

The Claisen Rearrangement

Methods and Applications

Edited by

Martin Hiersemann and Udo Nubbemeyer



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Preface

Historically, the thermal rearrangement of aromatic and aliphatic allyl vinyl ether was first published in 1912 by Ludwig Claisen. The neat carbon variant of this 3,3 sigmatropic bond reorganization, the Cope rearrangement, was reported in 1940, 38 years later. Thus, the Cope reaction should have been termed as a 3-carba-Claisen rearrangement. However, the reverse is found within the literature: the Claisen rearrangement is termed as a 3-oxa-Cope rearrangement. Consequently, the hetero Claisen reactions are found as 3-hetero-Cope conversions displaying heteroatoms such as nitrogen and sulfur in position 3 of the rearrangement framework. Carrying out a keyword supported literature search, this inconsistent use of synonyms describing one and the same process should be strongly considered. Within our book, we will use the historically exact name *Claisen* rearrangement. Considering the widespread applications of the Claisen rearrangement, we should keep in mind that Mother Nature has been utilizing the aliphatic version already for a much longer period of time: the enzyme-catalyzed rearrangement of chorismate into prephenate also follows the same mechanism.

Although nowadays almost anybody seems to know something about the Claisen rearrangement, the exact nature of the transition state and the way substituents and solvents influence the rate and the selectivity of the reaction can be very difficult to elucidate. However, for the vast majority of applications, qualitative guidelines are sufficient to predict and/or explain the course of a Claisen rearrangement. One of the main conclusions from this book is that there isn't *the* Claisen rearrangement but a truly amazing number of mechanistically related variations of it that have been and are being developed. In this context, the first *Claisen book* presents a platform concerning basics and the state of the art.

From the breathtaking number of applications in target-oriented synthesis it becomes evident that the Claisen rearrangement (and its variants) is one of the most powerful stereoselective carbon-carbon-bond forming reactions. The efficiency of the reaction clearly profits from its atom economy. However, to be honest, access to the actual substrate for the rearrangement may prove costly. A particular strength is the predictability of the stereochemical course of the rearrangement based on the knowledge of the geometry of the cyclic transition state.

Still, even after more than 90 years of development, optimization and application of Claisen rearrangements, there is still plenty of room for further research.

With this in mind, we intended to provide interested researchers with a useful guide to the scope and limitations of this versatile rearrangement. To realize this task, we had to rely on various specialists who were originally contacted in the beginning of 2003 and, indeed, many of them agreed to contribute to the *Claisen book*. We are deeply indebted to all the authors who spent their limited time resources to compile a truly outstanding collection of facts concerning the various Claisen rearrangements. This book will certainly serve as a reference for many years to come.

Dortmund and Mainz

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Chorismate-Mutase-Catalyzed Claisen Rearrangement*Hong Guo and Niny Rao*

