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Intramolecular Aldol Condensation Reactions And Transacetalization Equilibria

Junan Guo

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INTRAMOLECULAR
ALDOL CONDENSATION REACTIONS
and
TRANSACETALIZATION EQUILIBRIA

by

Junan Guo

Faculty of Science
Department of Chemistry

Submitted in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Ontario
August 1995

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ABSTRACT

Part I: Intramolecular aldol condensation reactions.

The detailed kinetics and equilibrium for the intramolecular aldol condensation reaction of 2,5-hexanediol, 2,6-heptanediol, 1-phenyl-1,5-hexanediol and 5-oxohexanal were studied and correlated in terms of Marcus theory. All the reactions, with the readily explained exception of the intramolecular aldol addition of 5-oxohexanal, gave us approximately constant intrinsic barriers: 14.49 ± 0.82 kcal/mol for the intramolecular aldol addition step and 13.99 ± 0.74 kcal/mol for the subsequent dehydration step, which are also in excellent agreement with the intrinsic barriers found for intermolecular aldol condensation reactions. This means that Marcus theory is applicable to intramolecular aldol condensation reactions. With an equilibrium constant estimated in some way, we can now predict the rate constant for an intramolecular aldol condensation reaction based on the results of this work!

Part II: Equilibrium constant determination for acetal formation reactions.

Three transacetalization equilibria were measured directly in methanol by $^1$H-NMR. This constructed a ladder of equilibrium constants from acetophenone, for which the equilibrium constant for acetal formation has been measured, to methyl formate, for which it has not. This is the first direct measurement of an equilibrium constant for formation of an acetal of an acyclic ester.
To

My wife: Yanying Jia

and

My parents: Yaqyun Guo and Guiyun Liu
ACKNOWLEDGEMENTS

My sincere thanks to professor J. Peter Guthrie for having been such a stimulating research advisor. His guidance and contagious enthusiasm have always been a source of inspiration for me. His knowledge known as library has been being a strong encouragement not only for this thesis but also for the pursuit of my career.

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PART I. INTRAMOLECULAR

ALDOL CONDENSATION REACTIONS
1.1 Introduction

In most bimolecular reactions, appreciable changes in various interatomic distances within each molecule occur during the course of a collision which leads to reaction. The potential energy of this system, arising from the stretching and compression of various chemical bonds, usually passes through a maximum in such a collision. The configuration of the atoms at the maximum is known as the activated complex. An encounter complex is defined as a noncovalent complex of reactants or products which are in contact inside a common solvent cage with no intervening solvent.

Marcus theory is a quantitative relationship between the activation free energy and the reaction free energy change for a reaction occurring within an encounter complex. In Kresge's notation\textsuperscript{1}, this quantitative relationship can be expressed as: \( \Delta G^= \Delta G^\circ \left(1 + \Delta G^\circ /4\Delta G^\circ \right)^2 \), in which \( \Delta G^= \) and \( \Delta G^\circ \) refer to the activation free energy and the reaction free energy change for the reaction occurring within the encounter complex. \( \Delta G^\circ \) is the intrinsic barrier, the activation free energy which would be obtained if \( \Delta G^\circ \) were zero.
Although it has been argued that the intrinsic barrier arises largely from solvent reorganization,\textsuperscript{2} the observation of intrinsic barriers for gas-phase reactions\textsuperscript{3,4,3}, demonstrates that structural reorganization within the reacting molecules also contributes in an important way.

Marcus initially derived his theory relating activation free energy and reaction free energy change for weak-overlap electron transfer reactions.\textsuperscript{6-10} With slight modifications, Marcus later extended his theory to reactions with considerable resonance splitting, such as atom transfer reactions, proton transfer reactions and strong-overlap electron transfer reactions.\textsuperscript{11} Marcus theory was also applied successfully to electrophile-nucleophile combination reactions by other scientists.\textsuperscript{2,12-13} Dr. Guthrie recently correlated rate and equilibrium constants for intermolecular aldol condensation reactions in terms of Marcus theory.\textsuperscript{14} As Dr. Guthrie pointed out,\textsuperscript{14} "although empirical observation is running well ahead of theoretical justification, it seems that Marcus theory captures a deep and general feature of chemical reactivity, possibly extending to most if not all classes of reactions".
1.2 Simple derivation of Marcus equation.

The theoretical derivation of the Marcus equation is quite mathematical, but it can be derived simply from the Intersecting Parabola Model.\textsuperscript{11, 17} This model assumes that the potential energy of a reaction along the reaction coordinate involves a pair of intersecting parabolas. They represent the potential energy of the reactants and the products respectively. Both parabolas have the same shape. The intersection point of these two parabolas represents the transition state of the reaction. This model is shown schematically in \textbf{Scheme 1}.

The general parabola describing the reactants is $G_1 = a + bx + cx^2$. If we simplify the derivation by setting the initial state of the reactants at $G_1 = 0$, and define the reaction coordinate $x$ to be 0 at the initial state of the reactants and 1 at the final state of the products (i.e. bond order coordinate), then we have $a = 0$. Since the minimum in the parabola describing the reactants must be at $x = 0$, then $\frac{\partial G_1}{\partial x} = b + 2cx$ must be 0 at $x = 0$, so we have $b = 0$. Thus the parabola describing the reactants is $G_1 = cx^2$. 
Scheme 1. The Intersecting Parabola Model for Marcus equation derivation.

For the products, the parabola is $G_2 = d + e(1-x) + f(1-x)^2$. The free energy change $\Delta G^\circ$ in the reaction defines $d$: $d = \Delta G^\circ$. We have assumed that two parabolas have the same shape, then $f = c$. Since $G_2$ must be a minimum at $x = 1$, then $\partial G_2/\partial x = -e - 2f(1-x)$ must be 0 at $x = 1$, so we have $e = 0$. Thus the parabola for the products is $G_2 = \Delta G^\circ + c(1-x)^2$.

At the intersection point of the two parabolas (the transition state of the reaction), the reaction coordinate $x = x^*$, and $G_1 = G_2 = \text{the activation free energy} \Delta G^\circ$. Then we have
\( c(x^*)^2 = \Delta G^0 + c(1-x^*)^2 = \Delta G^\ast \). By solving this equation, we have \( \Delta G^\ast = (1 + \Delta G^0/c)^2c/4 \). As we stated earlier, when the reaction free energy change \( \Delta G^0 = 0 \), the activation free energy is the intrinsic barrier \( \Delta G^\ast \), then \( \Delta G^\ast = c/4 \). Now we have the Marcus equation, \( \Delta G^\ast = \Delta G^\ast \cdot (1 + \Delta G^0/4\Delta G^\ast)^2 \).

1.3 Marcus theory for weak-overlap electron transfer reactions. 6-10

1.3.1 Introduction.

In most reactions there is a transfer of atoms or groups of atoms between the reactants, and a rearrangement of atoms within each reactant. In order for this to occur, there presumably must be a strong interaction of the electronic structures of the two reactants in the activated complex. That is, there would be a considerable spatial overlap of the electronic orbitals of the two reacting molecules in this complex.

In contrast to such reactions, some reactions may merely involve the transfer of an electron between the reacting molecules. For such reactions to occur, only a slight overlap of the electronic orbitals may be necessary. Only a slight electronic interaction may be sufficient to electronically couple the two molecules and permit the electron transfer to
occur. Marcus developed his quantitative theory relating the activation free energy and the reaction free energy change on the basis of the assumption that there is little overlap of the electronic orbitals of the two reacting particles in the activated complex.

1.3.2 The reaction model for the theory.

When the reactants are near each other a suitable solvent fluctuation can result in the formation of the intermediate state, $X^*$, for which the atomic configuration of the reacting pair and of the solvent is that of the activated complex, and whose electronic configuration is that of the reactants. This state $X^*$ can either reform the reactants by disorganization of some of the oriented solvent molecules, or it can form the intermediate state $X$ by an electronic transition, this new state having an atomic configuration which is the same as that of $X^*$ but having an electronic configuration which is that of the products. The state $X$ can either reform $X^*$ by an electronic transition, or alternatively, the products in this state can move apart.

When one electron configuration is formed from the other by an electronic transition, the electronic motion is so rapid that the solvent molecules do not have time to move during the electronic jump. That is, the reaction proceeds by way of two successive intermediate states, $X^*$ and $X$, which have the same
atomic configurations but different electronic configurations. Conservation of energy leads to the requirement that the total energy of these two states must be the same. The pair of intermediate states $X^*$ and $X$ constitute the activated complex.

The reaction model described above can be schematically shown in **Scheme 2**. $A$ and $B$ denote the reactants involved in the electronic transition. In more complex systems, however, $A$ and $B$ may not be the actual compounds introduced into the reaction system, but would be the active entities formed from them.

\[
A + B \xrightarrow{k_1 \, \cancel{k_1}} X^* \\
X^* \xrightarrow{k_2 \, \cancel{k_2}} X \\
X \xrightarrow{k_3} \text{Products}
\]

**Scheme 2.** The reaction model for weak-overlap electron transfer reactions in Marcus theory.

1.3.3 **Marcus equation for weak-overlap electron transfer reactions.**

Based on the reaction model described in **Scheme 2**, the overall rate constant for the bimolecular reaction, $k_{bi} = k_1/[1 + (1 + k_2/k_3)k_4/k_4]$, is obtained by solving the steady-state
equations for the concentrations of $X^*$ and $X$. The various rate constants appearing in the above expression for the overall rate constant were estimated carefully by Marcus. It was found that when $k_2$ is more probable, or about as probable, as $k_{-1}$, the expression for $k_{b1}$ reduces to a particularly simple form: $k_{b1} = k_1$. This simple expression is used extensively afterwards and constitutes the basis for the modern Marcus equation.

In order to estimate $k_1$, Marcus developed an equation to calculate the free energy of formation of the intermediate state $X^*$ from the isolated reactants in the medium. There are an infinite number of pairs of (thermodynamic) intermediate states, $X^*$ and $X$, just as there are an infinite number of thermodynamic states of any system, each pair satisfying the energy restriction that $X^*$ and $X$ have the same total energy. Actually it is the most probable pair of intermediate states which constitutes the activated complex. The most probable pair of intermediate states can be determined with the aid of the calculus of variations by minimizing the free energy of formation of $X^*$ from the reactants subject to the energy restriction described above. This minimization procedure serves to determine the electrical polarization of the solvent at each point of the system in the intermediate state. This was then used to calculate the free energy of formation of the
intermediate state $X^*$ from the isolated reactants in the medium.

The following equation was found for the free energy of formation of the intermediate state $X^*$ from the isolated reactants in the medium, $\Delta F^*$, (in terms of Marcus' notation):

$$\Delta F^* = w^r + \lambda (1 + \Delta F''/\lambda)^{2/4}$$  \hspace{1cm} (1)

$\Delta F''$ denotes $\Delta F'' + w^p - w^r$, $\Delta F''$ is the overall reaction free energy change, $w^r$ (or $w^p$) is the work required to bring the reactants (or products) together to the mean separation distance in the activated complex, $\lambda/4$ is the intrinsic contribution to the barrier for electron transfer reactions.

For the reactions within the encounter complex (the pair of reactants or products have the mean separation distance in the activated complex), \textit{Equation 1} can be easily rewritten to the modern Marcus equation (in terms of Kresge's notation\textsuperscript{1}):

$$\Delta G'' = \Delta G''_0 (1 + \Delta G'/4\Delta G'')^2.$$  

\textbf{1.4 Extension of Marcus theory to the reactions with considerable resonance splitting.\textsuperscript{11}}

Although Marcus stated originally that his equation is "not applicable to any electron transfer reaction having a large-overlap activated complex",\textsuperscript{2} he still extended his theory successfully to reactions with considerable resonance
splitting, including strong-overlap electron transfer reactions and atom transfer reactions.\textsuperscript{11}

Because the potential energy along the reaction coordinate is different for weak-overlap electron transfer reactions and atom transfer reactions, Marcus introduced a modification into his extension. For the atom transfer reactions, the curve, potential energy vs. reaction coordinate, is initially constant, then rises to a maximum, and then falls to another constant value. One can no longer, therefore, obtain the "inverted chemical effect" possible with \textbf{Equation 1} at large $|\Delta F_{s,\infty}|$. Then Marcus limited his original theory, \textbf{Equation 1}, to $|\Delta F_{s,\infty}| \leq \lambda$. Outside that limit, the following equation was introduced (in terms of Marcus' notation\textsuperscript{11}):

\[ \Delta F^* = w^* (-\Delta F_{s,\infty} \geq \lambda), \quad \Delta F^*_\infty = \Delta F_{s,\infty}^\infty + w^* (\Delta F_{s,\infty} \geq \lambda) \] (2)

For the symbols in \textbf{Equation 2}, please refer to Part 1.3.3. In terms of Kresge's notation,\textsuperscript{1} \textbf{Equation 2} can be easily rewritten as: \( \Delta G^\infty = 0 \) \((-\Delta G^\infty \geq 4\Delta G^s\infty\)), \( \Delta G^s = \Delta G^\infty \) \((\Delta G^\infty \geq 4\Delta G^s)\) for a reaction within an encounter complex.

\textbf{1.5 The objective of Part I of this thesis.}

Marcus theory provides a quantitative relationship between the rate of the reaction (activation free energy) and the equilibrium of the reaction (reaction free energy change).
If it proves to be true for a class of reactions (that is, if there is an approximately constant intrinsic barrier for that class of reactions), we can then predict the rate of any example of that class of reactions as long as we can obtain the equilibrium constant, either from the literature or from thermodynamic estimation. This will give us a quantitative understanding of organic reactions. The influence of such an understanding will be far-reaching. Although it has been successfully applied to many reactions, as we stated in Part 1.1, most organic reactions are so complicated that we couldn’t justify the application of the Marcus equation to them theoretically, so that experimental testing turns out be very important. Every correlation of rate and equilibrium constants based on experimental data will give us more understanding about the applicability of Marcus theory to organic reactions.

The recent successful correlation for intermolecular aldol condensation reactions reported by Dr. Guthrie\textsuperscript{16} encouraged us to study intramolecular aldol condensation reactions, which are synthetically more important. To study the applicability of Marcus theory to intramolecular aldol condensation reactions, we first need to study the kinetics and equilibrium for a series of these reactions with as much variation as possible in the rates and in the equilibria for both the intramolecular aldol addition step and the subsequent
dehydration step. We then need to extract the rate and equilibrium constants for the reaction within the encounter complex from the apparent rate and equilibrium constants, and correlate the rate and equilibrium constants in terms of Marcus theory.

Based on the results of the correlation in terms of Marcus theory, we will find out whether the intramolecular aldol condensation reactions also have an approximately constant intrinsic barrier.

We will first report the detailed kinetics and equilibria for four intramolecular aldol condensation reactions in Chapters 2-5, then the correlation of the results in terms of Marcus theory will be described in Chapter 6.
CHAPTER 2. THE REACTION OF 2,5-HEXANEDIONE

2.1 Introduction

As was explained in Chapter 1, one of the goals of this thesis is to attempt to apply Marcus theory to intramolecular aldol condensation reactions. There were three questions to be answered: 1) Could we correlate the reaction rate and equilibrium constants for intramolecular aldol condensation reactions by using the Marcus equation? 2) If we could, what would be the intrinsic barrier for intramolecular aldol condensation reactions? 3) Would the intrinsic barrier for intramolecular aldol condensation reactions be the same as that for intermolecular aldol condensation reactions? To answer those questions we need the rate and equilibrium constants for a set of intramolecular aldol condensation reactions. We first studied the base-catalyzed reaction of 2,5-hexanedione: both the intramolecular aldol addition step and the following dehydration step. The reaction rate and equilibrium constants are defined in Scheme 3.
Scheme 3. The reaction scheme for the base-catalyzed intramolecular aldol condensation reaction of 2,5-hexanodione (dione-1): $k_{12}$ is the rate constant for intramolecular aldol addition of dione-1; $k_{23}$ is the rate constant for dehydration of ketol-1; $k_{21}$ is the rate constant for retroaldol cleavage of ketol-1; $k_{32}$ is the rate constant for hydration of enone-1; $K_{12} = [\text{Ketol-1}]/[\text{Dione-1}]$; $K_{23} = [\text{Enone-1}]/[\text{Ketol-1}]$.

2.2 Results

2.2.1 Reaction starting with 2,5-hexanodione (dione-1).

Starting with dione-1, the kinetics of the base-catalyzed intramolecular aldol condensation reaction were studied with both HPLC and UV analysis. For analysis by UV, 3-methyl-2-cyclopenten-1-one (enone-1) was followed at 232 nm. HPLC analysis allowed us to follow the disappearance of dione-1 (see Figure 1) and the growth of enone-1 (see Figure 2) simultaneously. Both the disappearance of dione-1 and the growth of enone-1 exhibited simple first-order behavior. No
accumulation of 3-hydroxy-3-methylcyclopentanone (ketol-1) was observed during the reaction process, which suggests that dehydration of ketol-1 \((k_{23})\) is faster than intramolecular aldol addition of dione-1 \((k_{12})\). This implies that the measured rate constants represent the pseudofirst-order rate constant of approach to the equilibrium between dione-1 and enone-1, where the reaction from dione-1 to ketol-1 is rate-limiting: \((k_{12} + k_{21}k_{32}/(k_{21} + k_{23})) [OH^-]\). The apparent rate constants showed a first-order dependence on the hydroxide concentration, leading to a second-order rate constant \(k_{12} + k_{21}k_{32}/(k_{21} + k_{23}) = (3.35 \pm 0.47) \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}\). The measured pseudofirst-order rate constants and the calculated second-order rate constants are found in Table 1.
Table 1. Kinetics of Base-catalyzed Intramolecular Aldol Condensation of 2,5-Hexanedione (dione-1) from the Reaction Starting with Dione-1*

<table>
<thead>
<tr>
<th>No.</th>
<th>$10^4 C_0$</th>
<th>[NaOH]</th>
<th>$A_1$</th>
<th>$A_2$</th>
<th>$10^6 A_3$</th>
<th>$10^5 (k_{12} + k_{21}k_{32}/(k_{21} + k_{23}))$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M</td>
<td></td>
<td></td>
<td>M$^{-1}$s$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>1.99</td>
<td>0.998</td>
<td>2.595±0.002</td>
<td>-2.557±0.002</td>
<td>37.5±0.1</td>
<td>3.76±0.01</td>
</tr>
<tr>
<td>2*</td>
<td>1.99</td>
<td>0.096</td>
<td>2.635±0.007</td>
<td>-2.602±0.007</td>
<td>2.82±0.01</td>
<td>2.94±0.01</td>
</tr>
<tr>
<td>3*</td>
<td>9.89</td>
<td>0.090</td>
<td>9.42±0.28</td>
<td>-9.59±0.25</td>
<td>2.47±0.14</td>
<td>2.74±0.16</td>
</tr>
<tr>
<td>4*</td>
<td>9.89</td>
<td>0.090</td>
<td>0.03±0.26</td>
<td>9.62±0.18</td>
<td>2.47±0.16</td>
<td>2.74±0.17</td>
</tr>
</tbody>
</table>

Weighted mean

3.35±0.47

*In aqueous solution at 25°C, starting with dione-1, ionic strength = 1.0 M (KCl).

*Initial concentration of starting material, dione-1.

*Sodium hydroxide concentration.

*UV absorbance or HPLC peak height (A) – time (t) data were fitted to $A = A_1 + A_2 \times \exp(-A_3 \times t)$ by nonlinear least squares. $A_3$ corresponds to the apparent rate constant ($k_{12} + k_{21}k_{32}/(k_{21} + k_{23})$).
k_{21}k_{12}/(k_{21} + k_{23})[\text{OH}^-], and k_{12} + k_{21}k_{12}/(k_{21} + k_{23}) is the second-order rate constant for the rate of approach to the equilibrium between dione-1 and 3-methyl-2-cyclopenten-1-one (enone-1), where the reaction from dione-1 to 3-hydroxy-3-methylcyclopentanone (ketol-1) is rate-limiting. The standard deviations for the rate constants were calculated by the least squares procedure.

*Followed the growth of enone-1 by UV, monitoring the absorbance at 232 nm.

*Followed the growth of enone-1 by HPLC, monitoring the absorbance at 232 nm.

