Catalysis of an Intramolecular Aldol Condensation by Imidazole-Bearing Cyclodextrins

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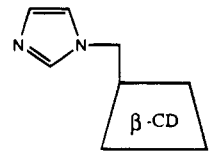
We have shown that β-cyclodextrin molecules bearing two imidazole groups cleave cyclic phosphodiesters at neutral pH using bifunctional acid/base catalysis[1] and also catalyze the enolization of *p-tert*-butylacetophenone.[2] Of the three β-cyclodextrin bis(imidazole) isomers, the A,B isomer, **3**[3] (imidazoles attached to the 6 positions of neighboring glucose units, 51° apart), shows the fastest cleavage of cyclic phosphodiesters,[1] but the A,D isomer of cyclodextrin bis(imidazole), **4** (imidazoles attached 154° apart), is the most efficient isomer for the enolization, detected by H−D exchange.[2] These preferences were explained in terms of the mechanisms of the two processes.



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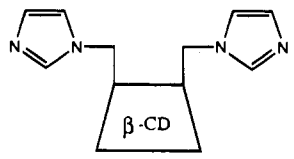

3, A,B isomer
4, A,D isomer

Of course enolization is an important first step in many synthetic chemical reactions, but it is not necessarily the rate-limiting step. Thus it was of interest to see whether our bifunctional catalysis of enolization would actually lead to a rate increase in a chemical process proceeding from the enol. We have now found that an internal aldol condensation does indeed show significant catalysis by our cyclodextrin imidazole molecules—and with geometric selectivity among the members of the catalyst family—even though we find that the first enolization step is in reversible equilibrium.

We studied the aldol cyclization of keto aldehyde **1** (Scheme 1) to trans keto alcohol **5** catalyzed by imidazole-bearing cyclodextrin molecules **2**−**4** (Table 1). Keto aldehyde **1** (0.7 mM) was incubated with catalysts **2**−**4** (0.8 mM) at ambient temperature (22 ± 1 °C) under neutral conditions (pH 7,[4] 40 mM Na_2HPO_4/40 mM NaH_2PO_4, 70:30 (v/v) H_2O/MeOH). Control reactions were run with buffer alone—in the presence of unsubstituted cyclodextrin (0.8 mM) to dissolve the substrate—at both pH 7 and pH 10. The reaction was monitored by HPLC (C_{18} reverse phase; CH_3CN/H_2O). The authentic cis and trans keto alcohols **5** and **6** were prepared from an independent synthesis.[5] The rate of cyclization was minimal in the presence of cyclodextrin at neutral pH (entry 4, Table 1), but cyclization was promoted by alkaline media (entry 5, Table 1). The trans isomer **5** was formed exclusively in all cases; there was no evidence for formation of the corresponding cis isomer **6**. Enantioinduction, determined by chiral HPLC of the isolated **5**, was minimal (<10% ee). Compounds **2**−**4** also catalyzed the slower dehydration of **5** to the corresponding enone.

Table 1. Catalysis of Aldol Formation by Imidazolyl Cyclodextrins[a]

entry	catalyst	pH	rate constant[b]
1	**2**	7	1.1 ± 0.1
2	**3**	7	1.44 ± 0.15
3	**4**	7	2.7 ± 0.3
4	β-CD	7	0.05 ± 0.02
5	β-CD	10	17.8 ± 2.0

[a] [Catalyst] = 0.8 mM; [**1**] = 0.7 mM; $[NaH_2PO_4] = [Na_2HPO_4]$ = 40 mM (entries 1−4), 25 mM carbonate/borate/hydroxide buffer (entry 5); 30% (v/v) CH_3OH in H_2O; ambient temperature. [b] Expressed in units of 10^{-6} s^{-1}.

Table 2. Rate Constants of H−D Exchange by Imidazolyl Cyclodextrins[a]

entry	catalyst	total[b]	catalyzed[c]	ketone[d]	selectivity[e]
1	β-CD	2.3 ± 1.3		<0.5	
2	**2**	6.9 ± 0.5	4.6	4.0 ± 0.3	0.85
3	**4**	12.2 ± 2.0	9.9	8.6 ± 0.8	0.85

[a] All rate constants expressed per proton in units of 10^{-6} s^{-1}. [b] Total exchange rate constant, determined by CI-GCMS (NH_3). [c] Defined as the total rate constant minus the background rate constant in the presence of cyclodextrin. [d] Exchange rate constant next to ketone, as determined by EI-GCMS or CI-GCMS (CH_4). [e] Defined as the ketone rate constant divided by the catalyzed rate constant.

The rate of cyclization of **1** at neutral pH is increased by a factor of 20 by CD-monoIm **2**, and 50 by the AD-$CDIm_2$ **4**, over that of the control with cyclodextrin and buffer. As in the enolization study, the AD isomer **4** is more effective than the AB isomer **3**, and by a similar rate ratio; the AB isomer **3** was only slightly better than the CD-monoIm **2**, apparently because the two catalytic groups in **3** are not correctly positioned for optimal bifunctional catalysis. As before, these differences presumably indicate some catalysis by the ImH^+ in addition to the Im, by simultaneous bifunctional catalysis.