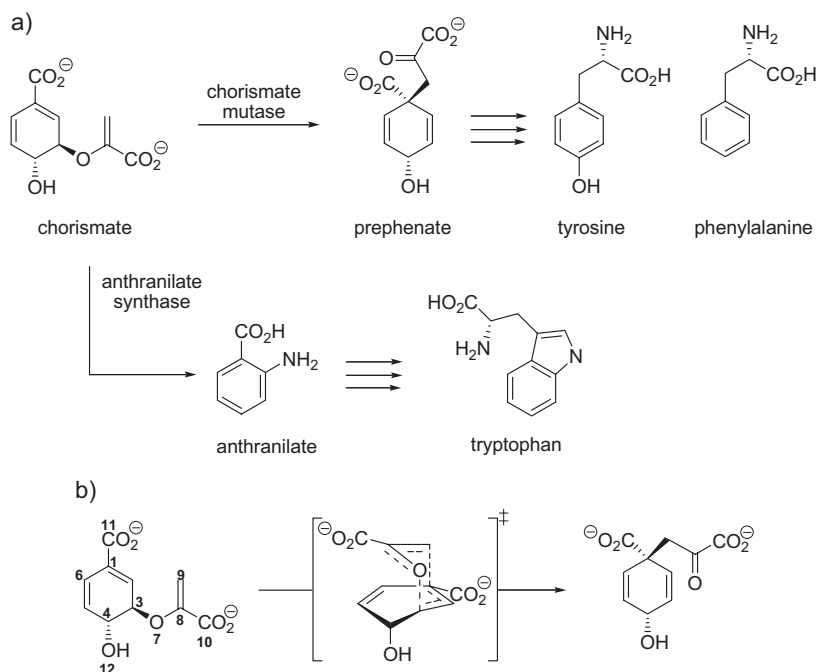
1.1

Introduction

Chorismic acid is the key branch point intermediate in the biosynthesis of aromatic amino acids in microorganisms and plants (Scheme 1.1a) [1]. In the branch that leads to the production of tyrosine and phenylalanine, chorismate mutase (CM, chorismate-pyruvate mutase, EC 5.4.99.5) is a key enzyme that catalyzes the isomerization of chorismate to prephenate (Scheme 1.1b) with a rate enhancement of about 10^6 – 10^7 -fold. This reaction is one of few pericyclic processes in biology and provides a rare opportunity for understanding how Nature promotes such unusual transformations. The biological importance of the conversion from chorismate to prephenate and the synthetic value of the Claisen rearrangement have led to extensive experimental investigations [2–43].

In addition, the reaction catalyzed by chorismate mutase is a paradigm for the study of enzyme mechanism and has been a subject of extensive computational investigations [44, 47–83]. One of the main reasons for the current focus on the mechanism of this enzyme is the fact that the reaction is a straightforward unimolecular rearrangement of the substrate with no chemical transformations in the enzyme or the solvent during the reaction. This eliminates many of the problems that arise for other cases and may help to settle some of the long-standing issues concerning the origin of the catalysis [84].

Experimental results for the CM-catalyzed and uncatalyzed reaction, as well as structural information for chorismate mutase, have been extensively discussed in two previous reviews [2, 3]. There has been a rapid growth of literature in computational studies of chorismate mutase in the last few years. In this chapter, we shall begin by summarizing some key experimental data related to the Claisen rearrangement along with existing structural information for chorismate mutase. We will then review the results of computational studies of chorismate mutase and discuss different proposals that have been suggested for the mechanism of the CM-catalyzed reaction.



Scheme 1.1

1.2

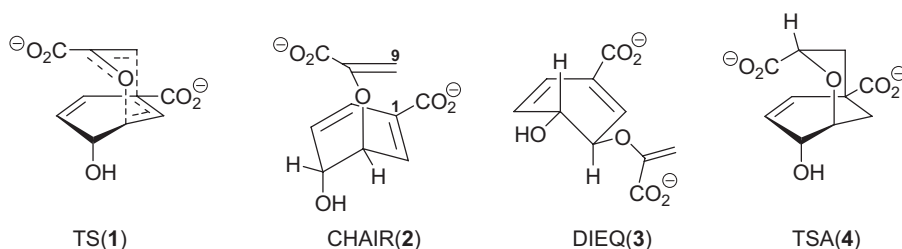
Experimental Studies

1.2.1

Substrate Binding

Knowles and coworkers [13, 14] demonstrated that the rearrangement of chorismate to prephenate proceeds through the same transition state (**1**, TS in Scheme 1.2) in solution and at the enzyme active site. The atoms of the [3,3]-pericyclic region in this TS are arranged in a “chair-like” configuration. The result of Knowles and coworkers has led to the suggestion that the bond breaking and making process starts from a chair-like pseudodioxane conformer of chorismate (**2**, CHAIR in Scheme 1.2), where C₁ and C₉ are positioned to form the carbon-carbon bond, as required for the Claisen rearrangement. Thus, one straightforward way for chorismate mutase to catalyze the rearrangement is to bind the CHAIR conformer preferentially from solution and then catalyze its chemical transformation at the active site. A requirement for such a mechanism is a sufficiently large population of the CHAIR conformer in solution. To determine the population of CHAIR in solution, Copley and Knowles [15] measured the temperature variation of the ¹H coupling constants for the protons in the ring of chorismate. It was shown that al-

though the dominant conformer(s) is a pseudodiequatorial conformation (see **3** of Scheme 1.2 for a schematic diagram), a pseudodiaxial conformer(s) exists at a reasonable level (~12%) in solution. Copley and Knowles [15] assumed that the pseudodiaxial conformer they observed in the NMR experiment was the CHAIR conformer and concluded that the enzyme could bind this reactive conformer directly from solution and catalyze its chemical transformation at the active site. But a later study of the transferred nuclear Overhauser effects for chorismate by Hilvert and his coworkers [17] failed to find evidence for the existence of CHAIR in solution. Recent molecular dynamics (MD) simulations [82, 83] suggested that the NMR data could correspond to other pseudodiaxial conformer(s) rather than CHAIR (see below).

