Communications to the Editor

Geometry of Enolization Using a Bifunctional Cyclodextrin-Based Catalyst

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We have described[1] a set of β-cyclodextrin (cycloheptaamylose) bisimidazoles in which the catalytic groups are located on the C-6 carbons of neighboring glucose units (AB), or separated by one unit (AC) or two units (AD). Thus the attachment points are respectively 51°, 103°, and 154° apart around the seven-unit cyclodextrin circle into which substrates can bind. We saw that the AB compound was the best catalyst for hydrolyzing a bound cyclic phosphate ester,[1] consistent with a mechanism we proposed[2] for that process. The availability of this set of catalysts should make it possible to explore the geometric preferences of other bifunctionally catalyzed processes and to mimic some enzymatic catalyses. We now wish to describe such a study with respect to the enolization of a bound ketone substrate.

The substrate was *p-tert*-butylacetophenone (**1**). We monitored the exchange of deuterium into the methyl group of **1** by GC/MS using CI (CH_4), examining[3] the peaks at [M + 29], [M + 30], [M + 31], and [M + 32]. Deuterium exchange measures the rate of enolization assuming that BH^+ of the catalyst exchanges rapidly with D_2O relative to the reketonization rate; if not, the enolization rate is even faster than deuteration. The catalyst was at 6 mM and the substrate at 2 mM, and the medium was phosphate buffer at 170 mM in D_2O with 14% CD_3OD.[4] The pH[6] did not change within 0.05 units during the experiments, which were performed at 35 °C. The results of experiments at pH 6.2 (where the imidazole groups should be ca. 50% protonated) are shown in Figure 1. Under our conditions, there is no detectable deuterium exchange catalyzed by buffer alone (or by a solution of β-cyclodextrin and imidazole), but there is significant catalysis by the three cyclodextrin bisimidazoles and also by cyclodextrin monoimidazole. As Figure 1 shows, the AB and AC bisimidazoles are not significantly better than the monoimidazole catalyst, but the rate with the AD isomer is faster. This indicates that the AD isomer is a true bifunctional catalyst, a conclusion supported by the pH vs rate constant profile in Figure 2.

By molecular modeling, all three of the bifunctional isomers can reach the carbonyl oxygen and the C–H bond being broken in a complex with substrate **1**. However, as shown in Figure 3, the stereoelectronics are different. With AB, the imidazole can reach the H approaching from the side toward the carbonyl group

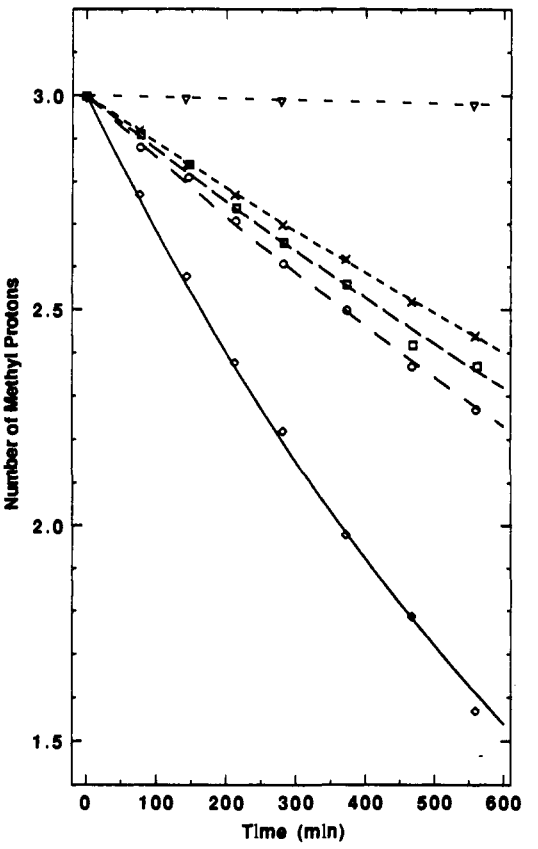

Figure 1. Deuterium exchange into substrate **1** under the conditions described in the text catalyzed by (▽) buffer alone; (×) cyclodextrin-6-imidazole; (□) cyclodextrin-6A,6B-bisimidazole; (○) cyclodextrin-6A,-6C-bisimidazole; (◇) cyclodextrin-6A,6D-bisimidazole. The lines drawn are exponential decay curves fitted to the points.

