Kinetic and Stereochemical Evidence for the Involvement of Only One Proline Molecule in the Transition States of Proline-Catalyzed Intra- and Intermolecular Aldol Reactions

Linh Hoang,[‡] S. Bahmanyar,[†] K. N. Houk,[†] and Benjamin List*,[‡]

Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Received September 20, 2002; E-mail: blist@scripps.edu

Developed in the early 1970s, the proline-catalyzed intramolecular aldol reaction is a milestone in asymmetric catalysis.[1] Not only used in numerous syntheses of steroids and other natural products,[2] this reaction also foretold the explosive area of enantioselective organocatalysis.[3] Despite its practicality and our recent development of an intermolecular variant,[4] a detailed mechanistic understanding of the Hajos−Parrish−Eder−Sauer−Wiechert reaction is only slowly emerging. Here we provide evidence for the involvement of only one proline molecule in the transition states of proline-catalyzed intra- and intermolecular aldol reactions. Our study contrasts mechanistic experiments by Agami et al.[5] who proposed the involvement of *two* proline molecules in the intramolecular variant. Nonetheless, our results are consistent with earlier concepts[6,7] and with the one-proline-mechanism we conceived for the intermolecular aldol reaction.[3d,4a] Complementary to recent density functional theory studies,[8,9] our results suggest a unified enamine catalysis mechanism of proline-catalyzed inter- and intramolecular aldol reactions.

Proline catalyzes asymmetric intramolecular aldolizations of triketones **1** to give aldol addition- (**2**) or condensation products (**3**), depending on the substrate and the reaction conditions.[1,10] Proline also catalyzes intermolecular aldolizations between two carbonyl compounds to give aldols **6** in high enantioselectivities.[4a−c,11−13]

Although rejected by Hajos,[1d−e] enamine catalysis as established by Spencer et al.[14] for the pyrrolidine-catalyzed aldolization of **1b** has been considered the most likely mechanism of proline-catalyzed aldol reactions.[5−7] The currently widely accepted view that two proline molecules are involved in the transition state of the Hajos−Parrish−Eder−Sauer−Wiechert reaction is based on experiments by Agami et al., who observed a modest nonlinear effect in the asymmetric catalysis and a concentration-dependent enantioselectivity.[5] According to the Agami mechanism, the first proline molecule forms an enamine with the side chain ketone of **1a** while the second proline mediates the proton transfer (transition state **A**). By contrast, we proposed one-proline mechanisms for both the intramolecular aldolization (transition state **B**)[8a] and its intermolecular variant (transition state **C**).[3d,4,8c] Model **C** was subsequently supported experimentally by the absence of nonlinear effects in the intermolecular aldol reaction,[3d,11a] and by density functional theory calculations.[8c,9]

An answer to the question of how many proline molecules truly participate in these C−C-bond-forming transition states may best be obtained from kinetic measurements. Our study therefore commenced with an investigation on the *retro*-aldolization kinetics of the fluorogenic aldol **7**. The study of a *retro*-aldolization as
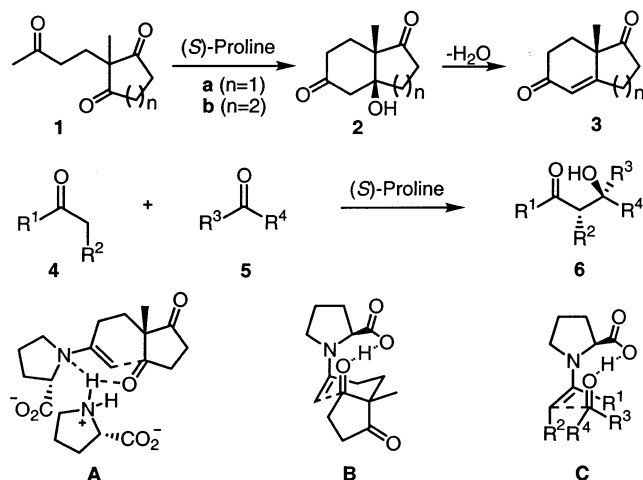
opposed to an aldolization has several advantages including the simpler experimental setup and the absence of complications from reversible unproductive reactions of proline with a substrate (parasitic equilibria).[3d] It may further be anticipated that *retro*-aldolization kinetics correspond to the actual rate-determining C−C-bond-cleaving step, which, based on the principle of microscopic reversibility, should proceed via the same transition state as the C−C-bond formation. Consequently, we expected first-order kinetics if a one-proline-mechanism would be operative and second-order kinetics for the Agami mechanism. We determined room temperature *retro*-aldolization kinetics of aldol **7** to ketone **8** fluorometrically and found the reaction to be first-order in proline (Figure 1a).