In our enolization study we saw a rate maximum at pH 6.2 in a bell-shaped curve with catalyst **4**, supporting the proposal of bifunctional catalysis. The pH vs rate profile is different for the aldol condensation. Reactions conducted at pH 6.2 (40 mM MES buffer), close to the pK_a of **2**, were slower than at pH 7 by a factor of approximately 3 for **2** and **3**, and by a factor of 2 for catalyst **4**. In the enolization study[2] the **4**/**2** rate ratio was also higher at pH 6.2 than at pH 7.0, but the rate of enolization itself was higher at pH 6.2 than at 7.0 for the bifunctional catalyst **4** (but not for the monofunctional catalyst **2**). The present reaction does not involve simple enolization as the rate-determining step.

The incorporation of deuterium into **1** from D_2O/CH_3OD in the presence of **2**, **4**, and cyclodextrin was studied with GCMS (Table 2). Total deuterium incorporation in **1** was determined by CI (NH_3), which provided a clean M + NH_4 peak. Deuterium incorporation on the carbon next to the keto group was determined by use of either CI (CH_4) or EI, which provided measurable quantities of the $tBuC_6H_4C(OH)CH_2$ cation.[6] The *catalyzed* exchange rate was found by subtraction of the significant background rate seen in the control reaction with cyclodextrin.

The absence of exchange next to the ketone group in the control reaction indicates that the background rate is due to exchange next to the *aldehyde* group, as would be predicted by both the lower pK_a and the higher deprotonation rate of acetaldehyde[7] vs acetophenone.[8,9] Comparison of the ketone

(1) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 5972−5973.
(2) Breslow, R.; Graff, A. *J. Am. Chem. Soc.* **1993**, *115*, 10988−10989.
(3) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317−324.
(4) The pH measurements were as read at a glass electrode and were not corrected for the solvent composition.
(5) The aldols lacking *tert*-butyl groups are known: (a) Ghera, E.; Shoua, S. *J. Org. Chem.* **1972**, *37*, 1292−1298. (b) Kwiatkowski, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1496−1498.
(6) Measurement of the corresponding aldehyde fragment (i.e., $CH_2CH(OH)$) was unreliable.
(7) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000−4009.
(8) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392−6395.

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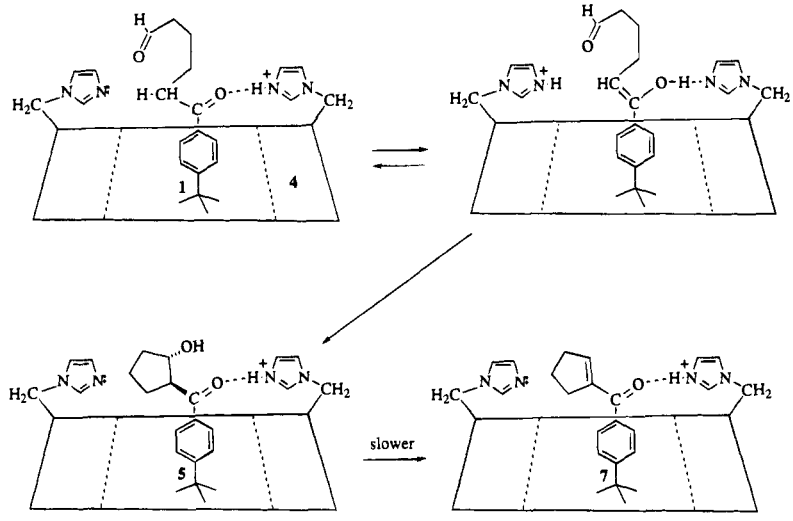
Scheme 1



exchange rate with the catalyzed exchange rate shows that approximately 85% of the deuterium incorporation caused by **2** and **4** occurs next to the ketone group, in contrast to the absence of deuterium incorporation at this site in the control. The selectivity for exchange next to the ketone, despite its inherent lower reactivity, is indicative of the significant regioselectivity of enolization caused by the geometry of the complex of **1** with **2** or **4**.

The deuterium exchange rate per molecule next to the keto group exceeds 6 times the rate of aldol formation for both **2** and **4**, indicating that enolization of the ketone is reversible and not the rate-limiting step in aldol formation with these catalysts. It might be rate limiting in the control reaction, explaining some of the catalysis. Alternatively, the concentration of the enol might be increased by binding to the imidazole group(s) of the catalysts, or the rate-limiting cyclization of the aldehyde group with the enol might also be catalyzed by the imidazoles. Some of our findings are better in line with one of the latter two proposals, but the evidence is not yet strong enough for a definitive choice.

Our results show that the selectivity of enolization in a bifunctional substrate can be reversed by the geometry of a substrate/catalyst complex and that we can see a useful rate acceleration of a synthetic carbon–carbon bond forming reaction. We do not have the same bell-shaped pH vs rate profile that previously indicated bifunctional acid–base catalysis for enzolization alone, but the preference of one isomer (**4**) over another (**3**) among the bifunctional catalysts presumably indicates some cooperative bifunctional catalysis even in this sequential reaction path. We are extending these studies to other interesting reactions that might show selective bifunctional catalysis, directed by the geometry of the catalyst/substrate complex.

Acknowledgment. This work was supported in part by the National Institutes of Health and the Office of Naval Research. J.M.D. is the recipient of a National Institutes of Health postdoctoral fellowship.

(9) For studies on keto–enol equilibria: (a) Capon, B.; Guo, B.-Z.; Kwok, F. C.; Siddhanta, A. K.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 135–140. (b) Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1988**, *21*, 442–449. (c) Chiang, Y.; Kresge, A. J.; Walsh, P. A.; Yin, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 869.