*Followed the disappearance of dione-1 by HPLC, monitoring the absorbance at 265 nm.
Figure 1. Base-catalyzed intramolecular aldol condensation reaction of 2,5-hexanedione (dione-1). The disappearance of dione-1 was followed by HPLC, monitoring the absorbance at 265 nm (see Entry 4 in Table 1).
Figure 2. Base-catalyzed intramolecular aldol condensation reaction of 2,5-hexanediode (dione-1). The growth of 3-methyl-2-cyclopenten-1-one (enone-1) was followed by HPLC, monitoring the absorbance at 232 nm (see Entry 3 in Table 1).

HPLC Peak Height (A) vs. Time (t, min)
2.2.2 Reaction starting with 3-hydroxy-3-methylcyclopentanone (ketol-1).

Starting with ketol-1, the kinetics of base-catalyzed dehydration were studied with both HPLC and UV analysis. For analysis by UV, 3-methyl-2-cyclopenten-1-one (enone-1) was followed at 232 nm (see Figure 3). HPLC analysis allowed us to follow both the disappearance of starting material, ketol-1, (see Figure 4), and the growth of product, enone-1, (see Figure 5) at the same time. Both the disappearance of ketol-1 and the growth of enone-1 showed first-order behavior. These measurements gave us the pseudofirst-order rate constant of approach to hydration-dehydration equilibrium \((k_{23} + k_{32})[\text{OH}^-]\), which effectively gave us the pseudofirst-order rate constant for dehydration of ketol-1 \((k_{23}[\text{OH}^-])\) because the equilibrium was far on the side of enone-1. The apparent rate constants showed a first-order dependence on the hydroxide concentration, leading to a second-order rate constant, \(k_{23} = 0.110 \pm 0.007\), for dehydration of ketol-1. At the end of the reaction, the equilibrium concentrations of both ketol-1 and enone-1 were measured directly by HPLC analysis, which allowed us to determine the equilibrium constant, \(K_{23}\), for the reaction converting ketol-1 into enone-1. The measured pseudofirst-
order rate constants, the calculated second-order rate constants and equilibrium constants are found in Table 2.
Table 2. Kinetics and Equilibrium for Base-catalyzed Dehydration of 3-Hydroxy-3-methylcyclopentanone (ketol-1) from the Reaction Starting with Ketol-1

<table>
<thead>
<tr>
<th>No</th>
<th>$C_0$, $^b$</th>
<th>$[OH^-]$, $^c$</th>
<th>$A_1$, $^d$</th>
<th>$A_2$, $^d$</th>
<th>$10^3A_3$, $^d$</th>
<th>$k_{23}$, $^d$</th>
<th>$10^{-2}K_{23}$, $^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1$^f$</td>
<td>$1.17\times10^{-3}$</td>
<td>0.010</td>
<td>0.19±0.14</td>
<td>10.44±0.09</td>
<td>1.01±0.04</td>
<td>0.101±0.004</td>
<td></td>
</tr>
<tr>
<td>2$^g$</td>
<td>$1.17\times10^{-3}$</td>
<td>0.010</td>
<td>10.6±0.2</td>
<td>-10.6±0.2</td>
<td>0.980±0.043</td>
<td>0.098±0.004</td>
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</tr>
<tr>
<td>3$^h$</td>
<td>$1.26\times10^{-5}$</td>
<td>0.034</td>
<td>0.4036±0.0002</td>
<td>-0.2496±0.0005</td>
<td>3.91±0.02</td>
<td>0.115±0.0006</td>
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<tr>
<td>4$^h$</td>
<td>$1.26\times10^{-5}$</td>
<td>0.046</td>
<td>0.4122±0.0002</td>
<td>-0.2561±0.0007</td>
<td>4.80±0.03</td>
<td>0.104±0.0007</td>
<td></td>
</tr>
<tr>
<td>5$^d$</td>
<td>$1.17\times10^{-1}$</td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.36±0.35</td>
</tr>
</tbody>
</table>

Weighted mean

|                  | $0.110±0.007$ |

$^a$All reactions were carried out in aqueous solution at 25°C, ionic strength = 1.0 M (KCl), starting with ketol-1. Ketol-1 and 3-methyl-2-cyclopenten-1-one (enone-1) were followed at 271 nm and 232 nm respectively.
Initial concentration of starting material, ketol-1.

Sodium hydroxide concentration.

The HPLC peak area or UV absorbance (A)-time (t) data were fitted to \( A = A_1 + A_2 \times \exp(-A_3 \times t) \) by nonlinear least squares. \( A_3 \) corresponds to the pseudofirst-order rate constant \( k_{23}[OH^-] \), and \( k_{23} \) in this table is the second-order rate constant for the dehydration of ketol-1. Standard deviations were calculated by the nonlinear least squares procedure.

\( K_{23} = [\text{enone-1}] / [\text{ketol-1}] \) is the equilibrium constant for the dehydration of ketol-1.

Followed the disappearance of ketol-1 by HPLC.

Followed the growth of enone-1 by HPLC.

Followed the growth of enone-1 by UV.

Did not follow kinetics, analyzed both species, by HPLC, at equilibrium.
Figure 3. Base-catalyzed dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1). The growth of 3-methyl-2-cyclopenten-1-one (enone-1) was followed by UV, monitoring the absorbance at 232 nm (see Entry 3 in Table 2).

UV Absorbance (A) vs. Time (t, sec).
Figure 4. Base-catalyzed dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1). The disappearance of ketol-1 was followed by HPLC, monitoring the absorbance at 271 nm (see Entry 1 in Table 2).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 5. Base-catalyzed dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1). The growth of 3-methyl-2-cyclopenten-1-one (enone-1) was followed by HPLC, monitoring the absorbance at 232 nm (see Entry 2 in Table 2).

HPLC Peak Area (A) vs. Time (t, sec).
2.2.3 Reaction starting with 3-methyl-2-cyclopenten-1-one (enone-1).

The equilibrium is far on the side of enone-1, so it is not practical for us to carry out kinetics starting with enone-1. However, to make sure that the true equilibrium has been reached when starting with 3-hydroxy-3-methylcyclopentanone (ketol-1), the hydration of enone-1 was carried out under the same conditions as described in Table 2. The measured equilibrium constant $K_{23}$ for the reaction converting ketol-1 to enone-1 is $(5.67 \pm 0.35) \times 10^2$ when starting with $1.15 \times 10^{-1}$ M of enone-1, which is in good agreement with the value obtained when starting with ketol-1. This demonstrates that true equilibrium has been reached.

2.2.4 Overall equilibrium constant.

Because no 2,5-hexanedione (dione-1) was detected directly at the end of reaction, we developed a DNPH approach (DNPH: 2,4-dinitrophenylhydrazone) to determine the equilibrium concentration of dione-1. By converting dione-1 to its bis-DNPH, two advantages were obtained: 1) the 2,4-dinitrophenyl groups served as strong UV chromophores leading to improved HPLC detection sensitivity; 2) they also served as strong hydrophobic groups leading to much longer retention time in reversed phase HPLC column (C18) and much better HPLC
resolution. Because the rate of approach to intramolecular aldol condensation equilibrium under acidic condition is much slower than that of the formation of DNPH, the bis-DNPH formed from dione-1 must represent the equilibrium concentration of dione-1. Using this DNPH approach, the overall equilibrium constants were determined both starting with dione-1 and starting with 3-methyl-2-cyclopenten-1-one (enone-1). The measured equilibrium constants are found in Table 3.

Table 3. Overall Equilibrium Constants for the Reaction Leading from 2,5-Hexanedione (dione-1) to 3-Methyl-2-cyclopenten-1-one (enone-1). Derived from the Reaction Starting with Dione-1 and the Reaction Starting with Enone-1

| Starting Point | Equilibrium Point | $10^{-3}K$
|----------------|-------------------|---
| [Dione-1], [Enone-1], M, M | [Dione-1]${}^{,b}$, [Enone-1]${}^{,e}$, M, M |  
| 7.40×10^{-4} 0 | 1.17×10^{-7} 7.40×10^{-4} | 6.32  
| 0 9.60×10^{-4} | 1.68×10^{-7} 9.58×10^{-4} | 5.70  
| Avg. | | 6.03±0.31  

*In 1.0 M NaOH aqueous solution at 25°C, ionic strength = 1.0 M, $K = [enone-1]/[dione-1]$. 
*Determined by the DNPH approach (see text), analysing by HPLC, monitored at 360 nm.

* Determined directly by HPLC, monitored at 232 nm.

2.2.5 Summary of the rate and equilibrium constants for the reaction of 2,5-hexanedione (dione-1).

The base-catalyzed intramolecular aldol addition of 2,5-hexanedione (dione-1) and the following base-catalyzed dehydration reaction of 3-hydroxy-3-methylcyclopentanone (ketol-1) were studied in aqueous solution with HPLC and UV analysis. The reactions were studied by starting with dione-1, ketol-1 and 3-methyl-2-cyclopenten-1-one (enone-1) respectively. Four rate constants and two equilibrium constants required to describe the reaction of dione-1 in terms of Scheme 3 were obtained. The calculated rate and equilibrium constants for the reaction of dione-1 are summarized in Table 4. The calculated rate constants show that base-catalyzed intramolecular aldol addition of dione-1 is about 3000 times slower than base-catalyzed dehydration reaction of ketol-1.
Table 4. Rate and Equilibrium Constants for the Reaction of 2,5-Hexanediene (dione-1) *

<table>
<thead>
<tr>
<th>No.</th>
<th>$10^3k_{12}^\dagger$</th>
<th>$10^5k_{12}^\circ$</th>
<th>$10^6k_{21}^\ddagger$</th>
<th>$k_{23}^\circ$</th>
<th>$10^4k_{32}^f$</th>
<th>$K_{12}^\alpha$</th>
<th>$10^{-2}K_{23}^h$</th>
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<td></td>
<td>M$^{-1}$S$^{-1}$</td>
<td>M$^{-1}$S$^{-1}$</td>
<td>M$^{-1}$S$^{-1}$</td>
<td>M$^{-1}$S$^{-1}$</td>
<td>M$^{-1}$S$^{-1}$</td>
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<td></td>
</tr>
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<td>3.35±0.47</td>
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<td></td>
<td>0.110±0.007</td>
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<td>6.36±0.35</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>5.67±0.35</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Avg.</td>
<td>3.35±0.47</td>
<td>3.35</td>
<td>3.35</td>
<td>0.110±0.007</td>
<td>1.83</td>
<td>10.0</td>
<td>6.02±0.49</td>
</tr>
</tbody>
</table>

*The values were calculated in this table unless otherwise noted.

**The second-order rate constant for the base-catalyzed rate of approach to the equilibrium between dione-1 and 3-methyl-2-cyclopenten-1-one (enone-1), where the reaction from dione-1 to 3-hydroxy-3-methylcyclopentanone (ketol-1) is rate-limiting, from Table 1.

---

The second-order rate constant for the base-catalyzed intramolecular aldol addition of dione-1.

---

The second-order rate constant for the base-catalyzed retroaldol cleavage reaction of ketol-1.
The second-order rate constant for the base-catalyzed dehydration reaction of ketol-1, from Table 2.

The second-order rate constant for the base-catalyzed hydration reaction of enone-1.

\[ K_{12} = \frac{[\text{ketol-1}]}{[\text{dione-1}]} \], the equilibrium constant for the reaction leading from dione-1 to ketol-1.

\[ K_{23} = \frac{[\text{enone-1}]}{[\text{ketol-1}]} \], the equilibrium constant for the reaction leading from ketol-1 to enone-1.

'From Table 2.

'Obtained from the reaction starting with enone-1.
2.2.6 Determination of the rate-limiting step.

2.2.6.1 The intramolecular aldol addition step for 2,5-hexanedione (dione-1).

The base-catalyzed intramolecular aldol addition of dione-1 has two major steps mechanistically: the formation of the enolate of dione-1 on the methyl side and the cyclization of this enolate to give the anion of 3-hydroxy-3-methylcyclopentanone (ketol-1). The activation energy for the enolate formation was estimated after Guthrie,\textsuperscript{16} where pK$\text{a}$ = 18.94 was used for the methyl side of dione-1 (see Chapter 6 for pK$\text{a}$ estimation). The activation energy for enolate formation was calculated to be 18.5 kcal/mol. On the other hand, the observed activation energy for the base-catalyzed intramolecular aldol addition step of dione-1 was found to be 23.6 kcal/mol. This result clearly demonstrated that the intramolecular aldol cyclization was the rate-limiting step, and that enolate formation was a fast pre-equilibrium.

2.2.6.2 The dehydration step for 3-hydroxy-3-methylcyclopentanone (ketol-1).

The base-catalyzed dehydration of ketol-1 also has two major steps: enolate formation of ketol-1 at carbon-2 and the departure of hydroxyl group (see Scheme 4).
Scheme 4. The mechanism of the base-catalyzed dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1).

The activation energy for the enolate formation was estimated as 19.3 kcal/mol after Guthrie with pKₐ = 17.37 was used for ketol-1 at carbon-2 (see Chapter 6 for pKa estimation). The observed activation energy for the base-catalyzed dehydration of ketol-1 was found to be 18.8 kcal/mol. This result showed that the observed activation energy was very close to the estimated activation energy for enolate formation of ketol-1 at carbon-2, leading to two possibilities: 1) enolate formation might be the rate-limiting step, with the departure of hydroxyl group from the formed enolate being a fast subsequent step. In this case, the observed rate constant would actually be the rate constant for enolate formation. 2) The departure of hydroxyl group from the pre-formed enolate might be the rate-limiting step or at least be partially rate-limiting. In this case, we could calculate, from the observed rate constant, the rate constant for the
departure of the hydroxyl group from the enolate of ketol-1 at carbon-2, which is needed for the Marcus analysis.

In order to identify which was the real case, we carried out the base-catalyzed dehydration reaction of ketol-1 in D$_2$O. The reaction path for dehydration in D$_2$O is shown in Scheme 5. By using the matrix method,$^{19}$ the growth of 3-methylo3-cyclopenten-1-one (enone-1) by the mechanism shown in Scheme 5 was found to be given by a triple exponential equation: $A = A_1 + A_2 \times \exp(-A_3t) + A_4 \times \exp(-A_5t) + A_6 \times \exp(-A_7t)$, where $A_3 = k_1^H$; $A_5 = k_1^H + (k_1^Dk_2^D)/(k_1^H + k_2^D)$; $A_7 = (k_1^Dk_2^D)/(k_1^H + k_2^D)$. Experimentally the growth of enone-1 only showed two-phase kinetics (see Figure 6), because $A_3$ and $A_5$ are very close, and thus are indistinguishable kinetically. This implies that the first phase might be a combination of $A_3$ and $A_5$ or $A_3$ only or $A_5$ only depending on the magnitude of the preexponential term. The second phase, however, certainly represents $A_7$, both chemically and mathematically. Then we have:

$$(k_1^Dk_2^D)/(k_1^H + k_2^D) = A_7/[OH^-] = (0.0286 \pm 0.0005) \text{ M}^{-1}\text{s}^{-1} \quad (3)$$

The standard deviation in equation (3) was calculated by the non-linear least squares procedure. The solvent kinetic isotope effects are very small, as discussed in Part 3.2.5.1
Scheme 5. The reaction path for the base-catalyzed dehydration reaction of 3-hydroxy-3-methylcyclopentanone (ketol-1) in D$_2$O.
Figure 6. Base-catalyzed dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1) in D$_2$O. The growth of 3-methyl-2-cyclopenten-1-one (enone-1) was followed by UV, monitoring the absorbance at 232 nm.

UV Absorbance vs. Time (t, sec)
in Chapter 3, on the other hand, the intrinsic barrier for the dehydration of the cyclic ketol is unknown at this stage, and we can not determine the position of the transition state which is needed for the estimation of the solvent kinetic isotope effect. We then ignore the solvent kinetic isotope effect in this case. If we also ignore the secondary kinetic isotope effects, we have:

\[ k_1' = k_1 / (k^{HD})_{primary} \]  
\[ k_2' = k_2 \]  
\[ k_{-1}' = k_{-1} / (k^{HD})_{primary} \]

where \( k_1, k_2 \) and \( k_{-1} \) are the rate constants in \( H_2O \) as defined in Scheme 4, \( (k^{HD})_{primary} \) is the primary kinetic isotope effect, which was estimated by using Kresge's model. \( ^{27} \) \( \ln (k^{HD})_{primary} = \ln (k^{HD})_{max}[1-(\Delta G^o/4\Delta G^w)^2] = 2.04 \), leading to \( (k^{HD})_{primary} = 7.7 \), where \( \Delta G^o = 4.21 \) kcal/mol was calculated by using the \( pK_a = 17.37 \) for ketol-1 at carbon-2 (see Chapter 6 for \( pK_a \) estimation). Then we have:

\[ k_1' = k_1 / 7.7 \]  
\[ k_{-1}' = k_{-1} / 7.7 \]

Substituting equations (5), (7) and (8) into equation (3), we have:

\[ k_1 / 7.7 \cdot k_2 / (k_{-1} / 7.7 + k_2) = 0.0286 \]

The base-catalyzed dehydration reaction of ketol-1 in \( H_2O \) should give us (see Table 2):

\[ k_2 \cdot k_2 / (k_{-1} + k_2) = k_{23} = 0.110 \]
Then we set $k_1 = nk_2$  \hspace{1cm} (11)

Solving equations (9), (10) and (11), we obtained $n = 1.35$ and $k_1 = 0.259 \text{ M}^{-1}\text{s}^{-1}$. This result clearly demonstrated that the departure of the hydroxyl group from the enolate of ketol-1 in H$_2$O ($k_2$ in Scheme 4) is partially rate-limiting. It also indicated that proton transfer process is partially rate-limiting and not a fast pre-equilibrium.

### 2.3 Experimental

#### 2.3.1 Instrumentation

NMR: Gemini 200 and Gemini 300.

MS: Finnigan MAT 8230.

UV: Shimadzu 160 for general measurement and Cary 210 for the kinetics measurement.

HPLC system: Millipore model 510 pumps, Millipore model 490 programmable and multiwavelength UV-Vis detector, Millipore model 680 automated gradient controller.

#### 2.3.2 Materials

2,5-Hexanedione (98%, dione-1), 3-methyl-2-cyclopenten-1-one (97%, enone-1) and 1,3-cyclopentanodione (97%) were obtained from Aldrich, and 2,4-dinitrophenylhydrazine (DNP) from Eastman. All compounds were used as supplied and checked by $^1$H-NMR and HPLC before being used in this work.
3-Hydroxy-3-methylcyclopentanone (ketol-1) was synthesized according to the literature procedure\textsuperscript{19} for the preparation of 3-hydroxy-3-phenylcyclohexanone as follows: An ethereal solution (250 mL) of methylmagnesium iodide from methyl iodide (11.4 mL, 0.18 mol) and magnesium turnings (4.5 g, 0.18 mol) was prepared in the pot of a Soxhlet extractor. The extraction thimble was charged with 1,3-cyclopentanедione (3.0 g, 30.6 mmol) and the extraction process continued under nitrogen for 24 h. The reaction mixture was cooled in an ice-bath and quenched by solid ammonium chloride (19.3 g, 0.36 mol), then water (10 mL). The ether layer was separated, the residue was extracted by ether (4 x 150 mL), and the combined ether extracts were dried over anhydrous MgSO\textsubscript{4}. Column chromatography (Silica gel-60, 0.063-0.2 mm, from Chemica Alta Ltd, eluting with 4:1 ethyl acetate-petroleum ether) gave 71 mg (2.0\%) of 3-hydroxy-3-methylcyclopentanone (ketol-1): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 1.51 (s, 3 H), 1.73 (s, 1 H), 1.84-2.50 (m, 6 H); MS m/z 114 (M\textsuperscript{+}, 30\%), 96 (100\%). Literature\textsuperscript{20} data for ketol-1: \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 1.50 (s, 3 H), 1.90-2.60 (m, 7 H); MS m/z 114 (M\textsuperscript{+}, 27\%), 96 (100\%).