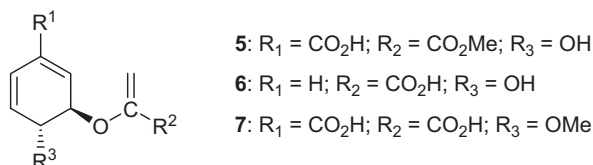


Scheme 1.2

1.2.2

Substrate Structural Requirements for Catalysis

The structural features of the substrate required for binding and catalysis by *Escherichia coli* chorismate mutase (P-protein EcCM) and *Bacillus subtilis* chorismate mutase (BsCM) have been studied [22, 23]. Besides the allyl vinyl ether, the two carboxylic acid groups in chorismic acid were found to be very important for the catalysis. For instance, experimental studies [22] showed that ester **5** (see Scheme 1.3) was not a substrate or inhibitor for EcCM, suggesting that the presence of the sidechain carboxyl group is crucial for the binding and catalysis. EcCM and BsCM were also unable to catalyze the rearrangement of **6** (which lacks the ring carboxylic acid group) [22, 23], even though **6** proved to be a weak to modest competitive inhibitor (K_i of **6** is 0.4 mM and 0.5 mM for EcCM and BsCM, respectively; for chorismate K_m is 0.32 mM and 0.28 mM, respectively). Thus, the existence of the ring carboxyl group is also essential for the catalysis, but may not



Scheme 1.3

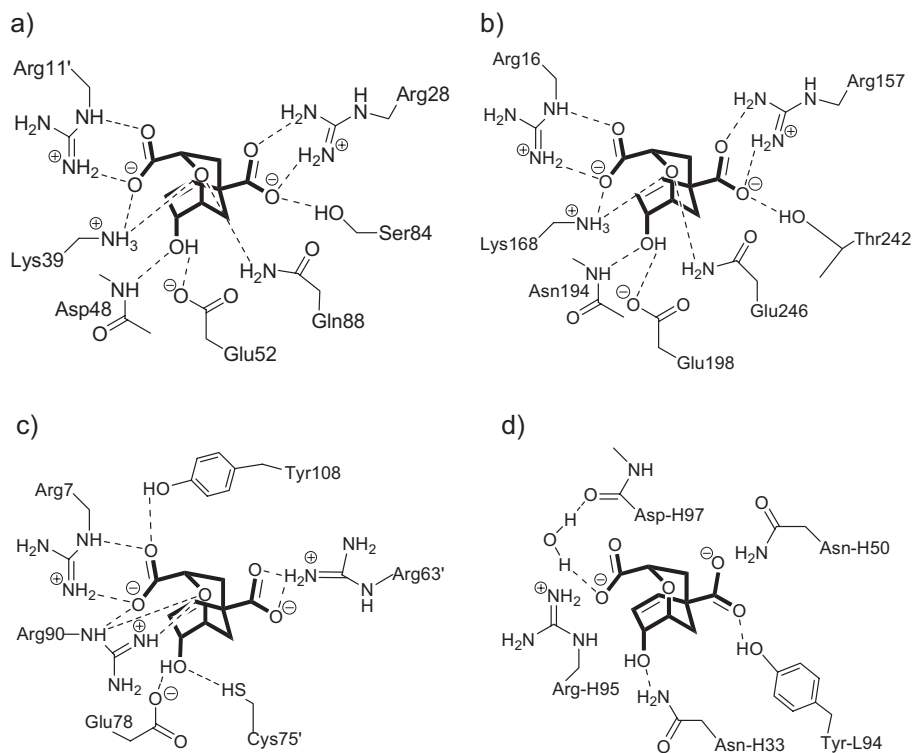
be required for the binding. Analog 7 was a reasonable substrate for EcCM ($K_m = 1.9 \text{ mM}$ and $k_{\text{cat}} = 0.56 \text{ s}^{-1}$) with a rate acceleration ($k_{\text{cat}}/k_{\text{uncat}}$) of 2×10^4 by the enzyme; for chorismic acid $k_{\text{cat}}/k_{\text{uncat}} = 2 \times 10^6$. Thus, the free hydroxyl group at C₄ may not be required for the catalysis by EcCM, but it is not clear whether this is also the case for BsCM (see below).