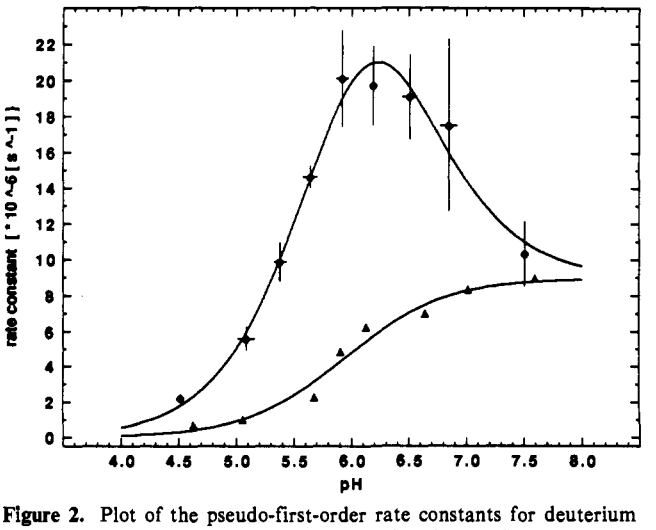

Figure 2. Plot of the pseudo-first-order rate constants for deuterium exchange into substrate **1** catalyzed by cyclodextrin-6A,6D-bisimidazole (top curve, ●) and by cyclodextrin-6-imidazole (bottom curve, ▲) as a function of pH (in D_2O).[6] The lines are titration curves fitted to the points, with pK_a values of 5.94 (bottom curve) and 6.11 (top curve). In the top curve, the high-pH downward leg was calculated assuming that the rate titrates down to the rate for cyclodextrin-6-imidazole, as seems to be the case, even though the catalyst carries *two* imidazole groups. The error bars are ±1 standard deviation.

(1) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 5972–5973.
(2) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317–324.
(3) These [M + C_2H_5] peaks were more reliable than were the [M + 1] peaks. [M + 29] results from **1**-H_3, while [M + 30] results from **1**-H_2D and also **1**-H_3-^{13}C. To follow the exchange of proton, [M + 30] was corrected for the ^{13}C abundance seen in the starting **1**, and similar corrections were applied to [M + 31] and [M + 32] to obtain the relative amount of the D_2 and D_3 compounds.
(4) Since the catalyst concentration is well in excess of that needed for saturation binding of a *tert*-butylphenyl group into β-cyclodextrin in water containing this concentration of ethanol[5] and ethanol is more hydrophobic than methanol, these must correspond to saturation binding conditions.
(5) Breslow, R.; Halfon, S. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 6916–6918.
(6) Measured with a normal pH electrode uncalibrated for our medium. Thus the relative values have meaning, not the absolute values.

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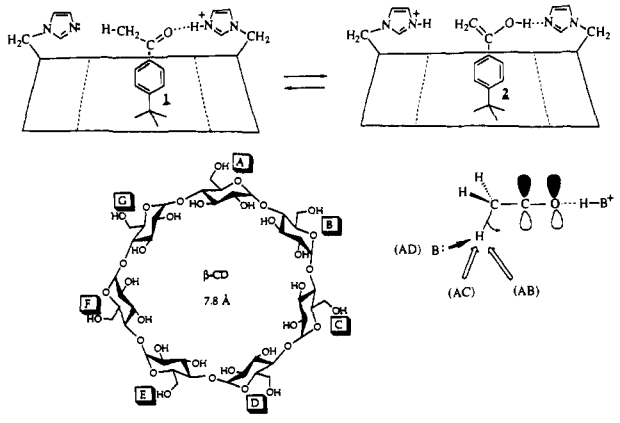

Figure 3. Catalyzed exchange reaction.

if the ImH^+ proton is placed directly on an oxygen unsharedelectron pair with O, H, and N in a line. With AC, the imidazole can reach the H in line with the C–H bond, while with AD it reaches the H from a direction somewhat behind the C–H bond (away from the carbonyl group). Since the electrons of the C–H bond move toward the carbonyl group on conversion to the enol**2** as the CH_3 carbon rehybridizes, a preference for such a nonlinear backside approach seems reasonable. This is probably the geometry for base abstraction of the H in all the cases, with the difference being whether the acid catalyst group can get in the right position to assist.

It will be interesting to see whether our catalysts—the first to combine a hydrophobic binding site with two acid–base catalytic groups in a well-defined position and to operate in aqueous solution[7]—can selectively promote other reactions involving enolization. The set of isomeric catalysts will also let us explore the occurrences and geometric preferences of other acid–base bifunctional catalyses. Meanwhile, the clear contrast with the geometric preference for bifunctional catalysis of phosphate ester hydrolysis, in which the AB isomer was the best, supports our interpretation of these preferences in terms of the mechanism and optimal geometry of the reactions involved.

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(7) For an example of bifunctional catalysis of enolization in wet $CHCl_3$, cf.: Wolfe, J.; Muehldorf, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1453–1454.