2,5-Hexanedione bis-2,4-dinitrophenylhydrazone (bis-DNPH). Dinitrophenylhydrazine (DNP) solution (150 mL) was
prepared by a standard method\textsuperscript{21}. To this DNP solution was added 10 mL of 2,5-hexanedione (0.8 mL) solution in 95\% EtOH. A yellow precipitate appeared immediately and the reaction mixture was allowed to stand for another 1 h at room temperature. 3.25 g (100\%) of yellow solid was obtained after filtration. Recrystallization from pyridine gave pure bis-DNPH (judged by HPLC): MS \textit{m/z} 474 (M\textsuperscript{`}, 5\%), 277 (100\%); mp 259\(^\circ\)C; UV(CHCl\textsubscript{3}) \(\lambda_{\text{max}} = 367\text{ nm (4.39)}\). Literature data for bis-DNPH: mp\textsuperscript{22} 260\(^\circ\)C; UV(CHCl\textsubscript{3})\textsuperscript{23} \(\lambda_{\text{max}} = 362\text{ nm (4.39)}\).

2.3.3 Methods

2.3.3.1 Kinetics

Reactions followed by UV were carried out using a Cary 210 spectrophotometer with a thermostatted 10 cm cell holder. A Neslab Exocal EX300 circulating constant temperature bath was used to maintain the temperature at 25\(\pm0.1\)\(^\circ\)C. Reactions were initiated by adding a suitable amount of aqueous sodium hydroxide solution to the quartz cell containing a solution of starting material in water, which had been in the thermostatted cell holder for about 15 min. Digital absorbance data were taken from the Digital Interface Port of the Cary 210 and stored in a microcomputer, which supplied time values, until the end of the experiment. The stored absorbance-time data were fitted
to the single exponential equation by a non-linear least squares procedure to obtain the rate constants.

Reactions followed by HPLC were carried out in a constant temperature bath at 25°C, from which reaction mixtures were removed at suitable intervals and quenched to pH 7 by the addition of phosphoric acid. Analysis was carried out using Waters C18 Radial-Pak columns and Waters 490 Programmable and Multiwavelength detector on quenched samples.

For reactions starting with dione-1, aqueous methanol was used as eluting solvent. The HPLC chromatograms were recorded by a Goerz Metrawatt SE 120 dual channel recorder. The HPLC peak height-time data were fitted to a single exponential equation by a non-linear least squares procedure to obtain the rate constants. The concentrations of materials eluted were monitored at suitable wavelengths and sensitivities: dione-1, 265 nm (AUFS 0.01); enone-1, 232 nm (AUFS 2). A calibration was carried out using a suitable stock solution.

For reactions starting with ketol-1, a solution of 5% acetonitrile in water was used as eluting solvent. The HPLC chromatograms were stored directly in a microcomputer by the Gilson 715 HPLC system controller software. The HPLC peak area-time data were fitted to the single exponential equations by non-linear least squares procedure to calculate
the rate constants. The materials eluted were followed at suitable wavelengths: 271 nm for ketol-1 and 232 nm for enone-1.

For the kinetics in D_2O, we started with 4.10 \times 10^{-3} \text{ M} of ketol-1 in 0.020 \text{ M} NaOD with ionic strength 1.0 \text{ M (KCl)}. The growth of the product, enone-1, was followed by UV at 232 nm. The UV absorbance - time data were fitted to a double exponential equation by a non-linear least squares procedure.

2.3.3.2 Overall equilibrium constant

The equilibrium concentration of enone-1 was determined in the same way as described for kinetics experiments for reactions starting with dione-1.

The equilibrium concentration of dione-1 was determined using the DNPH approach as follows:

The reaction mixtures were quenched by addition of phosphoric acid. To the quenched solution (100 mL) was added DNP solution (200 mL, 2 \times 10^{-3} \text{ M}) in 2 \text{ M hydrochloric acid.} The mixture was stirred for 2 h at room temperature, and then extracted with CHCl_3 (3 \times 50 \text{ mL}). The combined CHCl_3 extracts were concentrated to 3-5 mL using a rotary evaporator. The volume of concentrated chloroform solution was determined by using a 10 mL graduated cylinder. The concentration of bis-DNPH of dione-1 in the concentrated CHCl_3 solution was determined by HPLC: eluting solvent, 75\% acetonitrile in
water; detector, Waters 490, 360 nm (AUFS, 1); recorder, Waters 740, ATTN 16. The integration was used for quantitative analysis. The equilibrium concentration of dione-1 was obtained by calibration using a known mixture with similar composition to the equilibrium reaction mixture.
CHAPTER 3. THE REACTION OF 2,6-HEPTANEDIONE

3.1 Introduction

To test the applicability of Marcus theory for the intramolecular aldol condensation reactions, that is to test whether the intrinsic barrier for these reactions is constant or not, we need to vary the observed rate and equilibrium constants of both the intramolecular aldol addition step and the subsequent dehydration step as much as possible. In this way we could apply Marcus theory to a wide range of intramolecular aldol condensation reactions and get more reliable testing. For this reason, we studied the intramolecular aldol condensation reaction of 2,6-heptanedione, reported in this chapter, after we had finished the studies on the reaction of 2,5-hexanedione, reported in Chapter 2. From the reaction of 2,5-hexanedione to the reaction of 2,6-heptanedione, the intramolecular aldol addition step shifted from five-membered ring formation to six-membered ring formation, and we expect a significant change in reaction rate constants. The reaction rate and equilibrium constants are defined in Scheme 6.
Scheme 6. The reaction scheme for the base-catalyzed intramolecular aldol condensation of 2,6-heptanedione (dione-2): $k_{12}$ is the rate constant for intramolecular aldol addition of dione-2; $k_2$, is the rate constant for dehydration of ketol-2; $k_{21}$ is the rate constant for retroaldol cleavage of ketol-2; $k_{32}$ is the rate constant for hydration of enone-2; $K_{12} = [\text{Ketol-2}]/[\text{Dione-2}]$; $K_{23} = [\text{Enone-2}]/[\text{Ketol-2}]$.

3.2 Results

3.2.1 Reaction starting with 2,6-heptanedione (dione-2).

Starting with dione-2, the kinetics of the base-catalyzed intramolecular aldol addition reaction of dione-2 and dehydration of the formed 3-hydroxy-3-methylcyclohexanone (ketol-2) were studied with both HPLC and UV analysis. In the case of UV analysis only the growth of 3-methyl-2-cyclohexene-1-one (enone-2) could be followed (see Figure 7). HPLC analysis allowed us to follow the disappearance of dione-2 (see Figure 8), the concentration change of ketol-2 (see
Figure 9), and the growth of enone-2 (see Figure 10) at the same time. The identities of dione-2 and enone-2 were based on comparison with the authentic compounds, while that of ketol-2 was based on the observed chemical interconversion: in the reaction starting with dione-2, ketol-2 was formed from dione-2 and accumulated in the first stage, then was more slowly converted into enone-2 and finally ended up at the equilibrium point. The disappearance of dione-2 showed essentially single exponential kinetics, however, both the concentration change of ketol-2 and the growth of enone-2 showed two-phase kinetics, which allowed us to measure the pseudofirst-order rate constants for intramolecular aldol addition of dione-2 ($k_{12}[OH^-]$) and dehydration of ketol-2 ($k_{23}[OH^-]$) simultaneously (for the kinetic derivation, see Appendix 1). Strictly speaking, the measured values were the rates of approach to the equilibria, ($k_{12} + k_{21})[OH^-]$ and ($k_{23} + k_{32})[OH^-]$, but in this case the contributions of $k_{21}$ and $k_{32}$ were less than experimental errors. Then the measured rate constants actually represented the rate constants $k_{12}[OH^-]$ and $k_{23}[OH^-]$. The accumulation of ketol-2 in the reaction process suggests that the intramolecular aldol addition step of dione-2 ($k_{12}[OH^-]$) is faster than the dehydration of ketol-2 ($k_{23}[OH^-]$). The apparent rate constants showed a first-order dependence on hydroxide concentration. The measured pseudofirst-order and calculated second-order rate constants are found in Table 5.
Table 5. Kinetics of Base-catalyzed Intramolecular Aldol Addition of 2,6-Heptanedione (dione-2) and Dehydration of 3-Hydroxy-3-methylcyclohexanone (ketol-2) from the Reaction Starting with Dione-2\(^a\)

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<td>2.95±0.02</td>
<td>-1.453±</td>
<td>7.20±0.01</td>
<td>7.38±0.04</td>
<td>1.80±0.003</td>
</tr>
<tr>
<td>5(^b)</td>
<td>0.0388</td>
<td>0.150</td>
<td>1.124±</td>
<td>0.410±</td>
<td>11.1±0.1</td>
<td>-1.527±</td>
<td>29.7±0.1</td>
<td>7.40±0.08</td>
<td>1.98±0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weighted mean</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out in aqueous solution at 25°C, starting with dione-2, ionic strength = 1.0 M (KCl).
Initial concentration of starting material, dione-2.

Sodium hydroxide concentration.

HPLC peak area or UV absorbance (A) - time (t) data were fitted to \( A = A_1 + A_2 \times \exp(-A_3 \times t) + A_4 \times \exp(-A_5 \times t) \) by nonlinear least squares except that No.1 was fitted to \( A = A_1 + A_2 \times \exp(-A_3 \times t) \). \( A_3 \) and \( A_5 \) correspond to the pseudofirst-order rate constants \( k_{12}[\text{OH}^-] \) and \( k_{23}[\text{OH}^-] \), where \( k_{12} \) and \( k_{23} \) are the second-order rate constants for intramolecular aldol addition of dione-2 and dehydration of ketol-2 respectively. The standard deviations for the parameters were calculated by the non-linear least squares procedure.

Followed the disappearance of dione-2 by HPLC, monitoring the absorbance at 271 nm.

Followed the concentration change of ketol-2 by HPLC, monitoring the absorbance at 271 nm.

Followed the growth of 3-methyl-2-cyclohexen-1-one (enone-2) by HPLC, monitoring the absorbance at 240 nm.

Followed the growth of enone-2 by UV, monitoring the absorbance at 240 nm.
Figure 7. Base-catalyzed intramolecular aldol condensation reaction of 2,6-heptanedione (dione-2). The growth of 3-methyl-2-cyclohexen-1-one (enone-2) was followed by UV, monitoring the absorbance at 240 nm (see Entry 4 in Table 5).

UV Absorbance (A) vs. Time (t, sec).
Figure 8. Base-catalyzed intramolecular aldol condensation reaction of 2,6-heptanедione (dione-2). The disappearance of dione-2 was followed by HPLC, monitoring the absorbance at 271 nm (see Entry 1 in Table 5).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 9. Base-catalyzed intramolecular aldol condensation reaction of 2,6-heptanedicone (dione-2). The concentration of 3-hydroxy-3-methylcyclohexanone (ketol-2) was followed by HPLC, monitoring the absorbance at 271 nm (see Entry 2 in Table 5).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 10. Base-catalyzed intramolecular aldol condensation reaction of 2,6-heptanedione (dione-2). The growth of 3-methyl-2-cyclohexen-1-one (enone-2) was followed by HPLC, monitoring the absorbance at 240 nm (see Entry 3 in Table 5).

HPLC Peak Area (A) vs. Time (t, sec).
3.2.2 Reaction starting with 3-methyl-2-cyclohexen-1-one (enone-2)

Starting with enone-2, the kinetics and equilibrium of the base-catalyzed hydration reaction were studied with HPLC analysis. Although the equilibrium was far on the side of enone-2 and the change in the concentration of the starting material, enone-2, was not measurable, HPLC analysis allowed us to follow the growth of 3-hydroxy-3-methylcyclohexanone (ketol-2) (see Figure 11). The growth of ketol-2 showed pseudofirst-order kinetics and gave us the rate constant for dehydration of ketol-2 (k_{23}[OH^-]) again. Strictly speaking, the measured value was the rate to approach the hydration-dehydration equilibrium (k_{23} \cdot k_{12})[OH^-], however, in this case the contribution of k_{12} was less than experimental error. Thus the measured value actually represented the rate constant for dehydration of ketol-2 (k_{23}[OH^-]). The value obtained was consistent with that obtained from the reaction starting with 2,6-heptanedione (dione-2). The reaction starting with enone-2 also allowed us to measure the equilibrium constants for both steps: from dione-2 to ketol-2 (K_{12}) and from ketol-2 to enone-2 (K_{23}), by using higher initial concentrations. The measured pseudofirst-order rate constant, the calculated second-order rate constant and the equilibrium constants are found in Table 6.
Table 6. Kinetics of Base-catalyzed Dehydration of 3-Hydroxy-3-methylcyclohexanone (ketol-2) and Equilibrium Constants for the Reactions Leading from 2,6-Heptanedione (dione-2) to Ketol-2 and from Ketol-2 to 3-Methyl-2-cyclohexen-1-one (enone-2), All Derived from the Reaction Starting with Enone-2.\(^a\)

<table>
<thead>
<tr>
<th>No</th>
<th>[Enone-2],(^b)</th>
<th>[NaOH],(^c)</th>
<th>A1(^d)</th>
<th>A2(^d)</th>
<th>10(^4)A3(^d)</th>
<th>10(^2)k(_{23}),(^d)</th>
<th>k(_{12}),(^e)</th>
<th>K(_{23}),(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.29x10(^{-2})</td>
<td>0.010</td>
<td>2.03±0.09</td>
<td>-1.96±0.08</td>
<td>2.52±0.27</td>
<td>2.52±0.27</td>
<td>61.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>0.100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)All reactions were carried out in aqueous solution at 25°C, starting with enone-2, ionic strength = 1.0 M (KCl), followed by HPLC analysis on quenched samples. Enone-2 was followed at 240 nm, both dione-2 and ketol-2 were followed at 271 nm.

\(^b\)Initial concentration of starting material, enone-2.

\(^c\)Sodium hydroxide concentration.
pseudofirst-order rate constant $k_{23}[\text{OH}^-]$, where $k_{23}$ is the second-order rate constant for dehydration of ketol-2. The standard deviation for the rate constant was calculated by the least-squares procedure.

$^aK_{12} = [\text{ketol-2}]/[\text{dione-2}], \ K_{23} = [\text{enone-2}]/[\text{ketol-2}].$

$^b$The values were from triplicate experiments.
Figure 11. Base-catalyzed hydration reaction of 3-methyl-2-cyclohexen-1-one (enone-2). The growth of 3-hydroxy-3-methylcyclohexanone (ketol-2) was followed by HPLC, monitoring the absorbance at 271 nm (see entry 1 in Table 6).

HPLC Peak Height (A) vs. Time (t, sec).
3.2.3 Acid-catalyzed hydration reaction of 3-methyl-2-cyclohexen-1-one (enone-2).

To check the value for the hydration-dehydration equilibrium constant \((K_{23})\), the hydration reaction of enone-2 was also studied under acidic conditions with HPLC analysis. Because we expected\(^{24,25,26}\) that under acidic conditions the retroaldol cleavage and intermolecular coupling reactions would become much less significant relative to establishment of hydration equilibrium, we should obtain a cleaner hydration reaction of enone-2 and thus get a more accurate value for the hydration-dehydration equilibrium constant \((K_{23})\). The equilibrium constant obtained in this experiment was consistent with that obtained from \(t\). base-catalyzed hydration reaction of enone-2. In the process, the rate constant for approach to acid-catalyzed hydration-dehydration equilibrium \((k_{23} + k_{32})\) was also obtained by following the growth of 3-hydroxy-3-methylcyclohexanone (ketol-2) with HPLC. According to the equilibrium constant, \(K_{23}\), obtained in this experiment, the contribution from the rate constant for acid-catalyzed hydration of enone-2 \((k_{32})\) was less than experimental error in this case. Thus the measured rate of approach to hydration-dehydration equilibrium actually represented the rate constant for the acid-catalyzed dehydration of ketol-2 \((k_{33})\). The measured pseudofirst-order
rate constant. the calculated second-order rate constant and the measured equilibrium constants are found in Table 7.

Table 7. Kinetics and Equilibrium of the Acid-catalyzed Dehydration Reaction of 3-Hydroxy-3-methylcyclohexanone (ketol-2) from an Experiment Starting with 3-Methyl-2-cyclohexen-1-one (enone-2)*

<table>
<thead>
<tr>
<th>A1^b</th>
<th>A2^b</th>
<th>10^3A3^b</th>
<th>10^3k23,^b M^{-1}s^{-1}</th>
<th>K23^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.15±0.04</td>
<td>-0.88±0.08</td>
<td>4.17±0.78</td>
<td>4.17±0.78</td>
<td>58.6</td>
</tr>
</tbody>
</table>

*In aqueous solution at 25°C, starting with 2.47×10^{-2} M of enone-2 in 1.00 M HCl, analysed by HPLC: monitoring the absorbance 271 nm for ketol-2 and 240 nm for enone-2.

Following the growth of ketol-2: HPLC peak height (A)-time (t) data were fitted to A = A1 + A2 × EXP(-A3 × t) by non-linear least squares. A3 corresponds to pseudofirst-order rate constant k23[H^+], where k23 is the second-order rate constant for acid-catalyzed dehydration of ketol-2. Standard deviations for the parameters were calculated by least-squares procedure.

K23 = [enone-2]/[ketol-2] is the equilibrium constant for the dehydration reaction of ketol-2
3.2.4 Summary of the rate and equilibrium constants for the reaction of 2,6-heptanedione (dione-2).

The base-catalyzed intramolecular aldol addition reaction of dione-2 and the following base-catalyzed dehydration reaction of 3-hydroxy-3-methylcyclohexanone (ketol-2) were studied in aqueous solution with HPLC and UV analysis. The reactions were studied by starting with dione-2 and 3-methyl-2-cyclohexen-1-one (enone-2) respectively. Four rate constants and two equilibrium constants required to describe the reaction of dione-2 in terms of Scheme 6 were obtained. The calculated rate and equilibrium constants for the reaction of dione-2 are summarized in Table 8.
<table>
<thead>
<tr>
<th>No.</th>
<th>$10^2 k_{12}$</th>
<th>$10^3 k_{21}$</th>
<th>$10^2 k_{23}$</th>
<th>$10^4 k_{32}$</th>
<th>$K_{12}$</th>
<th>$K_{23}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.34±0.13</td>
<td>1.87±0.10</td>
<td></td>
<td></td>
<td>52.3±4.0</td>
<td>61.4±4.0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2.52±0.27</td>
<td></td>
<td></td>
<td></td>
<td>55.0±3.5</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58.6±4.0</td>
</tr>
<tr>
<td>Avg.</td>
<td>7.34±0.13</td>
<td>1.40</td>
<td>1.95±0.30</td>
<td>3.34</td>
<td>52.3±4.0</td>
<td>58.3±4.0</td>
</tr>
</tbody>
</table>

*The values were calculated in this table unless otherwise noted.

*The second-order rate constant for the base-catalyzed intramolecular aldol addition reaction of dione-2, from Table 5.

*The second-order rate constant for the base-catalyzed retroaldol reaction of 3-hydroxy-3-methylcyclohexanone (ketol-2).

*The second-order rate constant for the base-catalyzed dehydration reaction of ketol-2.

*The second-order rate constant for the base-catalyzed hydration reaction of 3-methyl-2-cyclohexen-1-one (enone-2).
\[ K_{12} = \frac{[\text{ketol-2}]}{[\text{dione-2}]} \] is the equilibrium constant for the reaction leading from dione-2 to ketol-2, from Table 6.

\[ K_{31} = \frac{[\text{enone-2}]}{[\text{ketol-2}]} \] is the equilibrium constant for the reaction leading from ketol-2 to enone-2.

\(^{\text{a}}\)From Table 5.

\(^{\text{b}}\)From Table 6.

\(^{\text{c}}\)The weighted mean.

\(^{\text{d}}\)From Table 7.

\(^{\text{e}}\)The simple mean.
3.2.5 Determination of the rate-limiting step.

3.2.5.1 The intramolecular aldol addition step for 2,6-heptanedione (dione-2).

The intramolecular aldol addition reaction of dione-2 has two major steps mechanistically: the formation of the enolate of dione-2 on the methyl side and the cyclization of this enolate to give the anion of 3-hydroxy-3-methylcyclohexanone (ketol-2) (See Scheme 7).

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\hline
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\hline
\end{align*}
\]

Scheme 7. The mechanism of the base-catalyzed intramolecular aldol addition reaction of 2,6-heptanedione (dione-2).

