ($\text{R} = \text{phenyl}$) mixture of the corresponding enone and dienone adducts (eq 4).¹²

To summarize, this work presents an unprecedented catalysis by a metal–organic solid in water. The present La^{3+} -network is not only stable against hydrolysis but also maintains microporosity to allow reversible substrate prebinding and activation in an enzyme-mimetic manner. Furthermore, the recoverable/reusable La host leaves *nothing* in the aqueous phase so that such an important and typically acid/base-promoted process as enolization and subsequent aldol reactions proceed in *pure* water at neutral pH.

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(12) The enone and dienone products were identified (glpc and ^1H NMR) with their authentic specimen obtained from NaOH-promoted aldol reactions. The trans configuration was confirmed by the coupling constants of $J \cong 16 \text{ Hz}$ for the olefinic protons in the acetone-derived products (eq 4).