1.2.3

X-ray Structures of Chorismate Mutase

A number of X-ray structures for chorismate mutase are available. The structures of BsCM and *Saccharomyces cerevisiae* (yeast) CM complexed with an *endo*-oxabicyclic transition state analog inhibitor (4, TSA in Scheme 1.2) [19] have been determined by Lipscomb and coworkers [6, 7, 12, 34]; the structures without TSA bound were also obtained for BsCM and yeast CM as well as for some of their mutants [8, 10, 12, 31]. The X-ray structures for the monofunctional amino-terminal chorismate mutase domain engineered from the P-protein (EcCM) and a less active catalytic antibody 1F7 complexed with TSA have been determined by Lee et al. [4] and Haynes et al. [33], respectively. Both EcCM and yeast CM are homodimers, whereas BsCM is a homotrimer. It has been demonstrated that the dimer of EcCM can be superimposed onto a monomer of yeast CM [4, 11, 34], indicating a common evolutionary origin of the two CMs with an ancestral protein that was structurally closer to EcCM than to yeast CM [34]. Moreover, there was a possible gene duplication event in the evolution of yeast CM [34], allowing the formation of the regulatory domain for this enzyme. The structure of BsCM, which consists mainly of β -sheets, is different from the almost all-helical structures of EcCM and yeast CM.

Scheme 1.4 shows the schematic diagrams for the active site structures of EcCM [4], yeast CM [12, 34], BsCM [6, 7] and catalytic antibody 1F7 [33]. The active site of BsCM is somewhat open and more solvent accessible than the more buried catalytic packets in EcCM and yeast CM. As is evident from Scheme 1.4a and b, most of the active site residues in EcCM and yeast CM are conserved. For instance, in the both cases the guanidinium groups of two Arg residues (Arg28 and Arg11' in EcCM and Arg16 and Arg157 in yeast CM, respectively) form salt bridges with the carboxylate groups of the inhibitor. Lys39 (Lys168) in EcCM (yeast CM) is in hydrogen bond distances to the sidechain carboxylate group and the ether oxygen of TSA. A major difference between the two active sites is that the other residue interacting with the ether oxygen is Gln in EcCM (Gln88), but is Glu in yeast CM (Glu246). It has been shown that Glu246 has to be protonated for functionality of yeast CM. The replacement of Glu246 by Gln changes the pH optimum for the activity from a narrow to a broad pH range, even though the kinetic parameters are not significantly affected by the mutation (e.g., the effect on k_{cat}/K_m is less than 10-fold) [28]. Consistent with these observations on yeast CM, the replacement of Gln88 in EcCM by Glu leads to loss of activity of 700-fold at pH 7.5, but the activity of the Gln88Glu mutant can be reduced almost 10^3 -fold by simply lowering the pH to 4.9 [27] (see Table 1.1 and the next section for more details on the effects of mutations).



Scheme 1.4 The active sites of the CM complexes, (a) EcCM; (b) yeast CM; (c) BsCM; (d) catalytic antibody 1F7.