What we need to use for the Marcus theory analysis, and what we are really interested in, is the rate constant for the carbon-carbon bond formation step, that is the cyclization of the pre-formed enolate of dione-2 (k_2 in Scheme 7). The activation energy for the enolate formation was estimated by using Guthrie’s correlation equation^{16} and using pK_a 19.14 for dione-2 (see Chapter 6 for estimation of the pK_a), it was found that \( \Delta G^\circ = 18.4 \) kcal/mol. The observed activation energy, \( \Delta G^\circ_{\text{obs}} \), was 19.0 kcal/mol for the intramolecular aldol
addition step. Thus the estimated activation energy for enolate formation was very close to the observed activation energy, leading to two possibilities: 1) Enolate formation might be the rate-limiting step, with the intramolecular aldol addition step of the pre-formed enolate being a fast subsequent step. In this case, the observed rate constant would actually be the rate constant for enolate formation.

2) The intramolecular aldol addition step of the pre-formed enolate might be the rate-limiting step or at least be partially rate-limiting. In this case, we can calculate from the observed rate constant, the rate constant for the intramolecular aldol addition reaction of the pre-formed enolate, which was needed for the Marcus theory analysis.

To identify which was the real case, we measured the ratio between the rate for the protonation of the pre-formed enolate (k₁ in Scheme 7) and the rate for the intramolecular aldol addition of the pre-formed enolate (k₂ in Scheme 7) by ¹H-NMR. Starting with dione-2, the reaction was carried out in a 0.010 M solution of NaOD in D₂O. The reaction was quenched after partial reaction and the mixture was then analyzed by ¹H-NMR (see Figure 12). It was found that the intramolecular aldol addition of the pre-formed enolate (k₂ in Scheme 7) was 5.5 ± 0.5 times faster than the protonation of the enolate (k₁ in Scheme 7) in D₂O by comparing the integrations of the methyl group in the formed ketol-2, at 1.42 ppm, and of the
CH₂D group in dione-2, at 2.28 p.m. However this result must be corrected by the kinetic isotope effects to represent the kinetics in H₂O. The kinetic isotope effects for the protonation of the formed enolate and the intramolecular aldol addition of the formed enolate were estimated as follows:

1) The kinetic isotope effect for the protonation of the enolate of dione-2 (k₋₁ in Scheme 7).

For k₋₁, we must estimate both the primary and the solvent kinetic isotope effects. The primary kinetic isotope effect was estimated by using Kresge's model,²⁷ where pKₐ = 19.14 was used for dione-2 (see Chapter 6 for the estimation of the pKₐ): \( \text{Ln}(k^{\text{H/D}}) = \text{Ln}(k^{\text{H/D}})_{\text{max}} [1-(\Delta G^°/4\Delta G^°)²] = 1.98 \), which leads to the primary kinetic isotope effect \( k^{\text{H/D}} = 7.27 \).

The solvent kinetic isotope effect was estimated by using Schowen's method.²⁸ (see Scheme 8). The ground-state fractionation factors were from the literature:²⁹ 1.22 for hydroxide and 0.70 for hydrogen bonding hydrogen to alkoxide. The fractionation factors for the transition state were estimated after Schowen²⁸ as \( \psi' = (\psi^s)₁₋ₓ (\psi^p)ₓ \), where \( \psi' \), \( \psi^s \) and \( \psi^p \) are the fractionation factors of the transition state, reactant and product, and \( \chi \) is the extent of progress along the reaction coordinate. We estimated \( \chi \) from the quadratic approximation to the Marcus equation as \( \chi = \Delta G^°/8\Delta G^° + 0.5 = \)
Figure 12. $^1$H-NMR Spectrum of the quenched reaction mixture at 130 s of 0.09575 M of 2,6-heptanedione, 0.010 M of NaOD in D$_2$O at 25ºC.
0.52, where the intrinsic barrier \( \Delta G^* \) was 10.70 kcal/mol for the protonation of the ketone enolate,\(^{16}\) and \( \Delta G^0 \) was calculated for the process leading to partly desolvated hydroxide. Thus the solvent kinetic isotope effect for the protonation of the enolate of dione-2 \( \text{ dik } = \frac{\Pi^R}{\Pi^2} = 0.70^2/(1.10 \times 0.84^2 \times 0.83^2) \) = 0.92.

The overall kinetic isotope effect for the protonation of the enolate = the primary kinetic isotope effect \( \times \) the solvent kinetic isotope effect = \( 7.27 \times 0.92 = 6.69 \).

Scheme 8. Schowen's model for the estimation of the solvent kinetic isotope effect of the protonation of the enolate of 2,6-heptanedione. The values are the fractionation factors for each exchangeable hydrogeonic site.
2) The kinetic isotope effect for the intramolecular aldol addition step of the enolate of dione-2.

The intramolecular aldol addition step for the enolate of dione-2 only has the solvent kinetic isotope effect, which can also be estimated by using Schowen's model\(^{28}\) as shown in Scheme 9.

In terms of this model, the solvent kinetic isotope effect for the intramolecular aldol addition of the enolate of dione-2 \(k^{\text{VD}}\) will be 1.00 for any value of \(\chi\). The fractionation factors for the exchangeable sites in the transition state will be \(\Phi^1 = 1^{1-x} 0.7^x = 0.7^x\) for the sites marked with double star and \(\Phi^2 = 0.7^{1-x} 1^x = 0.7^{1-x}\) for the sites marked with single star, so that the solvent kinetic isotope effect for the intramolecular aldol addition of the enolate of dione-2 \(k^{\text{VD}} = \Pi \Phi^1 / \Pi \Phi^2 = 0.7^2 / (0.7^x)^2 (0.7^{1-x})^2 = 1.00\) for any value of \(\chi\).
Scheme 9. Schowen's model for the estimation of the solvent kinetic isotope effect of the intramolecular aldol addition of the enolate of 2,6-heptan-dione. The values are the fractionation factors for each exchangeable hydrogenic site.

At this point, we can correct the result observed in D$_2$O by the kinetic isotope effects to obtain the rate constant ratio in H$_2$O. We found that the protonation of the enolate of dione-2 was $6.69/(5.5 \pm 0.5) = 1.22 \pm 0.11$ times faster than the intramolecular aldol addition of the enolate of dione-2. This demonstrated that the intramolecular aldol addition step of the enolate of dione-2 partially contributed to the observed rate constant, and was not a fast step after enolate formation. It also means that the proton transfer process was partially rate-limiting and not a fast pre-equilibrium.
3.2.5.2 The dehydration step for 3-hydroxy-3-methylcyclohexanone (ketol-2).

The dehydration of ketol-2 also has two major steps mechanistically: enolate formation from ketol-2 at carbon-2 and the departure of hydroxyl group. The activation energy for enolate formation was estimated as 18.2±0.22 kcal/mol after Guthrie\textsuperscript{16} by using pK\textsubscript{a} = 15.82 for ketol-2 at carbon-2 (for estimation of pK\textsubscript{a}, see Chapter 6). The observed activation energy was found to be 19.8±0.09 kcal/mol. Thus we feel confident in saying that the rate-limiting step is the departure of the hydroxyl group from the pre-formed enolate. For the calculation of standard deviations for the estimated and observed activation energy, please see Appendix 2.

3.3 Discussion

Compared to the reaction of 2,5-hexanedione (dione-1) discussed in Chapter 2, the rate of the intramolecular aldol addition of dione-2 (k\textsubscript{12}) is about 2,000 times faster and the equilibrium constant from dione to ketol is about 5 times more favorable. The kinetic picture also changed because of the changes in rate constants from dione-1 to dione-2; the reaction starting with dione-2 showed two-phase kinetics rather than the single-phase kinetics observed in reaction starting with dione-1.
It is at first surprising that the change in reaction rate for the intramolecular aldol addition step was observed on going from reaction of dione-1 to reaction of dione-2. However this is easily explained by consideration of reactive conformations.

The reactive conformations of the enolates were assumed to be the 3,4-eclipsed conformation of dione-1 enolate, and the conformation of dione-2 enolate with the enolate and acetyl in what is equivalent to a 1,3-diaxial interaction: see Scheme 10.

![Enolate of Dione-2](image1)
![Enolate of Dione-1](image2)

**Scheme 10.** The reactive conformations of enolates of 2,5-hexanodione (dione-1) and 2,6-heptanedione (dione-2).

The equilibrium constant ($K_{eq}$) for the conversion of the equilibrium conformation to the reactive conformation of the enolates was calculated using the difference in MM3 steric
energies for the two conformations. The MM3 calculation showed that $K_{\text{conf}} = 2.40 \times 10^{-6}$ for the enolate of \textit{dione-1}, and $3.86 \times 10^{-2}$ for that of \textit{dione-2}. This calculation indicated that the difference in reaction rates for the intramolecular aldol addition step primarily resulted from the different energetic costs of going from the equilibrium conformation to the reactive conformation.

3.4 Experimental

3.4.1 Instrumentation

See Part 2.3.1 in Chapter 2.

3.4.2 Materials

3-Methyl-2-cyclohexen-1-one (\textit{enone-2}, 98%) was from Aldrich, and diacetone alcohol (97%) from BDH. Both were used as supplied and checked by $^1\text{H-NMR}$ and HPLC before being used in this work.

\textit{2,6-Heptanediene} (\textit{dione-2}) was synthesized from formaldehyde and diketene by published procedures$^{10}$. Recrystallization from n-hexane gave pure 2,6-heptanediene (judged by HPLC): $^1\text{H NMR}$ (200 MHz, CDCl$_3$) $\delta$ 1.78-1.92 (quintet, 2 H, middle CH$_2$), 2.14 (s, 6 H, CH$_3$), 2.45-2.52 (t, 4 H, CH$_2$ adjacent to C=O).
3.4.3 Methods

Reactions followed by UV were carried out by using the same procedures described for reaction of 2,5-hexanediione in Part 2.3.3.1 in Chapter 2 except that the stored absorbance-time data were fitted to the double exponential equation by a non-linear least squares procedure to obtain the rate constants.

Reactions followed by HPLC were also carried out by using the same procedures described for reaction of 2,5-hexanediione in Part 2.3.3.1 in Chapter 2 except that the acid-catalyzed hydration reaction of enone-2 was quenched by the addition of aqueous sodium phosphate solution.

For reactions starting with dione-2, a solution of 20% acetonitrile in water was used as eluting solvent. The HPLC chromatograms were also recorded on a Goerz Metrawatt SE 20 dual channel recorder. The HPLC peak area was obtained by measuring the peak height and the peak width at half height on the amplified HPLC chromatograms. Then the HPLC peak area-time data were fitted to single or double exponential equations by a non-linear least squares procedure to obtain the rate constants. The concentrations of materials eluted were monitored at suitable wavelengths and sensitivities: dione-2 and ketol-2, 271 nm (AUFS 0.01); enone-2, 240 nm (AUFS 1). Calibrations were carried out using suitable stock solutions
of the pure compounds except that diacetone alcohol was used as a model compound for ketol-2.

For reactions starting with enone-2, a solution of 3-10% acetonitrile in water was used as HPLC mobile phase. The HPLC chromatograms were recorded on a Goerz Metrawatt SE 120 dual channel recorder. The HPLC peak height-time data were fitted to the single exponential equation by a non-linear least squares procedure to obtain the rate constants. The detection and calibration conditions were the same as those used in reactions starting with dione-2. At the end of the reactions starting with enone-2, the equilibrium concentrations of dione-2, ketol-2 and enone-2 were measured directly, which gave us the equilibrium constants.

3.4.4 Reaction in D₂O

A flask containing a 0.010 M solution of NaOD in D₂O with ionic strength 1.0 M (KCl) was placed in a Neslab Exacal EX300 circulating constant temperature bath at 25°C for more than 15 min. 0.8 mL of this solution was then added to 9.83 mg of 2,6-heptanedione (the initial concentration of 2,6-heptanedione = 9.58 × 10⁻² M). The reaction was then quenched by the addition of potassium dihydrogen phosphate after 130 s. Finally the quenched reaction mixture was analyzed by NMR.
CHAPTER 4. THE REACTION OF 1-PHENYL-1,5-HEXANEDIONE

4.1 Introduction

As we stated in Chapter 3, in order to try to apply the Marcus theory to intramolecular aldol condensation reactions, we need to study systems with as much variation as possible in the rates and equilibria of the intramolecular aldol addition step and of the subsequent dehydration step. For this reason, we studied the intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedione, described in this chapter, after we finished the study of the reaction of 2,6-heptanedione, described in Chapter 3. Changes in both rate and equilibrium constants for both the intramolecular aldol addition step and the subsequent dehydration step are to be expected when a methyl group in 2,6-heptanedione is replaced by a phenyl group to give 1-phenyl-1,5-hexanedione. For the intramolecular aldol addition step, conjugation of the benzene ring with the carbonyl group in 1-phenyl-1,5-hexanedione would decrease the reactivity of the carbonyl group and make the reaction slower and less favorable. For the subsequent dehydration
step, conjugation of the benzene ring with the \( \alpha,\beta \)-unsaturated ketone system in the product, 3-phenyl-2-cyclohexen-1-one (enone-3), would lower the energy of the enone and make the dehydration reaction more favorable. The reaction rate and equilibrium constants are defined in Scheme 11.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 & \quad \text{Ph} \\
\text{O} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
\text{K}_{12} & \quad \text{K}_{21} & \quad \text{K}_{12} & \quad \text{K}_{23}
\end{align*}
\]

**Scheme 11.** The reaction scheme for the base-catalyzed intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedione (dione-3): \( k_{12} \) is the rate constant for intramolecular aldol addition of dione-3; \( k_{23} \) is the rate constant for dehydration of ketol-3; \( k_{21} \) is the rate constant for retroaldol cleavage of ketol-3; \( k_{32} \) is the rate constant for hydration of enone-3; \( K_{12} = [\text{Ketol-3}]/[\text{Dione-3}] \); \( K_{23} = [\text{Enone-3}]/[\text{Ketol-3}] \).
4.2 Results

4.2.1 Reaction starting with 1-phenyl-1,5-hexanedicone (dione-3).

Starting with dione-3, the kinetics of the base-catalyzed intramolecular aldol condensation reaction of dione-3 were studied with both HPLC and UV analysis. Only the growth of the product, 3-phenyl-2-cyclohexen-1-one (enone-3), could be followed by UV analysis at 289 nm (see Figure 13). HPLC analysis allowed us to follow the disappearance of starting material, dione-3, (see Figure 14) and the growth of the product, enone-3, (see Figure 15) simultaneously by using an appropriate detection wavelength. Both the disappearance of dione-3 and the growth of enone-3 showed simple pseudo-first order kinetics. No 3-hydroxy-3-phenyl-cyclohexanone (ketol-3) was observed during the course of the reaction. However, at the end of the reaction, a small amount of ketol-3 was detected by special treatment (see Part 4.4.3 in Experimental), which allowed us to determine the equilibrium constants.

The non-accumulation of ketol-3 in the course of the reaction implies that the base-catalyzed dehydration of ketol-3 (k23) was faster than the base-catalyzed intramolecular aldol addition of dione-3 (k12). This was also consistent with the kinetics observed for the reaction starting with ketol-3 (see Part 4.2.2). The measured rate constants from experiments starting with dione-3 were for the rate of approach to the
equilibrium between dione-3 and enone-3, where the reaction from dione-3 to ketol-3 is rate-limiting: 
\((k_{12} + k_{21}k_{32}/(k_{21} + k_{23}))[\text{OH}^-]\). The apparent rate constants showed a first-order dependence on hydroxide concentration, leading to a second-order rate constant 
\((k_{12} + k_{21}k_{32}/(k_{21} + k_{23})) = (1.40 \pm 0.005) \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}\) for the rate of approach to the equilibrium between dione-3 and enone-3, where the reaction from dione-3 to ketol-3 is rate-limiting. The measured pseudofirst-order rate constants, the calculated second-order rate constants and the measured equilibrium constants are found in Table 9.
Table 9. Kinetics and Equilibria of Base-catalyzed Intramolecular Aldol Condensation of 1-Phenyl-1,5-hexanodione (dione-3) from the Reaction Starting with Dione-3*

<table>
<thead>
<tr>
<th>No</th>
<th>$10^6$C&lt;sub&gt;b&lt;/sub&gt;</th>
<th>OH&lt;sup&gt;-&lt;/sup&gt;</th>
<th>A&lt;sub&gt;1&lt;/sub&gt;</th>
<th>A&lt;sub&gt;2&lt;/sub&gt;</th>
<th>$10^4$A&lt;sub&gt;3&lt;/sub&gt;</th>
<th>$10^2(k_{12}+k_{21}k_{32})$/</th>
<th>$k_{12}$</th>
<th>$10^{-2}k_{23}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>M</td>
<td>M</td>
<td>M</td>
<td>M&lt;sup&gt;-1&lt;/sup&gt;s&lt;sup&gt;-1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;°&lt;/sup&gt;</td>
<td>3.52</td>
<td>0.010</td>
<td>0.05±0.33</td>
<td>4.27±0.23</td>
<td>1.70±0.35</td>
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<tr>
<td>2&lt;sup&gt;°&lt;/sup&gt;</td>
<td>3.52</td>
<td>0.010</td>
<td>8.48±1.09</td>
<td>-8.71±1.06</td>
<td>1.31±0.23</td>
<td>1.31±0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;°&lt;/sup&gt;</td>
<td>3.52</td>
<td>0.010</td>
<td></td>
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<td>7.3±0.4</td>
<td>9.3±0.7</td>
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<tr>
<td>4&lt;sup&gt;°&lt;/sup&gt;</td>
<td>0.0311</td>
<td>0.180</td>
<td>0.1226±0.0001</td>
<td>-0.0978±0.0002</td>
<td>25.2±0.1</td>
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<tr>
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<td>0.0311</td>
<td>0.580</td>
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<td>81.0±0.5</td>
<td>1.40±0.009</td>
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<tr>
<td>Weighted Mean</td>
<td></td>
<td></td>
<td>0.1268±0.0001</td>
<td>-0.1048±0.0005</td>
<td>81.0±0.5</td>
<td>1.40±0.005</td>
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<td></td>
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</tbody>
</table>

*All reactions were carried out in aqueous solution at 25°C, starting with dione-3, ionic strength = 1.0 M (KCl).

<sup>b</sup>Initial molar concentration of starting material, dione-3.
Sodium hydroxide concentration.

HPLC peak area or UV absorbance (A) data as a function of time (t) were fitted to $A = A_1 + A_2 \times \exp(-A_3 \times t)$ by nonlinear least squares. $A_3$ corresponds to the pseudofirst-order rate constant $(k_{12} + k_{21}k_{32}/(k_{21} + k_{23}))[^{OH^-}]$, and $(k_{12} + k_{21}k_{32}/(k_{21} + k_{23})$ is the second-order rate constant for the rate of approach to the equilibrium between dione-3 and enone-3, where the reaction from dione-3 to 3-hydroxy-3-phenylcyclohexanone (ketol-3) is rate-limiting. The standard deviations for the parameters were calculated by the least-squares procedures.

$K_{12} = [\text{ketol-3}]/[\text{dione-3}]$ is the equilibrium constant for the reaction leading from dione-3 to ketol-3.

$K_{23} = [\text{3-phenyl-2-cyclohexen-1-one (enone-3)}]/[\text{ketol-3}]$ is the equilibrium constant for the reaction leading from ketol-3 to enone-3.

Followed the disappearance of dione-3 by HPLC, monitoring the absorbance at 246 nm.

Followed the growth of enone-3 by HPLC, monitoring the absorbance at 289 nm.

The equilibrium concentration of ketol-3 was measured by HPLC analysis, monitoring the absorbance at 205 nm.

Followed the growth of enone-3 by UV analysis, monitoring the absorbance at 289 nm.
Figure 13. Base-catalyzed intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedione (dione-3). The growth of 3-phenyl-2-cyclohexen-1-one (enone-3) was followed by UV, monitoring the absorbance at 289 nm (see Entry 4 in Table 9).

UV Absorbance (A) vs. Time (t, sec).
Figure 14. Base-catalyzed intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedicone (dione-3). The disappearance of dione-3 was followed by HPLC, monitoring the absorbance at 246 nm (see Entry 1 in Table 9).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 15. Base-catalyzed intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedione (dione-3). The growth of 3-phenyl-2-cyclohexen-1-one (enone-3) was followed by HPLC, monitoring the absorbance at 289 nm (see Entry 2 in Table 9).