Although our kinetics cover only a relatively small concentration range, taken together with the earlier linearity studies,[3d,11a] and the recent calculations,[8c,9] we interpret this result as evidence for a transition state of the critical C−C-bond-cleaving step that involves only a single proline molecule. However, if we accept a one-proline mechanism of the intermolecular aldol reaction, the question arises whether the *intramolecular* variant occurs via a different mechanism. If the two reactions differ and the intramolecular reaction proceeds via a two-proline-transition state, then one would have to assume that the density functional theory calculations are incomplete.[8a,15] An alternative solution for the apparent discrepancy, however, would be that the earlier nonlinearity experiments[5] were erroneous. Because the observed effect was modest, based on only five data points, and because enantioslectivities were measured polarimetrically, a relatively inaccurate method, we decided to reinvestigate Agami's experiments.

We initially studied the proline-catalyzed cyclization of triketone **1b**, which directly furnishes condensation product **3b**, the ee of

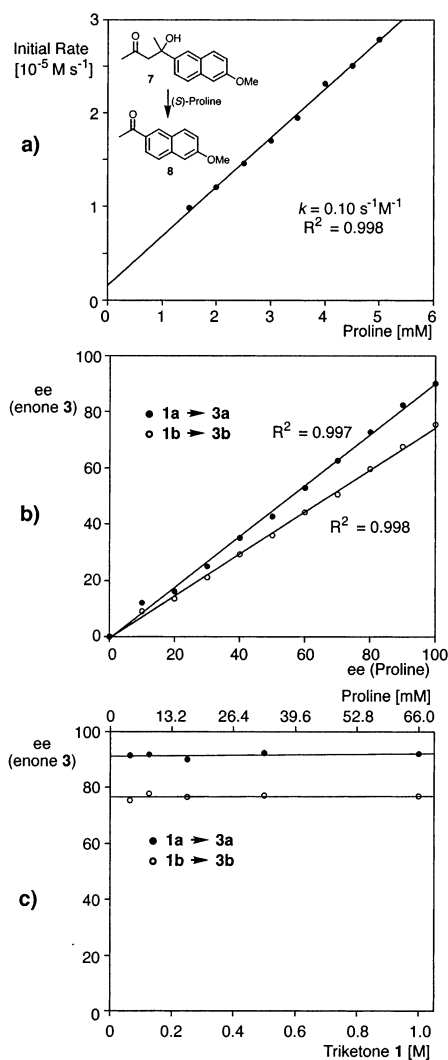‡ The Scripps Research Institute.
† University of California.

Figure 1. (a) *retro*-Aldolization kinetics of aldol **7**. (b) Absence of nonlinear effects in the Hajos−Parrish−Eder−Sauer−Wiechert reaction. (c) Absence of dilution effects on the enantioselectivity.

which can be precisely determined using reverse chiral phase HPLC measurements. Plotting the ee of proline versus that of **3b** showed an excellent linear correlation (Figure 1b). Furthermore, the reaction of triketone **1a** to give aldol **2a** and, after in situ acid-catalyzed dehydration, enone **3a**, also showed no significant deviation from linearity (Figure 1b). As in the case of ketone **3b**, ee's of enone **3a** were accurately determined using reverse chiral phase HPLC. Both experiments were repeated twice and studied in DMSO as well as in DMF without significant deviations. Our results are consistent with the one-proline mechanism.

Finally, we investigated whether there are concentration effects on the enantioselectivity of the aldolizations of triketones **1a** and **1b** (Figure 1c). An observed decreased enantioselectivity upon diluting the reaction mixture has been interpreted as evidence for the two-proline-mechanism.[5d] However, no such effects were observed, again consistent with the one-proline mechanism.[15]

In summary, kinetic, stereochemical, and dilution experiments support a one-proline-mechanism of proline-catalyzed aldolizations. Although the two-proline mechanism cannot be completely ruled

out at the present time, there is no remaining experimental evidence supporting this mechanism. Significantly, our results, along with recent theoretical studies,[8,9,16] suggest a unified mechanism of proline-catalyzed inter- and intramolecular aldol reactions.

Supporting Information Available: Computational, experimental, and HPLC data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Additional detailed B3LYP/6-31G* calculations do not support a second proline molecule in the proton-transfer step (see Supporting Information). While previous calculations (ref 8) showed that intramolecular proton transfer from the proline carboxylic acid to the developing alkoxide gives a good accounting for the observed stereoselectivity, inclusion of dimethylamine as a proton-transfer mediator, produces transition states with higher activation energies and predicts that both enantiomers would be formed with nearly equal facility. Neither calculated activation energies nor stereoselectivies are consistent with a two-proline mechanism.

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