Scheme 1.4c shows that the active site of BsCM also consists of highly charged residues. Arg7 forms a similar salt bridge with the sidechain carboxylate group of TSA as Arg11' in the EcCM complex. Arg90 interacts with the both ether oxygen and sidechain carboxylate group. Arg63 was not visible in the electron-density map in an earlier X-ray structure determination [7]. But a more recent X-ray structure [8] of higher resolution (1.3 Å) without TSA bound showed that Arg63 is turned inward toward the active site and may therefore interact with the ring carboxylate group of TSA. Another interaction that exists in all the three CMs is the hydrogen bond between the C₄-hydroxyl group of TSA and a Glu residue (Glu52 in EcCM, Glu198 in yeast CM and Glu78 in BsCM). This Glu residue appears to play a more important role for the reaction catalyzed by BsCM than by EcCM (see below). Comparison of the active site structures of EcCM, BsCM and yeast CM with that of the catalytic antibody (1F7) (Scheme 1.4d) shows that the enzymes provide many more hydrogen bonding and electrostatic interactions to the functional groups of TSA than does the antibody. The lack of the multiple interactions is believed to be responsible for the observed 10⁴-times lower activity of the antibody relative to that of the natural chorismate mutase [33].

1.2.4

Effects of Mutations

For the uncatalyzed Claisen rearrangement k_{uncat} is about 10^{-5} s^{-1} [20, 31], and the k_{cat} value for the CM-catalyzed reaction is approximately $46\text{--}72 \text{ s}^{-1}$ (Table 1.1). Thus, the enzyme is able to accelerate the rate of the reaction by 10^6 to 10^7 -fold. To identify the key residues that play an important role in the catalysis, a number of active site mutants were generated and characterized for EcCM [27, 35], yeast CM [28] and BsCM [25, 29, 31, 36] and the effects of mutations on the activity have been determined.

For EcCM, Arg28, Arg11' and Lys39 are involved in the direct interactions with the two carboxylate groups as well as the ether oxygen of TSA in the X-ray structure (Scheme 1.4a). Table 1.1 shows that these positively charged residues play a very important role in the catalysis [27]. For instance, the $k_{\text{cat}}/K_{\text{m}}$ values for the Arg28Lys and Arg11Lys are approximately 10^3 lower than wild-type, whereas the values for Lys39Ala and Lys39Arg are about 10^4 lower. Similar observations were made for the related yeast CM, where the Arg157Ala, Arg16Ala and Lys168Ala mutants showed no detectable chorismate mutase activity [28]. The hydrogen bond between Gln88 (Glu246 in yeast CM) and the ether oxygen was also found to be very important. For instance, the replacement of Gln88 by Ala leads to a reduction of the activity by 10^4 -fold. For the Glu52 mutants, the order of activity is Glu52 > Gln52 > Asp52 > Ala52. Glu52 interacts with the C₄-hydroxyl group in the X-ray structure. The higher activity of Glu52Gln than Glu52Asp seems to indicate that the existence of a carboxylate group in the vicinity of the C₄-hydroxyl may not be necessary. This seems to be consistent with the earlier discussions of substrate structural requirements for the catalysis where it was shown that the free hydroxyl group at C₄ may not be required in the case of the EcCM-catalyzed reaction (see above).

The kinetic parameters for BsCM mutants are also available [25, 29, 31, 36] and listed in Table 1.1. Arg7, which forms a similar interaction with TSA as Arg11' in EcCM, was found to be very important. For instance, the replacement of Arg7 by Ala leads to an approximately 5×10^5 -fold reduction in $k_{\text{cat}}/K_{\text{m}}$. Arg90, which interacts with the both ether oxygen and sidechain carboxylate group (Scheme 1.4c), is also crucial for the catalysis. For instance, the k_{cat} and $k_{\text{cat}}/K_{\text{m}}$ values for Arg90Gly are more than five orders of magnitude lower than those of the wild-type enzyme. Moreover, the importance of the positive charge on Arg90 was demonstrated by Hilvert and coworkers [36] who showed that there is a significant reduction of the activity ($> 10^4$ -fold in k_{cat}) when Arg90 was replaced by citrulline, an isosteric but neutral arginine analog. Interestingly, the double mutants Cys88Lys/Arg90Ser and Cys88Ser/Arg90Lys restore a factor of more than 10^3 in k_{cat} compared to Arg90Gly [31]. Another important residue for the catalysis is Glu78. Glu78 is in a similar location as Glu52 in EcCM. Table 1.1 shows that the $k_{\text{cat}}/K_{\text{m}}$ values for Glu78Ala and Glu78Gln are about 10^4 lower than wild-type. By contrast, the activity of Glu78Asp is only 30-fold lower. This seems to suggest that the existence of a carboxylate group in the vicinity of the C₄-hydroxyl is more important for the

Table 1.1 Kinetic constants for EcCM and BsCM mutants.