HPLC Peak Area (A) vs. Time (t, sec).
4.2.2 Reaction starting with 3-hydroxy-3-phenylcyclohexanone (ketol-3).

Starting with ketol-3, the kinetics of the base-catalyzed dehydration and retroaldol cleavage reaction of ketol-3 were studied with both HPLC and UV analysis. For reactions followed by UV analysis, only the growth of the dehydration product, 3-phenyl-2-cyclohexen-1-one (enone-3), was followed at 289 nm (see Figure 16). For reactions followed by HPLC analysis, the disappearance of the starting material, ketol-3, (see Figure 17) and the growth of the dehydration product, enone-3, (see Figure 18) were conveniently followed at appropriate wavelengths. At the same time, we clearly observed the initial increase and subsequent decrease in the concentration of 1-phenyl-1,5-hexanedione (dione-3), formed from the retroaldol cleavage reaction of ketol-3 (see Figure 19), although it never amounted to more than about 1% of the total concentration. The concentration of dione-3 gradually increased and reached a maximum, then it decreased and ended up at an equilibrium level.

The product distribution, i.e. the ratio between the formation of the dehydration product, enone-3, and the formation of the retroaldol cleavage product, dione-3, in the initial stages of the reaction indicated that the base-catalyzed dehydration reaction of ketol-3 (k23) was 85 times faster than the base-catalyzed retroaldol cleavage reaction of
ketol-3 \((k_{21})\). On the other hand, the equilibrium constant for the reaction leading from dione-3 to ketol-3 \((K_{21})\) was only 7.3 (see Table 9), that is, the base-catalyzed intramolecular aldol addition reaction of dione-3 \((k_{12})\) was only 7.3 times faster than the base-catalyzed retroaldol cleavage reaction of ketol-3 \((k_{21})\). This implied that the base-catalyzed dehydration reaction of ketol-3 \((k_{23})\) was faster than the base-catalyzed intramolecular aldol addition reaction of dione-3 \((k_{12})\), which was consistent with the kinetics observed in the reaction starting with dione-3 (see Part 4.2.1 in Chapter 4).

Both the disappearance of ketol-3 and the growth of enone-3 showed pseudofirst-order kinetics, which gave us the pseudofirst-order rate constant for the approach to hydration-dehydration equilibrium between ketol-3 and enone-3 \((k_{23} + k_{32})[OH^-]\). In this case the contribution from the rate constant for the hydration reaction of enone-3 \((k_{32})\) was much less than the experimental error, so that the measured rate constants actually represented the pseudofirst-order rate constants for the base-catalyzed dehydration reaction of ketol-3 \((K_{23}[OH^-])\).

The concentration data for dione-3 as a function of time showed two-phase kinetics, which gave us the pseudofirst-order rate constants for both the rate of approach to the intramolecular aldol addition - retroaldol cleavage equilibrium between dione-3 and ketol-3 \((k_{12} + k_{21})[OH^-]\) and
the rate of approach to hydration - dehydration equilibrium between ketol-3 and enone-3 \((k_{23} + k_{32})[OH^-]\). For the reasons stated above, the rate constant of approach to the hydration - dehydration equilibrium between ketol-3 and enone-3 \((k_{23} + k_{32})[OH^-]\) obtained here actually represents the pseudofirst-order rate constant for the dehydration of ketol-3 \((k_{23}[OH^-])\). The pseudofirst-order rate constant obtained for the approach to the intramolecular aldol addition - retroaldol cleavage equilibrium between dione-3 and ketol-3 \((k_{12} + k_{21})[OH^-]\) leads to a second-order rate constant \((k_{12} + k_{21}) = (1.31 \pm 0.21) \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}\), which is consistent with the results of experiments starting with dione-3 (See Table 12).

The apparent pseudofirst-order rate constants for the dehydration of ketol-3 \((k_{23}[OH^-])\) showed a first-order dependence on hydroxide concentration, leading to a second-order rate constant \(k_{23} = (0.140 \pm 0.006) \text{ M}^{-1}\text{s}^{-1}\). The measured pseudofirst-order rate constants, and the calculated second-order rate constants are found in Table 10.
Table 10. Kinetics of Base-catalyzed Dehydration and Retroaldol Cleavage Reaction of 3-Hydroxy-3-phenylcyclohexanone (ketol-3) from the Reaction Starting with Ketol-3

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<th>No</th>
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<th>10^2A3 d</th>
<th>A4 d</th>
<th>10^6A5 d</th>
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<th>k_{23}, d</th>
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<td>0.3487±0.0002</td>
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<td></td>
<td></td>
<td>1.30±0.21</td>
<td>0.140±0.006</td>
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</tbody>
</table>

*All reactions were carried out in aqueous solution at 25°C, starting with ketol-3, ionic strength = 1.0 M (KCl).

bInitial molar concentration of starting material, ketol-3.

cSodium hydroxide concentration.
For No.1, HPLC peak area (A) - time (t) data were fitted to double exponential equation
A = A1 + A2 × EXP(-A3 × t) + A4 × EXP(-A5 × t) by nonlinear least squares. For No.2 to No.5,
HPLC peak area or UV absorbance (A) - time (t) data were fitted to A = A1 + A2 × EXP(-A3 ×
t). A3 and A5 correspond to the pseudofirst-order rate constants of k23[OH-] and (k12 + k21)[OH-]
respectively. k23 and (k12 + k21) are the second order rate constants for the base-catalyzed
dehydration reaction of ketol-3 and the rate to approach the base-catalyzed intramolecular
aldol addition - retroaldol cleavage equilibrium between 1-phenyl-1,5-hexanedione (dione-3)
and ketol-3.

Standard deviations for the parameters were calculated by the least-squares procedures.

*Followed the concentration change of dione-3 by HPLC analysis, monitoring the
absorbance at 246 nm.

*Followed the disappearance of ketol-3 by HPLC analysis, monitoring the absorbance at
205 nm.

*Followed the growth of 3-phenyl-2-cyclohexen-1-one (enone-3) by HPLC analysis,
monitoring the absorbance at 289 nm.

*Followed the growth of enone-3 by UV analysis, monitoring the absorbance at 289 nm.
Figure 16. Base-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone \((\text{ketol-3})\). The growth of 3-phenyl-2-cyclohexen-1-one \((\text{enone-3})\) was followed by UV, monitoring the absorbance at 289 nm (see Entry 4 in Table 10).

UV Absorbance \((A)\) vs. Time \((t, \text{sec})\).
Figure 17. Base-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone (ketol-3). The disappearance of ketol-3 was followed by HPLC, monitoring the absorbance at 205 nm (see Entry 2 in Table 10).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 18. Base-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone (ketol-3). The growth of 3-phenyl-2-cyclohexen-1-one (enone-3) was followed by HPLC, monitoring the absorbance at 289 nm (see Entry 3 in Table 10).

HPLC Peak Area (A) vs. Time (t, sec).
Figure 19. Base-catalyzed dehydration and retroaldol cleavage reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3). The concentration change of 1-phenyl-1,5-hexanedione (dione-3) was followed by HPLC, monitoring the absorbance at 246 nm (see Entry 1 in Table 10).

HPLC Peak Area (A) vs. Time (t, sec).
4.2.3 Reaction starting with 3-phenyl-2-cyclohexan-1-one (enone-3).

As we observed in the reaction starting with 1-phenyl-1,5-hexanodione (dione-3) (see Part 4.2.1), the equilibrium is far on the side of enone-3, so it was not practical to do kinetics experiments starting with enone-3. However, reaction starting with enone-3 would allow us to check whether or not the equilibria have truly been reached in reactions starting with dione-3. Similar values of the equilibrium constants for both the intramolecular aldol addition-retroaldol cleavage equilibrium between dione-3 and 3-hydroxy-3-phenylcyclohexanone (ketol-3) (K_{12}) and the dehydration-hydration equilibrium between ketol-3 and enone-3 (K_{23}) were obtained either in the reaction starting with enone-3 or in the reaction starting with dione-3, suggesting that true equilibria have been reached. The measured equilibrium constants are found in Table 11.
Table 11. Equilibrium Constants for the Equilibrium between 1-Phenyl-1,5-hexanedicone (dione-3) and 3-Hydroxy-3-phenylcyclohexanone (ketol-3) and for the Equilibrium between Ketol-3 and 3-Phenyl-2-cyclohexen-1-one (enone-3), All Derived from the Reaction Starting with Enone-3

<table>
<thead>
<tr>
<th>$K_{12}$</th>
<th>$K_{23}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3±0.5</td>
<td>(1.0±0.1)×10³</td>
</tr>
</tbody>
</table>

*In aqueous solution at 25°C, [NaOH] = 0.010 M, ionic strength = 1.0 M (KCl), starting with 1.21 × 10⁻³ M of enone-3.

The equilibrium concentrations of dione-3, ketol-3 and enone-3 were determined by HPLC analysis, monitoring the absorbance at 246 nm, 205 nm and 289 nm respectively.

$K_{12} = \frac{[ketol-3]}{[dione-3]}.$

$K_{23} = \frac{[enone-3]}{[ketol-3]}.$
4.2.4 Summary of the rate and equilibrium constants for the reaction of 1-phenyl-1,5-hexanedione (dione-3).

The base-catalyzed intramolecular aldol addition reaction of 1-phenyl-1,5-hexanedione (dione-3) and the following dehydration reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3) were studied in aqueous solution with both HPLC and UV analysis. The reactions were studied by starting with dione-3, ketol-3 and 3-phenyl-2-cyclohexen-1-one (enone-3) respectively. Four rate constants and two equilibrium constants required to describe the reaction of dione-3 in terms of Scheme 11 were obtained, which provided the necessary experimental data for the application of Marcus theory to both the intramolecular aldol addition reaction of dione-3 and the dehydration reaction of ketol-3. The calculated rate and equilibrium constants for the reaction of dione-3 are summarized in Table 12. Compared to the reaction of 2,6-heptanedione (dione-2) described in Chapter 3, the base-catalyzed intramolecular aldol addition step (k_{12}) becomes 5.7 times slower and the intramolecular aldol addition-retroaldol cleavage equilibrium between dione and ketol (K_{12}) becomes 6.8 times less favorable, as we expected, because the conjugation effect between the benzene ring and the carbonyl group in dione-3 decreased the reactivity of the
carbonyl group; on the other hand, as we expected, the base-catalyzed dehydration step \( (k_{23}) \) becomes 7.4 times faster and the dehydration-hydration equilibrium between ketol and enone \( (K_{23}) \) becomes 16.3 times more favorable because of the conjugation effect between the benzene ring and the \( \alpha,\beta \)-unsaturated ketone system in \textit{enone-3}. These variations of reaction rate and equilibrium constants would allow us to test the Marcus theory on a wider range of reactivity in the intramolecular aldol condensation reaction. This should lead to more reliable conclusions on the applicability of Marcus theory to intramolecular aldol condensation reaction.
<table>
<thead>
<tr>
<th>No.</th>
<th>$10^2k_{12}$</th>
<th>$10^3k_{21}$</th>
<th>$k_{23}$</th>
<th>$10^4k_{12}$</th>
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<th>$10^{-2}K_{23}$</th>
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</tr>
<tr>
<td>1$^h$</td>
<td>7.3±0.4</td>
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<td>3$^j$</td>
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<tr>
<td>4$^k$</td>
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<tr>
<td>5$^l$</td>
<td>1.15</td>
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<tr>
<td>Avg.</td>
<td>1.28±0.13</td>
<td>1.61±0.12</td>
<td>0.140±0.006</td>
<td>1.47</td>
<td>7.7±0.7</td>
<td>9.5±0.5</td>
</tr>
</tbody>
</table>

*The values were calculated in this table unless otherwise noted.

$^b$Second-order rate constant for the base-catalyzed intramolecular aldol addition reaction of dione-3.

$^c$Second-order rate constant for the base-catalyzed retroaldol cleavage reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3).
Second-order rate constant for the base-catalyzed dehydroxylation reaction of ketol-3.

\[ k_{2} = \frac{[\text{ketol-3}]}{[\text{dione-3}]} \]

Second-order rate constant for the base-catalyzed hydration reaction of 3-phenyl-2-cyclohexen-1-one (enone-3).

\[ k_{3} = \frac{[\text{enone-3}]}{[\text{ketol-1}]} \]

From Table 9.

From Table 10.

From Table 11.

\[ \text{Calculated from } (k_{2}+k_{3})/\text{(ketol-1)} \] in Table 9.

\[ \text{Calculated from } k_{2}+k_{3} \text{ in Table 10.} \]
4.2.5 Determination of the rate-limiting step.

4.2.5.1 The intramolecular aldol addition step for 1-phenyl-1,5-hexanediione (dione-3).

The base-catalyzed intramolecular aldol addition reaction of dione-3 has two major steps mechanistically: the formation of the enolate of dione-3 on the methyl side and the cyclization of this enolate to give the anion of 3-hydroxy-3-phenylcyclohexanone (ketol-3) (see Scheme 12).

![Scheme 12. The mechanism of the base-catalyzed intramolecular aldol addition reaction of 1-phenyl-1,5-hexanediione (dione-3).](image)

The rate constant for the proton transfer of dione-3 \( (k_1) \) was estimated as 0.10 M\(^{-1}\)s\(^{-1}\) after Guthrie,\(^{16}\) where pKa 19.38 was used for dione-3 (see Chapter 6 for pKa estimation). The observed rate constant for the base-catalyzed intramolecular aldol addition reaction of dione-3 \( (k_{12}) \) was \( 1.28 \times 10^{-2} \) M\(^{-1}\)s\(^{-1}\) (see Table 12), which gave us: \( (0.10 \times k_2) / (k_1 + k_2) = 1.28 \times 10^{-2} \), leading to \( n = k_1 / k_2 = 6.81 \). This means that the protonation of the enolate of dione-3 \( (k_1 \) in Scheme 12) was
6.81 times faster than the intramolecular aldol addition of the enolate of dione-3 ($k_2$ in Scheme 12). This result clearly demonstrated that the intramolecular aldol addition of the pre-formed enolate was mainly rate-limiting, but that enolate formation was also partially rate-limiting, rather than a fast pre-equilibrium.

4.2.5.2 The dehydration step for 3-hydroxy-3-phenylcyclohexanone (ketol-3).

The base-catalyzed dehydration reaction of ketol-3 also has two major steps: enolate formation from ketol-3 at carbon-2 and the departure of hydroxyl group from the pre-formed enolate (see Scheme 13).

![Scheme 13](image)

Scheme 13. The mechanism of the base-catalyzed dehydration reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3).

The activation energy for the enolate formation was estimated as 18.2 kcal/mol after Guthrie where $pK_a = 15.43$
was used for ketol-3 at carbon-2 (see Chapter 6 for pKa estimation). The observed activation energy for the base-catalyzed dehydration of ketol-3 was found to be 18.6 kcal/mol. This result showed that the observed activation energy was very close to the estimated activation energy for the enolate formation of ketol-3 at carbon-2, leading to two possibilities: 1) the enolate formation might be the rate-limiting step, with the departure of hydroxyl group from the pre-formed enolate being a fast subsequent step. In this case, the observed rate constant would actually be the rate constant for enolate formation. 2) The departure of hydroxyl group from the pre-formed enolate might be the rate-limiting step or at least be partially rate-limiting. In this case, we could calculate, from the observed rate constant, the rate constant for the departure of hydroxyl group from the enolate of ketol-3 at carbon-2, which was needed for the Marcus analysis.

In order to identify which was the real case, we carried out the base-catalyzed dehydration reaction of ketol-3 in D_2O. The kinetics in D_2O are interpreted in terms of the mechanism shown in Scheme 14. By using the matrix method, the growth of 3-phenyl-2-cyclohexen-1-one (enone-3) in Scheme 14 was found to be a triple exponential equation: A = A_1 + A_2 \times \exp(-A_3t) + A_4 \times \exp(-A_5t) + A_6 \times \exp(-A_7t), where A_3 = k_1^N; A_5 = k_1^N + \frac{(k_2^N k_4^D)}{(k_1^D + k_4^N)}; A_7 = \frac{(k_1^D k_2^D)}{(k_1^D + k_2^D)}.
Scheme 14. The kinetics of the base-catalyzed dehydration reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3) in D₂O.
Figure 20. Base-catalyzed dehydration reaction of 3-hydroxy-3-phenylcyclohexanone (ketol-3) in D₂O. The growth of 3-phenyl-2-cyclohexen-1-one (enone-3) was followed by UV, monitoring the absorbance at 289 nm.

UV Absorbance (A) vs. Time (t, sec).
Experimentally the growth of enone-3 only showed two-phase kinetics (see Figure 20), because A3 and A5 are very close, and they are indistinguishable kinetically. This implies that the first phase might be the combination of A3 and A5 or A3 only or A5 only depending on the magnitude of the preexponential term. The second phase, however, certainly represents A7, both chemically and mathematically. Then we have:

\[
\frac{(k_1'k_2^D)}{(k_1' + k_2^D)} = A7/[OH^-] = (0.101 \pm 0.002) \text{ M}^{-1}\text{s}^{-1}
\]  

(12)

The standard deviation in equation (12) was calculated by a non-linear least squares procedure. For the reasons discussed in Part 2.2.6.2 in Chapter 2, we ignore the secondary kinetic isotope effects and the solvent kinetic isotope effects in this case. Then we have:

\[
k_1' = k_1 / (k_{H/D})_{primary}
\]  

(13)

\[
k_2^D = k_2
\]  

(14)

\[
k_{-1}' = k_{-1} / (k_{H/D})_{primary}
\]  

(15)

where \(k_1\), \(k_2\) and \(k_{-1}\) are the rate constants in \(H_2O\) as defined in Scheme 13, \((k_{H/D})_{primary}\) is the primary kinetic isotope effect, which was estimated by using Kresge's model.\textsuperscript{27} \[
\ln(k_{H/D})_{primary} = \ln(k_{H/D})_{max}[1-\Delta G^o/4\Delta G^o]^2 = \ln 8 [1-(2.08/4\times8)^2] = 2.07,
\]

leading to \((k_{H/D})_{primary} = 7.9\), where \(\Delta G^o = 2.08\) kcal/mol was calculated by using the \(pK_a = 15.43\) for ketol-3 at carbon-2 (see Chapter 6 for \(pK_a\) estimation). Then we have:
\[ k_1' = \frac{k_1}{7.9} \quad (16) \]
\[ k_{-1}' = \frac{k_{-1}}{7.9} \quad (17) \]

After substituting equations (14), (16) and (17) into equation (12), we have:
\[ \frac{(k_1 / 7.9)k_2}{(k_{-1} / 7.9 + k_2)} = 0.101 \quad (18) \]

The base-catalyzed dehydration reaction of ketol-3 in H_2O should give us (see Table 10):
\[ \frac{k_1k_2}{(k_{-1} + k_2)} = k_{23} = 0.140 \quad (19) \]

Then we set \( k_{-1} = nk_2 \) \quad (20)

Solving equations (18), (19) and (20), we obtained \( n = 16.6 \) and \( k_1 = 2.47 \text{ M}^{-1}\text{s}^{-1} \). This means that the protonation of the enolate of ketol-3 (\( k_1 \) in Scheme 13) was 16.6 times faster than the departure of the hydroxyl group from the pre-formed enolate (\( k_2 \) in Scheme 13). This result clearly demonstrates that the departure of the hydroxyl group from the enolate of ketol-3 in H_2O was the rate-limiting step, and the proton transfer process was a fast pre-equilibrium.
4.3 Experimental

4.3.1 Instrumentation

See Part 2.3.1 in Chapter 2.

4.3.2 Materials

1-Phenyl-1,5-hexanedione (dione-3) was synthesized by published procedures\textsuperscript{31} (see Scheme 15). The product from the reaction was found to be pure (judged by HPLC) and the structure was confirmed by NMR: \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \textsuperscript{\textdagger} 2.05 (quintet, 2 H, middle CH\textsubscript{2}), 2.19 (s, 3 H, CH\textsubscript{3}), 2.60 (t, 2 H, CH\textsubscript{2} on the methyl side), 3.05 (t, 2 H, CH\textsubscript{2} on the phenyl side), 7.4-8.0 (m, 5 H, aromatic H). UV (H\textsubscript{2}O): \textlambda_{\text{max}} = 246 nm (3.96).

The starting materials required by this procedure were prepared as follows: 1-tosylethyl isocyanide was prepared by Leusen's procedure\textsuperscript{32} and \textalpha-Tosylbenzyl isocyanide was prepared from formamide, benzaldehyde and sodium p-toluenesulfinate by a published two-step procedure\textsuperscript{33}. 
Scheme 15. The preparation of 1-phenyl-1,5-hexanedioine (dione-3).

3-Hydroxy-3-phenylcyclohexanone (Ketol-3) and 3-phenyl-2-cyclohexan-1-one (enone-3) were prepared by Woods' procedure.19

Recrystallization from ether gave pure 3-hydroxy-3-phenylcyclohexanone (judged by HPLC): $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 1.94-2.12 (m, 2 H), 2.16-2.30 (m and s(OH), 3 H), 2.36-2.58 (m, 2 H), 2.60-3.00 (AB system, 2 H, CH$_2$ at C-2), 7.3-7.6 (m, 5 H,
aromatic H). $^1$C-NMR (75 MHz, CDCl$_3$) δ 21.8 (C-5), 38.0 and 41.0 (C-4 and C-6), 49.0 (C-3), 55.0 (C-2), 124.0, 127.8, 128.2 and 147.0 (aromatic C), 210 (C-1). $^1$H-$^1$H and $^1$H-$^1$C COSY experiments were also carried out for ketol-3, which confirmed the structure assignments. UV (H$_2$O): 257 nm (2.66).

Recrystallization from petroleum ether (35-60°C) gave pure 3-phenyl-2-cyclohexen-1-one (judged by HPLC): $^1$H-NMR (300 MHz, CDCl$_3$), δ 2.2 (quintet, 2 H, CH$_2$ at C-5), 2.5 (t, 2 H, CH$_2$ at C-6), 2.8 (t, 2 H, CH$_2$ at C-4), 6.45 (s, 1 H, olefinic H), 7.4-7.6 (m, 5 H, aromatic H). UV(H$_2$O): 289 nm (4.31).

Phenylmagnesium bromide needed for Woods' procedure was prepared by Allen's procedure.$^{34}$

4.3.3 Methods

Reactions followed either by UV or by HPLC were carried out by using the same procedures as described for the reaction of 2,5-hexanedione in Part 2.3.3.1 in Chapter 2.

For reactions followed by HPLC analysis, 35% acetonitrile in water was used as eluting solvent. The HPLC chromatograms were stored directly in a microcomputer by the Gilson 715 HPLC system controller software. The HPLC peak area-time data were fitted to a single or double exponential equation by a non-linear least squares procedure to calculate the rate constants. The materials eluted were calibrated by
using suitable stock solutions of the pure compounds and followed at suitable wavelengths: 246 nm for dione-3, 205 nm for ketol-3 and 289 nm for enone-3.

For kinetics experiments, three channels of the Waters 490 detector were used at the same time to follow all three species in the reaction process: dione-3, ketol-3 and enone-3. For the determination of the equilibrium concentrations of dione-3 and ketol-3, only one channel of the Waters 490 detector was used (the other three were turned off) to increase the detection sensitivity. At the same time, the computer started to collect the HPLC chromatograms after 2.5 min to get rid of the negative peak at the beginning and make the amplification of HPLC chromatograms easy.

For the kinetics in D₂O, we started with 4.01 x 10⁻⁵ M of ketol-3 in 0.010 M NaOD with ionic strength 1.0 M (KCl). The growth of the product, enone-3, was followed by UV at 289 nm. The UV absorbance - time data were fitted to a double exponential equation by a non-linear least squares procedure.
CHAPTER 5. THE REACTION OF 5-OXOHEXANAL

5.1 Introduction

As we stated in Chapter 3, in order to try to apply the Marcus theory to intramolecular aldol condensation reactions, we need to study systems with as much variation as possible in the rates and equilibria of the intramolecular aldol addition step and of the subsequent dehydration step. For this reason, we studied the intramolecular aldol condensation reaction of 5-oxohexanal, described in this chapter, after we finished the study of the reaction of 2,5-hexanedione, described in Chapter 2, the reaction of 2,6-heptanedione, described in Chapter 3, and the reaction of 1-phenyl-1,5-hexanedione, described in Chapter 4. Changes in both rate and equilibrium constants for both the intramolecular aldol addition step and the subsequent dehydration step are to be expected when a methyl group in 2,6-heptanedione is replaced by a hydrogen to give 5-oxohexanal. For the intramolecular aldol addition step, the change from a methyl ketone to a aldehyde will increase the reactivity of the carbonyl group and make the reaction faster and more favorable. For the subsequent dehydration step of the ketol, 3-hydroxycyclohexanol (the ketol formed from 5-oxohexanal), two effects will lead to a less
favorable dehydration reaction: 1) this ketol has less steric repulsion and then will be more stable than 3-hydroxy-3-methylcyclohexanol (the ketol formed from 2,6-heptanedione) because a methyl group is replaced by a hydrogen; 2) the dehydration product of this ketol, 2-cyclohexen-1-one, lost the hyperconjugation of the methyl group with the α, β-unsaturated ketone structure unit in the 3-methyl-2-cyclohexen-1-one (the condensation product from 2,6-heptanedione), it will be less stable than 3-methyl-2-cyclohexen-1-one. Compared to the changes observed upon the replacement of the methyl group in 2,6-heptanedione by a phenyl group (described in Chapter 4), the replacement of the methyl group in 2,6-heptanedione by a hydrogen will drive the rates and equilibria for both intramolecular aldol addition step and the subsequent dehydration step in the opposite direction. The reaction rate and equilibrium constants are defined in Scheme 16.
Scheme 16. The reaction scheme for the base-catalyzed intramolecular aldol condensation reaction of 5-oxohexanal (dione-4): $k_{12}$ is the rate constant for intramolecular aldol addition of dione-4; $k_{23}$ is the rate constant for dehydration of ketol-4; $k_{21}$ is the rate constant for retroalaldol cleavage of ketol-4; $k_{32}$ is the rate constant for hydration of enone-4; $K_{12} = [\text{Ketol-4}]/[\text{Dione-4}]$; $K_{23} = [\text{Enone-4}]/[\text{Ketol-4}]$.

5.2 Results

5.2.1 Reaction starting with 5-oxohexanal (dione-4).

Starting with dione-4, the kinetics of the base-catalyzed intramolecular aldol condensation reaction were studied with UV analysis. The appearance of the condensation product, 2-cyclohexen-1-one (enone-4) was followed at 240 nm (see Figure 21). The reaction showed two-phase kinetics, which allowed us to determine the rate constants for intramolecular aldol addition step and for the subsequent dehydration step.
simultaneously. For the kinetic derivation, please see Appendix 1. By comparison with the kinetics for the reaction starting with enone-4 (described in Part 5.2.2, this chapter), it is clear that the second phase represents the kinetics for the dehydration step. This indicates that the smaller rate constant from the second phase is the pseudofirst-order rate constant of approach to the dehydration-hydration equilibrium \((k_{23} + k_{32})[\text{OH}^-]\). The apparent rate constants showed a first-order dependence on hydroxide concentration, leading to a second-order rate constant \(k_{32} + k_{23} = (2.46 \pm 0.05) \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}\) for the rate of approach to dehydration-hydration equilibrium.

The apparent rate constant from the first phase represents the pseudofirst-order rate constant for the intramolecular aldol addition step in terms of the total concentration of dione-4, including its diketone form, its aldehyde hydrate and the hydrate anion. Strictly speaking, the measured values are the pseudofirst-order rate constant of the rate of approach to intramolecular aldol addition-retroaldol cleavage equilibrium, however, in this case the contribution from the rate constant of retroaldol cleavage is less than experimental error, so that the measured value actually represents the rate constant for the intramolecular aldol addition step only.

To extract the rate constant for the intramolecular aldol addition of dione-4 in terms of its diketo form from the
apparent rate constant, we first measured the equilibrium constant for the hydration of dione-4 by \(^1\)H-NMR. The equilibrium constant \(K_h = [\text{the aldehyde hydrate of dione-4}] / [\text{the diketo form of dione-4}]\) was found to be 1.11. The concentration of the diketo form of dione-4 was based on the integration of its aldehyde hydrogen at 10 ppm (s), and the concentration of the aldehyde hydrate of dione-4 was based on the integration of its methine hydrogen at 5.4 ppm (t).

The concentration of the hydrate anion was then evaluated by assuming that its \(pK_a\) value was equal to that of acetaldehyde hydrate, which is 13.57.\(^3\) It was found that the concentration of the hydrate anion was negligible under the experimental conditions, since it is only 3% of the total concentration even at the highest hydroxide concentration we used (0.024 M). The first-order dependence of the apparent rate constants on hydroxide concentration for intramolecular aldol addition step also denies the significant involvement of the hydrate anion.

We can then extract the pseudofirst-order rate constant for intramolecular aldol addition reaction of dione-4 in terms of its diketo form, \(k_{12}[\text{OH}^-]\), from the apparent rate constant, \(A_3\), by correcting for aldehyde hydration as follows: \(k_{12}[\text{OH}^-] = A_3(1 + K_h) = 2.11A_3\), leading to a second-order rate constant \(k_{12} = (7.12 \pm 0.16) \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}\).
The measured pseudofirst-order rate constants and the calculated second-order rate constants are found in Table 13.
Table 13. Kinetics of Base-catalyzed Intramolecular Aldol Condensation of 5-Oxohexanal (dione-4). *

<table>
<thead>
<tr>
<th>No</th>
<th>$10^2[OH^-]$</th>
<th>A1$^c$</th>
<th>A2$^c$</th>
<th>$10^4A3^c$</th>
<th>A4$^c$</th>
<th>$10^4A5^c$</th>
<th>$10^2k_{12}^d$</th>
<th>$10^2(k_{23}+k_{32})^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$M^{-1}s^{-1}$</td>
<td>$M^{-1}s^{-1}$</td>
</tr>
<tr>
<td>1</td>
<td>1.1</td>
<td>0.5353</td>
<td>1.44</td>
<td>3.61</td>
<td>-1.95</td>
<td>2.72</td>
<td>6.92±0.06</td>
<td>2.47±0.02</td>
</tr>
<tr>
<td></td>
<td>±0.0005</td>
<td>±0.10</td>
<td>±0.03</td>
<td>±0.10</td>
<td>±0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.8</td>
<td>0.5269</td>
<td>1.16</td>
<td>6.15</td>
<td>-1.68</td>
<td>4.38</td>
<td>7.21±0.05</td>
<td>2.43±0.01</td>
</tr>
<tr>
<td></td>
<td>±0.0005</td>
<td>±0.04</td>
<td>±0.04</td>
<td>±0.04</td>
<td>±0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>0.5260</td>
<td>1.34</td>
<td>8.18</td>
<td>-1.85</td>
<td>6.09</td>
<td>7.19±0.06</td>
<td>2.54±0.02</td>
</tr>
<tr>
<td></td>
<td>±0.0009</td>
<td>±0.06</td>
<td>±0.07</td>
<td>±0.06</td>
<td>±0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weighted mean 7.12±0.16 2.46±0.05

*In aqueous solution at 25°C, ionic strength = 1.0 M (KCl), starting with dione-4 at an initial concentration of $1.86 \times 10^{-3}$ M, following the growth of the product, 2-cyclohexen-1-one (enone-4) by UV at 240 nm.
Sodium hydroxide concentration.

UV absorbance (A) - time (t) data were fitted to $A = A_1 + A_2 \times \exp(-A_3 \times t) + A_4 \times \exp(-A_5 \times t)$ by nonlinear least squares. $A_3$ corresponds to the pseudo-first-order rate constant for the intramolecular aldol addition of dione-4 in terms of the total concentration of dione-4. $A_5$ corresponds to the pseudofirst-order rate constant for the approach to dehydration-hydration equilibrium between 3-hydroxycyclohexanone (ketol-4) and enone-4. The standard deviations for the rate constants were calculated by the least squares procedure.

The second-order rate constant for the intramolecular aldol addition reaction of dione-4 in terms of the concentration of its diketo form, calculated from $A_3$ as described in Part 5.2.1.

The second-order rate constant for the rate of approach to the dehydration-hydration equilibrium between ketol-4 and enone-4.
Figure 21. Base-catalyzed intramolecular aldol condensation reaction of 5-oxohexanal (dione-4). The growth of 2-cyclohexen-1-one (enone-4) was followed by UV, monitoring the absorbance at 240 nm (see Entry 1 in Table 13).

UV Absorbance (A) vs. Time (t, sec).
5.2.2 Reaction starting with 2-cyclohexen-1-one (enone-4).

Starting with enone-4, the kinetics and equilibrium of the base-catalyzed hydration reaction were studied with HPLC analysis. Both the growth of 3-hydroxycyclohexanone (ketol-4) (see Figure 22) and the decrease of starting material, enone-4, (see Figure 23) were followed simultaneously, monitoring at appropriate wavelengths. Both of them showed pseudofirst-order kinetics, and gave us the rate constant for the rate of approach to the dehydration-hydration equilibrium between enone-4 and ketol-4 from different aspects. The reaction starting with enone-4 also allowed us to measure the equilibrium constant between enone-4 and ketol-4 ($K_{23}$) conveniently. The measured pseudofirst-order rate constant, the calculated second-order rate constant and the measured equilibrium constant are found in Table 14.
Table 14. Kinetics of Base-catalyzed Hydration Reaction of 2-Cyclohexen-1-one (enone-4) and Equilibrium Constant for the Reaction Leading from 3-Hydroxycyclohexanone (ketol-4) to Enone-4. All Derived from the Reaction Starting with Enone-4.

<table>
<thead>
<tr>
<th>No</th>
<th>$A_1^b$</th>
<th>$A_2^b$</th>
<th>$10^4A_3^b$</th>
<th>$10^2(k_{23}+k_{12})^b$</th>
<th>$K_{23}^c$ M$^{-1}$s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>2.95±0.10</td>
<td>-2.99±0.09</td>
<td>2.52±0.20</td>
<td>2.52±0.20</td>
<td></td>
</tr>
<tr>
<td>2e</td>
<td>3.63±0.03</td>
<td>1.23±0.05</td>
<td>2.44±0.24</td>
<td>2.44±0.24</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.51 ±0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weighted mean 2.49±0.06</td>
</tr>
</tbody>
</table>

*All reactions were carried out in 0.010 M NaOH aqueous solution at 25°C, starting with enone-4 at the initial concentration of 6.20 x 10$^{-2}$ M, ionic strength = 1.0 M (KCl), followed by HPLC analysis.

*The HPLC peak area (A)-time (t) data were fitted to $A = A_1 + A_2 \times \exp(-A_3 \times t)$ by nonlinear least squares. $A_3$ corresponds to the pseudofirst-order rate constant ($k_{23} + k_{32}$)[OH$^-$/], where $k_{23} + k_{32}$ is the second-order rate constant for the rate of approach to dehydration-hydration equilibrium between ketol-4 and enone-4. The standard deviation for the parameters was calculated by the least-squares procedure.*
\[ K = \frac{[\text{enone-4}]}{[\text{ketol-4}]} \text{, from triplicate measurements.} \]

The growth of ketol-4 was followed by HPLC analysis, monitoring at 271 nm.

The decrease of enone-4 was followed by HPLC analysis, monitoring at 240 nm.
Figure 22 Base-catalyzed hydration of 2-cyclohexen-1-one (enone-4). The growth of 3-hydroxycyclohexanone (ketol-4) was followed by HPLC, monitoring the absorbance at 271 nm (see Entry 1 in Table 14).
Figure 23 Base-catalyzed hydration of 2-cyclohexen-1-one (enone-4). The decrease of enone-4 was followed by HPLC, monitoring the absorbance at 240 nm (see Entry 2 in Table 14).

HPLC Peak Area (A) vs. Time (t, sec)
5.2.3. Estimation of the equilibrium constant ($K_{eq}$) for the intramolecular aldol addition step.

The equilibrium of the intramolecular aldol addition step is too far on the side of the ketol to be measured directly by experiment. We then estimated this equilibrium constant by disproportionation reactions.

We started this estimation with the experimental equilibrium constant for the intramolecular aldol addition reaction of 2,6-heptanedione (dione-2), which is 52.3 (see Part 3.2.4 in Chapter 3). If we set the free energy of formation for dione-2 in aqueous solution as $\Delta G_f(dione-2)$, then that for 3-hydroxy-3-methylcyclohexanone (ketol-2) will be $\Delta G_f(dione-2) + (-RT \ln 52.3) = \Delta G_f(dione-2) - 2.35 \text{ kcal/mol}$.

Once we have the free energies of formation for dione-2 and ketol-2, we can then estimate those for 5-oxohexanal (dione-4) and 3-hydroxycyclohexanone (ketol-4) by disproportionation reactions.

The free energy of formation for dione-4 can be calculated by using the disproportionation reaction:

$$\text{H}_2\text{C} = \text{O} + \text{CH}_3\text{C} = \text{O} \rightarrow \text{H}_2\text{C} = \text{O} + \text{CH}_3\text{C} = \text{O}$$

for which we assume $\Delta G = 0.0$. So that the free energy of formation for dione-4: $\Delta G_f(dione-4) = -32.97 \text{ kcal/mol}$ [\Delta G_f of
acetaldehyde\textsuperscript{34} + ΔG_\text{f}(\text{dione-2}) - (-38.48 \text{ kcal/mol}) [ΔG_\text{f} of acetone\textsuperscript{36}] = ΔG_\text{f}(\text{dione-2}) + 5.51 \text{ kcal/mol}.

The free energy of formation for ketol-4 can be estimated by using the disproportionation reaction:

\[
\begin{array}{ccc}
\text{OH} & \text{O} & \text{OH} \\
& \leftrightarrow & \\
\text{HO} & \text{O} & \text{OH}
\end{array}
\]

for which we assume ΔG is equal to the difference in MM3 steric energies corrected for the change in symmetry. The difference in MM3 steric energy = 5.38 kcal/mol [t-butanol] + 9.91 kcal/mol [ketol-4] - 3.66 kcal/mol [isopropanol] - 12.28 kcal/mol [ketol-2] = -0.65 kcal/mol. The change in symmetry is 3 because of the internal rotation symmetry of t-butanol for rotation about the C-O bond. Thus ΔG for this disproportionation reaction = -0.65 - RTln3 = -1.30 kcal/mol. Then we have ΔG_\text{f}(\text{ketol-4}) = -1.30 \text{ kcal/mol} + (ΔG_\text{f}(\text{dione-2}) - 2.35 \text{ kcal/mol}) [ΔG_\text{f} of ketol-2, estimated above] + (-44.41 kcal/mol) [ΔG_\text{f} of isopropanol\textsuperscript{36}] - (-45.12 kcal/mol) [ΔG_\text{f} of t-butanol\textsuperscript{36}] = ΔG_\text{f}(\text{dione-2}) - 1.77 \text{ kcal/mol}.

The free energy change for the intramolecular aldol addition reaction of dione-4 = ΔG_\text{f}(\text{ketol-4}) - ΔG_\text{f}(\text{dione-4}) = (ΔG_\text{f}(\text{dione-2}) - 1.77 \text{ kcal/mol}) - (ΔG_\text{f}(\text{dione-2}) + 5.51 \text{ kcal/mol})
= -7.28 kcal/mol, leading to an equilibrium constant of $2.15 \times 10^3$.