Enzyme	Mutant	k_{cat} (s ⁻¹)	K_m (μM)	k_{cat}/K_m (M ⁻¹ s ⁻¹)	K_i for 4 (μM)	Reference
EcCM	Wild type	72	296	2.4×10^5	3.66	[27]
	R11A		>2000	26		[27]
	R11K		>2000	230		[27]
	R28A		>2000	170		[27]
	R28K		>2000	230		[27]
	K39A		>2000	4.3		[27]
	K39R		>2000	1.9		[27]
	E52A	0.49	4580	110	218	[27]
	E52D	3.1	1440	2.2×10^3	78.4	[27]
	E52Q	24	1080	2.3×10^4	26.8	[27]
	Q88A		>2000	12		[27]
	Q88E		>2000	361		[27]
	Q88E (pH 4.9)	72	296	2.4×10^5	3.66	[27]
BsCM	Wild type	46	67	6.9×10^5	3	[36]
	R90G	2.7×10^{-4}	150	31		[31]
	R90K			31		[25]
	R90A			< 1		[25]
	R7K			717		[25]
	R7A			1		[25]
	C75D/E78A			1.66×10^3		[25]
	E78D	35.7	1297	2.75×10^4	43.6	[25]
	E78Q			75		[25]
	E78A			33		[25]
	C88K/R90K	0.29	4300	67	>>1000	[31]
	C88K/R90S	0.32	1900	170	1100	[31]
	R90Cit	0.0026	270	230	6.8	[36]

BsCM-catalyzed reaction than for the EcCM-catalyzed reaction. Consistent with this suggestion, the activity of the Glu78Ala mutant is rescued 50-fold by replacing C75 (which is also near the C₄-hydroxyl group) with Asp in double mutant Glu78Ala/C75Asp [25]. The studies of substrate structural requirements for the catalysis (see above) showed that **6**, which lacks the ring carboxylate group, is not a substrate for EcCM [22] and BsCM [23]. For EcCM, the residue that interacts with the ring carboxylate group is Arg 28, and the replacement of Arg28 by another residue leads to a significant reduction of the activity. However, for BsCM the corresponding residue has not been clearly identified. A recent X-ray structure [8] for BsCM suggested that Arg63 may interact with the ring carboxylate group, but the mutagenesis study for the Arg63 mutants has not been available.

1.2.5

Activation Parameters

The activation parameters for the CM-catalyzed and uncatalyzed Claisen rearrangement are listed in Table 1.2 [20, 21, 26, 42]. For the uncatalyzed reaction, the activation barrier (ΔG^\ddagger) is 24.5 kcal/mol. Chorismate mutase is able to reduce the activation barrier by 7–10 kcal/mol. Table 1.2 shows that the rate acceleration is due to a reduction in the entropy of activation to near zero and a decrease in the enthalpy of activation by about 5 kcal/mol; the only exception is the BsCM-catalyzed reaction for which there is a significant unfavorable ΔS^\ddagger . However, the reliability of these data has been called into question [44], and it was suggested [44] that both the substrate binding and product leaving are expected to show large solvent compensation effects involving ΔH^\ddagger and ΔS^\ddagger [45, 46].

Table 1.2 Activation parameter for the catalyzed and uncatalyzed reaction^{a)}.

Enzyme	ΔH^\ddagger (kcal·mol ⁻¹)	ΔS^\ddagger (e.u.)	ΔG^\ddagger (kcal·mol ⁻¹)	$\Delta\Delta G^\ddagger$ (kcal·mol ⁻¹)
BsCM	12.7	−9.1	15.4	−8.9
EcCM	16.3	−3.0	17.2	−7.3
<i>K. pneumoniae</i>	15.9	−1.1	16.2	−8.3
<i>S. aureofaciens</i>	14.5	−1.6	15.0	−9.5
Uncatalyzed	20.5	−12.9	24.5	—

a) All entries are as cited in Refs. [21] and [26]. ΔG^\ddagger calculated at 25 °C.