5.2.4 Summary of the rate and equilibrium constants for the reaction of 5-oxohexanal (dione-4).

The base-catalyzed intramolecular aldol addition reaction of dione-4 and the following base-catalyzed dehydration reaction of 3-hydroxycyclohexanone (ketol-4) were studied in aqueous solution with HPLC and UV analysis. The reactions were studied by starting with dione-4 and 2-cyclohexen-1-one (enone-4) respectively. Four rate constants and two equilibrium constants required to describe the reaction of dione-4 in terms of Scheme 16 were obtained. The rate and equilibrium constants for the reaction of dione-4 are summarized in Table 15.
Table 15. Rate and Equilibrium Constants for the Reaction of 5-Oxohexanal (dione-4)\(^a\)

<table>
<thead>
<tr>
<th>No.</th>
<th>(10^2k_{12},^b)</th>
<th>(10^7k_{21},^c)</th>
<th>(10^2(k_{23}+k_{32}),^d)</th>
<th>(10^3k_{23},^d)</th>
<th>(10^3k_{32},^o)</th>
<th>(K_{12})</th>
<th>(K_{23})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M(^{-1})S(^{-1})</td>
<td>M(^{-1})S(^{-1})</td>
<td>M(^{-1})S(^{-1})</td>
<td>M(^{-1})S(^{-1})</td>
<td>M(^{-1})S(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^b)</td>
<td>7.12±0.16</td>
<td>2.46±0.05</td>
<td>4.51±0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(^d)</td>
<td></td>
<td>2.49±0.06</td>
<td>4.51±0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg</td>
<td>7.12±0.16</td>
<td>9.18</td>
<td>2.47±0.02(^j)</td>
<td>2.02</td>
<td>4.48</td>
<td>2.15×10^3</td>
<td>4.51±0.01</td>
</tr>
</tbody>
</table>

\(^a\)The values were calculated in this table unless otherwise noted.

\(^b\)The second-order rate constant for the base-catalyzed intramolecular aldol addition reaction of dione-4 in terms of the concentration of its diketone form only.

\(^c\)The second-order rate constant for the base-catalyzed retroaldol reaction of 3-hydroxycyclohexanone (ketol-4).

\(^d\)The second-order rate constant for the base-catalyzed dehydration reaction of ketol-4.

\(^o\)The second-order rate constant for the base-catalyzed hydration reaction of 2-cyclohexen-1-one (enone-4).
$K_{12} = [\text{ketol-4}] / [\text{dione-4}]$ is the equilibrium constant for the reaction leading from dione-4 to ketol-4, see Part 5.2.3.

$K_{23} = [\text{enone-4}] / [\text{ketol-4}]$ is the equilibrium constant for the reaction leading from ketol-4 to enone-4.

From Table 13.

From Table 14.

The weighted mean.
5.2.5 Determination of the rate-limiting step.

5.2.5.1 The intramolecular aldol addition step for 5-oxohexanal (dione-4).

The base-catalyzed intramolecular aldol addition reaction of dione-4 has two major steps mechanistically: the formation of the enolate of dione-4 on the methyl side and the cyclization of this enolate to give the anion of 3-hydroxycyclohexanone (ketol-4) (see Scheme 17).

![Scheme 17. The mechanism of the base-catalyzed intramolecular aldol addition reaction of 5-oxohexanal (dione-4).](image)

The rate constant for the proton transfer of dione-4 ($k_1$) was estimated as 0.10 M$^{-1}$s$^{-1}$ after Guthrie, where pKa 19.44 was used for dione-4 (see Chapter 6 for pKa estimation). The observed rate constant for the base-catalyzed intramolecular aldol addition reaction of dione-4 ($k_{12}$) was found to be $7.12 \times 10^{-2}$ M$^{-1}$s$^{-1}$ (see Table 13), which gave us: $(0.10 \times k_2) / (k_1 + k_2) = 7.12 \times 10^{-2}$, leading to $n = k_1/k_2 = 0.40$. That means the intramolecular aldol addition of the enolate of dione-4 ($k_2$ in Scheme 17) was $1/0.40 = 2.50$ times faster than the protonation.
of the enolate of dione-4 (k_4 in Scheme 17). However, this estimated partitioning factor may only be used as an upper limit, the actual value could be smaller.

5.2.5.2 The dehydration step for 3-hydroxycyclohexanone (ketol-4).

The base-catalyzed dehydration of ketol-4 also has two major steps mechanistically: enolate formation from ketol-4 at carbon-2 and the departure of the hydroxyl group from the pre-formed enolate. The activation energy for enolate formation was estimated as 18.2 kcal/mol after Guthrie^{16} by using pK_a = 15.82 for ketol-4 at carbon-2 (for estimation of pK_a, please see Chapter 6). The observed activation energy was found to be 19.7 kcal/mol. Thus we are confident in saying that the rate-limiting step is the departure of the hydroxyl group from the pre-formed enolate.

5.3 Experimental

5.3.1 Instrumentation

The ozonized oxygen was generated from a Hankin type S, model 13 ozone generator. For the rest of the instrumentation, please see Part 2.3.1 in Chapter 2.
5.3.2 Materials

2-Cyclohexen-1-one (enone-4, 98%) was from Aldrich, and diacetone alcohol (97%) from BDH. Both were used as supplied and checked by $^1$H-NMR and HPLC before being used in this work.

1-Methylcyclopentene was synthesized from cyclopentanone and methylmagnesium iodide as follows. A solution of cyclopentanone (20.0 g, 0.238 mol) in ether (100 mL) was added to an ethereal solution of methylmagnesium iodide (3 M, 95 mL) under nitrogen within 30 min. The reaction mixture was stirred at room temperature for another 3 h, then the reaction was quenched by the addition of hydrochloric acid (3 M, 100 mL). The ether layer was separated, and the aqueous layer was extracted by ether (3 × 100 mL). The combined ether extracts were dried over anhydrous Na$_2$SO$_4$. Distillation gave pure 1-methylcyclopentene (6.79 g, 34.8%) at 71°C: $^1$H-NMR (300 MHz, CDCl$_3$) δ 1.70-1.75 (m, 3 H, CH$_3$), 1.78-1.95 (m, 2 H, CH$_2$ at C-4), 2.16-2.35 (m, 4 H, CH$_2$ at C-3 and C-5), 5.27-5.34 (m, 1 H, olefinic hydrogen).

5-Oxohexanal (dione-4) was synthesized by the ozonolysis of 1-methylcyclopentene as follows. The ozonized oxygen was bubbled through a solution of 1-methylcyclopentene (0.77 g, 9.4 mmol) in methanol (60 mL) at -78°C until a persistent blue color was observed$^{37}$ (about 1 h). Excess ozone was purged from
the reaction mixture with oxygen for 15 min, then with nitrogen until the blue color disappeared (about 45 min).

The reaction mixture was then added to a solution of thiourea (0.36 g, 4.7 mmol) in methanol (6 mL) in the presence of Na₂HPO₄ (2.0 g, 14.1 mmol) at 0°C under vigorous stirring. The function of Na₂HPO₄ is to destroy any acids in the reaction mixture and to prevent the formation of the dimethyl acetal of the formed aldehyde, which was reported as the major product in the literature under these reduction conditions.³⁸

The reaction mixture was then stirred vigorously at 0°C for 55 min. The by-product, thiourea S-dioxide, and phosphate salts were filtered off, and the methanol in the filtrate was removed by rotary evaporation. The formed 5-oxohexanal was extracted by CH₂Cl₂ (3 x 20 mL), the CH₂Cl₂ was then removed by rotary evaporation. Distillation gave pure 5-oxohexanal at 90°C/3 mmHg (0.41 g, 38.4%): ¹H NMR (300 MHz, CDCl₃) δ 9.75 (s, 1 H, CHO), 2.42-2.52 (m, 4 H, CH₂ adjacent to carbonyl group), 2.11 (s, 3 H, CH₃), 1.86 (quintet, 2 H, middle CH₂).

Literature:³⁹ ¹H NMR (CDCl₃) δ 9.86 (s, CHO), 2.70 (broad t, CH₂), 2.36 (s, CH₃), 1.8 (m, CH₂).

5.3.3 Methods

Reactions followed by UV were carried out by using the same procedures described for the reaction of 2,5-hexanedione
in Part 2.3.3.1 in Chapter 2 except that the stored absorbance-time data were fitted to a double exponential equation by a non-linear least squares procedure to obtain the rate constants.

Reactions followed by HPLC were also carried out by using the same procedures described for the reaction of 2,5-hexanedione in Part 2.3.3.1 in Chapter 2. A mixture of 5% acetonitrile in water was used as eluting solvent. The HPLC chromatograms were stored directly in a microcomputer by the Gilson 715 HPLC system controller software. The HPLC peak area-time data were fitted to a single exponential equation by a non-linear least squares procedure to obtain the rate constants. The concentrations of materials eluted were monitored at suitable wavelengths: ketol-4, 271 nm, and enone-4, 240 nm. Calibrations were carried out using suitable stock solutions of the pure compounds except that diacetone alcohol was used as a model compound for ketol-4.

5.3.4 The equilibrium constant for the hydration of 5-oxohexanal.

The 0.010 M solution of NaOD in D₂O with ionic strength 1.0 M (KCl) was placed in a Neslab Exacal EX300 circulating constant temperature bath at 25°C for more than 15 min. 0.8 mL of the above base solution was then added to 4.66 mg of 5-oxohexanal (the initial concentration of 5-oxohexanal = 5.11 ×
$10^{-2}$ M). The reaction was then quenched by the addition of potassium dihydrogen phosphate at the time of 50 s. Finally the quenched reaction mixture was analyzed by $^1$H NMR.
CHAPTER 6 ANALYSIS OF
INTRAMOLECULAR ALDOL CONденSATION REACTIONS
IN TERMS OF MARCUS THEORY.

6.1 Introduction

Rate and equilibrium constants are now available for four intramolecular aldol condensation reactions, described in Chapters 2-5. In order to analyze the intramolecular aldol condensation reactions in terms of Marcus theory, these data, for the overall observable reactions, must be corrected for pre- and post-equilibria to allow the microscopic rate and equilibrium constants for the process of interest to be extracted. The detailed mechanism for intramolecular aldol condensation is shown in Scheme 18, including both the intramolecular aldol addition step and the dehydration step. In addition to the usual mechanistic steps, we have explicitly included two more: these are the conversion of the equilibrated enolate ion of the initial dione into the conformation where the nucleophilic carbon of the enolate is in contact with the carbonyl carbon (the equivalent of the diffusional encounter step for
intermolecular reaction), and the conversion of the equilibrated enolate of the ketol to the conformation where the hydroxyl group which is to leave to form the enone is perpendicular to the plane of the enolate.

To extract the microscopic rate and equilibrium constants ($k_{\text{micro}}^{\text{a(d)}}$ and $K_{\text{micro}}^{\text{a(d)}}$ in Scheme 18) for the analysis in terms of Marcus theory, we will need equilibrium constants for each step in Scheme 18. Thus we need to estimate $pK_a$ values for diones and ketols as carbon acids, as well as $pK_a$ values for the hydroxyl group in ketols. We also need to estimate the equilibrium constants from the equilibrated conformation to the reactive conformation ($K_{\text{conf}}^{\text{a(d)}}$ in Scheme 18).

We will then analyze the intramolecular aldol condensation reactions in terms of Marcus theory, after we obtain the microscopic rate and equilibrium constants. If similar intrinsic barriers are obtained for four intramolecular aldol condensation reactions, then we can say that the correlation between rate and equilibrium for the intramolecular aldol condensation reactions can also be expressed in terms of Marcus theory, we can then predict the rate constants for any example of this important reaction from the equilibrium constants, either obtained from literature data or estimated thermodynamically. We will also compare these results with the average value for
intermolecular aldol condensation reactions, to check whether both of them fall in the same class of reaction in terms of Marcus theory, that is whether both of them have similar intrinsic barriers.

Both the intramolecular aldol addition step and the dehydration step will be analyzed in terms of Marcus theory.
Scheme 18. The detailed mechanism for the base-catalyzed intramolecular aldol condensation reactions for the analysis in terms of Marcus theory. Capital K's represent the
equilibrium constants, and lower case k's represent the rate constants. The superscripts \(^*\) and \(^d\) stand for the intramolecular aldol addition step and the dehydration step respectively. The abbreviations used in this thesis are defined as follows:

<table>
<thead>
<tr>
<th>R</th>
<th>n</th>
<th>Reaction</th>
<th>( \text{O} )</th>
<th>( \text{O} )</th>
<th>( \text{O} )</th>
<th>( \text{O} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_3 )</td>
<td>2</td>
<td>RXN-1</td>
<td>DIONE-1</td>
<td>KETOL-1</td>
<td>ENONE-1</td>
<td></td>
</tr>
<tr>
<td>( \text{CH}_3 )</td>
<td>3</td>
<td>RXN-2</td>
<td>DIONE-2</td>
<td>KETOL-2</td>
<td>ENONE-2</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>3</td>
<td>RXN-3</td>
<td>DIONE-3</td>
<td>KETOL-3</td>
<td>ENONE-3</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>3</td>
<td>RXN-4</td>
<td>DIONE-4</td>
<td>KETOL-4</td>
<td>ENONE-4</td>
<td></td>
</tr>
</tbody>
</table>
6.2 Results

6.2.1 Analysis of the intramolecular aldol addition step in terms of Marcus theory.

6.2.1.1 pKₐ Estimation.

To extract the microscopic rate and equilibrium constants from the observed overall rate and equilibrium constants for intramolecular aldol addition step, we need to estimate the pKₐ values for the diones (methyl side) and for the hydroxyl groups in the ketols.

The pKₐ values for the diones were estimated starting with acetone. The enol contents (pKₐ in Scheme 19) of dione-1 and dione-2 (for the enolization to the methyl groups) were assumed to be the same as for acetone, for which pKₐ is 8.33.⁴⁰-⁴¹ Because both dione-3 and dione-4 have only one enolizable methyl group, the enol content was obtained by correcting that of acetone by a statistical factor of 2. The pKₐ of the enol (pKₐ in Scheme 19) was assumed to respond to polar substituents with the same p' = -1.316 as an alcohol.⁴² Starting with the pKₐ value for the acetone enol = 10.94,⁴⁰-⁴¹ we have pKₐ = 10.94 - 1.316 σ for the enol of a substituted ketone. Based on Scheme 19, the pKₐ value for a ketone is pKₐ = pKₐ + pKₐ. The estimated pKₐ values for the diones are found in Table 16.
\[
\begin{align*}
\text{RCH}_3\text{CH}_2\text{O} & \xrightleftharpoons[pK_{a\text{dione}}]{pK_{E}}\text{RCH}_2\text{O}^- + \text{H}^+
\end{align*}
\]

**Scheme 19.** Scheme for the p\(K_a\) estimation of diones.

**Table 16.** Estimated p\(K_a\) Values for the Diones (For the Enolization to the Methyl Groups).\(^a\)

<table>
<thead>
<tr>
<th>Dione</th>
<th>p(K_a)^b</th>
<th>p(K_a)^c</th>
<th>p(K_a)^d_{dione}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.33</td>
<td>10.61</td>
<td>18.94</td>
</tr>
<tr>
<td></td>
<td>8.33</td>
<td>10.81</td>
<td>19.14</td>
</tr>
<tr>
<td>Ph</td>
<td>8.63</td>
<td>10.75</td>
<td>19.38</td>
</tr>
<tr>
<td></td>
<td>8.63</td>
<td>10.81</td>
<td>19.44</td>
</tr>
</tbody>
</table>

\(^a\)All in aqueous solution at 25°C.
Defined in Scheme 19, estimated as described in the text in Part 6.2.1.1.

Defined in Scheme 19, calculated by using $pK_a^\circ = 10.94 - 1.316 \sigma^\circ$ (see text in Part 6.2.1.1). $\sigma^\circ$ values used were as follows: \textsuperscript{43} CH$_3$COCH$_2$, 0.62; HCOCH$_2$, 0.62 and PhCO, 2.2. A fall-off factor of 0.4 for each CH$_2$ was used, as recommended by Perrin et al. \textsuperscript{43}

Estimated $pK_a$ values for the diones.

The $pK_a$ values for the hydroxyl group in the ketols were estimated starting from diacetone alcohol, for which $pK_a = 16.21$. \textsuperscript{16} For ketol-3, the effect of a phenyl group was corrected for by using the $pK_a$ difference between ethanol ($pK_a = 15.83$) \textsuperscript{44} and benzyl alcohol ($pK_a = 15.48$). \textsuperscript{45} For ketol-4, the effect of a methyl group was corrected for by using the $pK_a$ difference between isopropanol ($pK_a = 16.57$) \textsuperscript{44} and t-butanol ($pK_a = 16.84$) \textsuperscript{44}. The estimated $pK_a$ values for the hydroxyl group in ketols are found in Table 17.
Table 17. Estimated pKa Values for the Hydroxyl Group in Ketols.

<table>
<thead>
<tr>
<th>Ketol</th>
<th>pK$_a^\text{OH}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Ketol Structure 1]</td>
<td>16.21</td>
</tr>
<tr>
<td>![Ketol Structure 2]</td>
<td>16.21</td>
</tr>
<tr>
<td>![Ketol Structure 3]</td>
<td>15.86</td>
</tr>
<tr>
<td>![Ketol Structure 4]</td>
<td>15.94</td>
</tr>
</tbody>
</table>

*All in aqueous solution at 25°C.

6.2.1.2 Calculation of the equilibrium constant for the conversion of the equilibrated conformation to the reactive conformation ($K_{\text{conf}}$ in Scheme 18).

To calculate the microscopic rate and equilibrium constants needed for an analysis in terms of Marcus theory, we need a special equilibrium constant ($K_{\text{conf}}$ in Scheme 18): the equilibrium constant for the conversion of the equilibrated conformation of the enolate of a dione to its reactive conformation. The reactive conformation is the equivalent of the diffusional encounter complex for intermolecular reaction. The reactive conformation of the enolate of dione-1 was assumed to be the 3,4-eclipsed conformation. The reactive conformation for the enolates of dione-2, dione-3 and dione-4 was assumed to be one with the enolate and the carbonyl group in what is equivalent to a
1,3-diaxial interaction. These reactive conformations can be converted to the ketol anion products simply by bond rotation accompanied by bond formation: See Scheme 20.

The equilibrium constant for this conformational shift was calculated using the difference in MM3 steric energies for the two conformations of the enols. For MM3 calculations, please see Appendix 3. The calculated results are found in Table 18.

Scheme 20. The microscopic step for intramolecular aldol addition reaction: from the reactive conformation of the enolate of dione to the ketol anion product.
Table 18. Calculated Equilibrium Constants for the Conversion of the Equilibrated Conformations of the Enolates of the Diones to Their Reactive Conformations.

<table>
<thead>
<tr>
<th>Dione</th>
<th>MM3 $E_a$</th>
<th>MM3 $E_r$</th>
<th>$\Delta$MM3 $E^\circ$</th>
<th>$K_{conf}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td></td>
</tr>
<tr>
<td>Dione-1</td>
<td>4.71</td>
<td>12.38</td>
<td>7.67</td>
<td>2.40 x 10^{-6}</td>
</tr>
<tr>
<td>Dione-2</td>
<td>7.30</td>
<td>9.23</td>
<td>1.93</td>
<td>3.86 x 10^{-2}</td>
</tr>
<tr>
<td>Dione-3</td>
<td>9.00</td>
<td>9.79</td>
<td>0.79</td>
<td>0.260</td>
</tr>
<tr>
<td>Dione-4</td>
<td>7.13</td>
<td>8.51</td>
<td>1.38</td>
<td>9.77 x 10^{-2}</td>
</tr>
</tbody>
</table>

*Steric energy for the equilibrated conformation of the enol, calculated by MM3.

*Steric energy for the reactive conformation of the enol, calculated by MM3.

$\Delta$MM3 $E = MM3 E_r - MM3 E_a$, the calculated steric energy difference between the reactive conformation and the equilibrated conformation.

6.2.1.3 Calculation of the microscopic equilibrium constants.

We now can calculate the microscopic equilibrium constants for the analysis in terms of Marcus theory, after estimating the equilibrium constants for the conversion of
the equilibrated conformations of the enolates of the diones to their reactive conformations, and the $pK_a$ values for the diones and the hydroxyl groups in the ketols. The calculation equations used are as follows:

$$K_1^a = \frac{K_{a_dione}^a}{K_w}$$

$$K_3^a = \frac{K_w}{K_{a_{OH}}^a}$$

$$K_2^a = \frac{K_{12}}{(K_1^a \times K_3^a)}$$

$$K_{micro}^a = \frac{K_2^a}{K_{conf}^a}$$

$K_1^a$, $K_2^a$, $K_3^a$, $K_{conf}^a$ and $K_{micro}^a$ were defined in Scheme 18. $K_{12}$ is the observed equilibrium constant for the intramolecular aldol addition reaction. $K_{micro}^a$ is the microscopic equilibrium constant, which is required for the analysis of the intramolecular aldol addition step in terms of Marcus theory. $K_{a_dione}^a$ and $K_{a_{OH}}^a$ are acidity constants for the diones (on the methyl side), and for the hydroxyl group in the ketols, respectively. $K_w$ is the dissociation constant of water.

The calculated microscopic equilibrium constants for four intramolecular aldol addition reactions are found in Table 19.
**Table 19. Calculated Microscopic Equilibrium Constants for the Intramolecular Aldol Addition Step.**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$K_{12}^{b}$</th>
<th>pK$_{a}^{\text{dione}}^{c}$</th>
<th>pK$_{a}^{\text{OH}}^{d}$</th>
<th>$K_{\text{conf}}^{e}$</th>
<th>$10^6K_{1}^{e,f}$ M$^{-1}$</th>
<th>$K_{3}^{e,f}$ M</th>
<th>$K_{2}^{e,f}$</th>
<th>$K_{\text{micro}}^{e,g}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>10.0$^{b}$</td>
<td>18.94</td>
<td>16.21</td>
<td>2.40x10$^{-6}$</td>
<td>11.5</td>
<td>162.1</td>
<td>5.37x10$^{3}$</td>
<td>2.24x10$^{3}$</td>
</tr>
<tr>
<td>RXN-2</td>
<td>5$^{c}$</td>
<td>19.14</td>
<td>16.21</td>
<td>3.86x10$^{-2}$</td>
<td>7.24</td>
<td>162.1</td>
<td>4.45x10$^{4}$</td>
<td>1.15x10$^{6}$</td>
</tr>
<tr>
<td>RXN-3</td>
<td>7$^{c}$</td>
<td>19.38</td>
<td>15.86</td>
<td>0.260</td>
<td>4.17</td>
<td>72.46</td>
<td>2.55x10$^{4}$</td>
<td>9.80x10$^{4}$</td>
</tr>
<tr>
<td>RXN-4</td>
<td>2.15x10$^{5}$</td>
<td>19.44</td>
<td>15.94</td>
<td>9.77x10$^{-2}$</td>
<td>3.63</td>
<td>86.96</td>
<td>5.39x10$^{8}$</td>
<td>5.51x10$^{9}$</td>
</tr>
</tbody>
</table>

$^{a}$As defined in Scheme 18.

$^{b}$The observed equilibrium constant for intramolecular aldol addition step.

$^{c}$The pK$_{a}$ value for the dione (on the methyl side), from Table 16.

$^{d}$The pK$_{a}$ value for the hydroxyl group in the ketol, from Table 17.

$^{e}$The equilibrium constant from the equilibrated conformation of the enolate of the dione to its reactive conformation, from Table 18.
As defined in Scheme 18, calculated as described in Part 6.2.1.3.

The microscopic equilibrium constant for intramolecular aldol addition step, defined in Scheme 18, calculated as described in Part 6.2.1.3.

See Part 2.2.5 in Chapter 2.

See Part 3.2.4 in Chapter 3.

See Part 4.2.4 in Chapter 4.

See Part 5.2.3 in Chapter 5.
6.2.1.4 Calculation of the microscopic rate constants.

We now calculate the microscopic rate constants for the intramolecular aldol addition step. As is shown in Scheme 18, the intramolecular aldol addition has three major steps. What we are interested in for the analysis in terms of Marcus theory is the rate constant for the carbon-carbon bond formation from the reactive conformation of the enolate of the dione. To extract the microscopic rate constant from the observed rate constant, we first need to determine the rate-limiting step for the whole intramolecular aldol addition reaction.

The last step is a proton transfer between alkoxide and hydroxide, which should be a very fast, diffusion-controlled process. It will not be the rate-limiting step for intramolecular aldol addition reaction.

The first step is hydroxide-catalyzed enolate formation of the dione. Generally speaking, this step might be a fast pre-equilibrium, or a partially or fully rate-limiting step. We have already examined this concern individually for four intramolecular aldol addition reactions in Chapters 2-5. As was explained in Part 2.2.6.1 in Chapter 2, the hydroxide-catalyzed enolate formation is a fast pre-equilibrium, and the carbon-carbon bond formation step is fully rate-limiting for the intramolecular aldol addition reaction of dione-1.
The hydroxide-catalyzed enolate formation, as was described in Part 3.2.5.1 in Chapter 3, Part 4.2.5.1 in Chapter 4 and Part 5.2.5.1 in Chapter 5, turned out to be partially rate-limiting for intramolecular aldol addition reactions of dione-2, dione-3 and dione-4. That is to say that the carbon-carbon bond formation is only partially rate-limiting for the latter three reactions.

We can then calculate the microscopic rate constants from the observed rate constants for intramolecular aldol addition reactions. If the carbon-carbon bond formation is only partially rate-limiting as is the case for the intramolecular aldol addition reactions of dione-2, dione-3 and dione-4, we can calculate the microscopic rate constant as follows:

\[ k_{2*} = k_{12} \left(1 + 1/n^s\right) / K_1^s \]

\[ k_{\text{micro}*} = k_{2*} / K_{\text{conf}*} \]

\[ n^s = k_{-1*} / k_{2*} \]

\( k_{12} \) is the observed second-order rate constant for the base-catalyzed intramolecular aldol addition reaction. \( k_{2*}, k_{-1*}, K_1^s \) and \( K_{\text{conf}*} \) are defined in Scheme 18. \( k_{\text{micro}*} \) is the microscopic rate constant for intramolecular aldol addition reaction, which is also defined in Scheme 18.

If the carbon-carbon bond formation is fully rate-limiting as is the case for the intramolecular aldol
Addition reaction of dione-1, the calculation of the microscopic rate constant can be simplified as:

\[ k_2^* = \frac{k_{12}}{K_1^*} \]

\[ k_{\text{micro}}^* = \frac{k_2^*}{K_{\text{conf}}^*} \]

The calculated microscopic rate constants for four intramolecular aldol addition reactions are found in Table 20.
Table 20. Calculated Microscopic Rate Constants for the Intramolecular Aldol Addition Reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$10^5 k_{12,1} \text{ M}^{-1}\text{s}^{-1}$</th>
<th>$n$</th>
<th>$10^6 k_1 \text{ M}^{-1}$</th>
<th>$k_2 \text{ s}^{-1}$</th>
<th>$K_{conf} \text{ f}$</th>
<th>$k_{micro} \text{ g s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>0.00335$^b$</td>
<td>&gt;10$^k$</td>
<td>11.5</td>
<td>2.92</td>
<td>$2.40 \times 10^{-6}$</td>
<td>$1.22 \times 10^6$</td>
</tr>
<tr>
<td>RXN-2</td>
<td>7.34$^d$</td>
<td>1.22$^j$</td>
<td>7.24</td>
<td>$1.84 \times 10^4$</td>
<td>$3.86 \times 10^{-2}$</td>
<td>$4.78 \times 10^3$</td>
</tr>
<tr>
<td>RXN-3</td>
<td>1.28$^j$</td>
<td>6.81$^m$</td>
<td>4.17</td>
<td>$3.52 \times 10^3$</td>
<td>0.260</td>
<td>$1.35 \times 10^4$</td>
</tr>
<tr>
<td>RXN-4</td>
<td>7.12$^n$</td>
<td>0.40$^o$</td>
<td>3.63</td>
<td>$6.87 \times 10^4$</td>
<td>$9.77 \times 10^{-2}$</td>
<td>$7.03 \times 10^5$</td>
</tr>
</tbody>
</table>

$^a$As defined in Scheme 18.

$^b$The observed second-order rate constant for the base-catalyzed intramolecular aldol addition reaction.

$^c n = k_{-1} / k_2$, $k_{-1}$ and $k_2$ are defined in Scheme 18.

$^d$As defined in Scheme 18, from Table 19.

$^e$Calculated as described in Part 6.2.1.4, defined in Scheme 18.

$^f$From Table 18.
The microscopic rate constant for intramolecular aldol addition reaction, calculated as described in Part 6.2.1.4, defined in Scheme 18.

See Part 2.2.5 in Chapter 2.

See Part 3.2.4 in Chapter 3.

See Part 4.2.4 in Chapter 4.

This means that the carbon-carbon bond formation is fully rate-limiting, see Part 2.2.6.1 in Chapter 2.

See Part 3.2.5.1 in Chapter 3.

See Part 4.2.5.1 in Chapter 4.

See Part 5.2.4 in Chapter 5.

See Part 5.2.5.1 in Chapter 5.
6.2.1.5 Calculation of the intrinsic barriers in terms of Marcus theory.

The microscopic rate and equilibrium constants are now available for four intramolecular aldol addition reactions. We can now calculate the intrinsic barriers for these intramolecular aldol addition reactions by using the Marcus equation: \( \Delta G^* = \Delta G^e \left(1 + \Delta G^e / 4\Delta G^* \right)^2 \), where \( \Delta G^* \) and \( \Delta G^e \) refer to the activation energy and the reaction free energy change for the microscopic step, calculated from the microscopic rate and equilibrium constant respectively, and \( \Delta G^* \) is the intrinsic barrier, the activation energy that would be obtained if \( \Delta G^e \) were zero.

The calculated intrinsic barriers for four intramolecular aldol addition reactions are found in Table 21.
Table 21. Calculated Intrinsic Barriers for the Intramolecular Aldol Addition Reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$K_{\text{micro}}$</th>
<th>$k_{\text{micro}}$</th>
<th>$\Delta G^{\circ}$</th>
<th>$\Delta G^{\circ}$</th>
<th>$\Delta G^{\circ}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>$2.24 \times 10^9$</td>
<td>$1.22 \times 10^6$</td>
<td>$-12.77$</td>
<td>$9.17$</td>
<td>$14.87$</td>
</tr>
<tr>
<td>RXN-2</td>
<td>$1.15 \times 10^6$</td>
<td>$4.78 \times 10^5$</td>
<td>$-8.28$</td>
<td>$9.73$</td>
<td>$13.55$</td>
</tr>
<tr>
<td>RXN-3</td>
<td>$9.80 \times 10^4$</td>
<td>$1.35 \times 10^4$</td>
<td>$-6.82$</td>
<td>$11.84$</td>
<td>$15.05$</td>
</tr>
<tr>
<td>RXN-4</td>
<td>$5.51 \times 10^9$</td>
<td>$7.03 \times 10^5$</td>
<td>$-13.30$</td>
<td>$9.50$</td>
<td>$15.43$</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>$14.49 \pm 0.82$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As defined in Scheme 18.

bThe microscopic equilibrium constant for intramolecular aldol addition reaction, from Table 19.

cThe microscopic rate constant for intramolecular aldol addition reaction, from Table 20.

dThe reaction free energy change for the microscopic step, calculated from $K_{\text{micro}}$.

eThe activation energy for the microscopic step, calculated from $k_{\text{micro}}$. 
The calculated intrinsic barrier for intramolecular aldol addition reaction.

Only the first three reactions were included, for explanation, see Part 6.3.
6.2.2 Analysis of the dehydration step in terms of Marcus theory.

6.2.2.1 pKₐ Estimation.

To extract the microscopic rate and equilibrium constants from the observed rate and equilibrium constants for the dehydration step, we need to estimate the pKₐ values for the ketols at their carbon-2 positions.

The carbon-2 pKₐ values for the ketols were estimated starting from the corresponding cycloalkanone without a β-hydroxyl group, then correcting for 1) the effect of a β-hydroxyl group by adding the difference in pKₐ between 4-hydroxy-2-butanone and 2-butanone (-2.57)¹⁶ and 2) the statistical factor log2, because both sides of the corresponding unsubstituted cycloalkanone are enolizable and equivalent.

The pKₐ value for cyclopentanone was estimated from the enol content. The enol content, pKₐ, for cyclopentanone is 7.94.¹⁶ We then assume the enol of cyclopentanone has the same pKₐ as for that of cyclohexanone, for which pKₐ² = 11.70.¹⁷ This gave us the pKₐ = 7.94 + 11.70 = 19.64 for cyclopentanone.

The pKₐ value for 3-phenylcyclohexanone was also estimated from the enol content. We assume 3-phenylcyclohexanone has the same enol content as for
cyclohexanone, for which $pK_a = 6.39$. The $pK_a$ of enol was then assumed to respond to polar substituent with the same $\rho^* = 1.316$ as an alcohol. Starting with the $pK_a^b$ value for cyclohexanone enol = 11.70, we have $pK_a^b = 11.70 - 1.316 \sigma^* = 11.70 - 1.316 \times 0.75 \times 0.4 = 11.31$ for 3-phenylcyclohexanone enol, where 0.75 is the $\sigma^*$ value for phenyl group and 0.4 is the fall-off factor for a double bond recommended by Perrin et al. This gave us the $pK_a = pK_a^b + pK_a^b = 6.39 + 11.31 = 17.70$ for 3-phenylcyclohexanone.

We can now estimate the carbon-2 $pK_a$ values for all ketols. The estimated values are found in Table 22.

**Table 22. Estimated Carbon-2 pK$_a$ Values for the Ketols.**

<table>
<thead>
<tr>
<th>Ketol</th>
<th>$pK_a^b$</th>
<th>$pK_a^{ketol \sigma}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19.64$^d$</td>
<td>17.37</td>
</tr>
<tr>
<td></td>
<td>18.09$^e$</td>
<td>15.82</td>
</tr>
<tr>
<td></td>
<td>17.70$^d$</td>
<td>15.43</td>
</tr>
<tr>
<td></td>
<td>18.09$^e$</td>
<td>15.82</td>
</tr>
</tbody>
</table>

$^a$All in aqueous solution at 25°C.

$^b$The $pK_a$ value for the corresponding cycloalkanone.
The estimated carbon-2 pKₐ values for the ketols, calculated from the pKₐ value for the corresponding cycloalkanone as described in Part 6.2.2.1.

*Estimated as described in Part 6.2.2.1.

*Reference 47.

6.2.2.2 Calculation of the equilibrium constant for the conversion of the equilibrated conformation to the reactive conformation ($K_{\text{conf}}^{d}$ in Scheme 18).

As stated in Part 5.2.1.2, to calculate the microscopic rate and equilibrium constants needed for an analysis in terms of Marcus theory, we need a special equilibrium constant ($K_{\text{conf}}^{d}$ in Scheme 18): the equilibrium constant for the conversion of the equilibrated conformation of the enolate of a ketol to its reactive conformation. The reactive conformation for the enolates of the ketols was assumed to be the conformation with the hydroxyl leaving group perpendicular to the plane of the enolate.

The equilibrium constants for this conformational shift were estimated from the difference between the MM3 steric energies of the equilibrium form of the enol and the perpendicular form. The latter energies were calculated using the dihedral driver routines to alter the dihedral
angle between the hydroxyl and the double bond. For MM3 calculations, please see Appendix 3.

The calculated results are found in Table 23.

6.2.2.3 Estimation of the equilibrium constant $K_3^d$ in Scheme 18.

The hydroxide created in dehydration step is generated in contact with the enone product. The equilibrium constant for the conversion of the enone-hydroxide encounter complex to the fully separate and solvated enone and hydroxide, $K_3^d$ in Scheme 18, is then needed to extract the microscopic rate and equilibrium constants for the analysis in terms of Marcus theory.

In such an encounter complex, the hydroxide has necessarily lost one solvating water with negligible hydrogen bonding in return. The energetic cost of this partial desolvation is 7.13 kcal/mol, estimated from the difference in $pK_a$ between water and DMSO, which was assumed to reflect the cost of losing three hydrogen bonds to the anion. The energetic cost for bring two species together was estimated as 2.42 kcal/mol after Hine. Then the total energetic cost for the enone-hydroxide encounter complex is 9.55 kcal/mol, leading to $K_3^d = 9.86 \times 10^6$ M.
Table 23. Calculated Equilibrium Constants for the Conversion of the Equilibrated Conformation of the Enolates of the Ketols to Their Reactive Conformation.

<table>
<thead>
<tr>
<th>Ketol</th>
<th>MM3 $E_\text{r}$</th>
<th>MM3 $E_\text{c}$</th>
<th>$\Delta$MM3 $E$</th>
<th>$K_{\text{conf}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td>(kcal/mol)</td>
<td></td>
</tr>
<tr>
<td>Ketol-1</td>
<td>15.63</td>
<td>15.98</td>
<td>0.35</td>
<td>0.554</td>
</tr>
<tr>
<td>Ketol-2</td>
<td>8.63</td>
<td>9.25</td>
<td>0.62</td>
<td>0.352</td>
</tr>
<tr>
<td>Ketol-3</td>
<td>10.58</td>
<td>11.13</td>
<td>0.55</td>
<td>0.396</td>
</tr>
<tr>
<td>Ketol-4</td>
<td>7.44</td>
<td>8.38</td>
<td>0.94</td>
<td>0.205</td>
</tr>
</tbody>
</table>

*As defined in Scheme 18.

$b$ Steric energy for the equilibrated conformation, calculated by MM3.

$c$ Steric energy for the reactive conformation, calculated by MM3.

$d\Delta$MM3 $E = MM3 \ E_\text{r} - MM3 \ E_\text{c}$, the calculated steric energy difference between the reactive conformation and the equilibrated conformation.
6.2.2.4 Calculation of the microscopic equilibrium constants.

We can now calculate the microscopic equilibrium constants for the analysis in terms of Marcus theory, the calculation equations used are as follows:

$$K_1^d = K_{a^{\text{keto}}} / K_w$$
$$K_2^d = K_{23} / (K_1^d \times K_3^d)$$
$$K_{\text{micro}}^d = K_2^d / K_{\text{conf}}^d$$

$K_1^d$, $K_2^d$, $K_3^d$, $K_{\text{conf}}^d$ and $K_{\text{micro}}^d$ were defined in Scheme 18. $K_{23}$ is the observed equilibrium constant for dehydration step. $K_{\text{micro}}^d$ is the microscopic equilibrium constant, which is required by the analysis for dehydration step in terms of Marcus theory. $K_{a^{\text{keto}}}$ is acidity constant for the ketols at carbon-2. $K_w$ is the dissociation constant of water.

The calculated microscopic equilibrium constants for four dehydration reactions are found in Table 24.
Table 24. Calculated Microscopic Equilibrium Constants for the Dehydration Step.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>K&lt;sub&gt;23&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;&lt;sup&gt;ketol&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</th>
<th>10&lt;sup&gt;2&lt;/sup&gt;K&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;d&lt;/sup&gt; M&lt;sup&gt;−&lt;/sup&gt;</th>
<th>10&lt;sup&gt;−6&lt;/sup&gt;K&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt; M</th>
<th>10&lt;sup&gt;3&lt;/sup&gt;K&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;−1&lt;/sup&gt;</th>
<th>K&lt;sub&gt;conf&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;f&lt;/sup&gt;</th>
<th>10&lt;sup&gt;3&lt;/sup&gt;K&lt;sub&gt;micro&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>602&lt;sup&gt;h&lt;/sup&gt;</td>
<td>17.37</td>
<td>0.0427</td>
<td>9.86</td>
<td>143</td>
<td>0.554</td>
<td>246</td>
</tr>
<tr>
<td>RXN-2</td>
<td>58.3&lt;sup&gt;i&lt;/sup&gt;</td>
<td>15.82</td>
<td>1.51</td>
<td>9.86</td>
<td>0.391</td>
<td>0.352</td>
<td>1.11</td>
</tr>
<tr>
<td>RXN-3</td>
<td>950&lt;sup&gt;j&lt;/sup&gt;</td>
<td>15.43</td>
<td>3.72</td>
<td>9.86</td>
<td>2.59</td>
<td>0.396</td>
<td>6.55</td>
</tr>
<tr>
<td>RXN-4</td>
<td>4.51&lt;sup&gt;k&lt;/sup&gt;</td>
<td>15.82</td>
<td>1.51</td>
<td>9.86</td>
<td>0.0303</td>
<td>0.205</td>
<td>0.148</td>
</tr>
</tbody>
</table>

<sup>a</sup>As defined in Scheme 18.

<sup>b</sup>The observed equilibrium constant for dehydration step.

<sup>c</sup>The carbon-2 pK<sub>a</sub> value for the ketol, from Table 22.

<sup>d</sup>As defined in Scheme 18, calculated as described in Part 6.2.2.4.

<sup>e</sup>Defined in Scheme 18, estimated as described in Part 6.2.2.3.

<sup>f</sup>The equilibrium constant from the equilibrated conformation of the enolate of the ketol to its reactive conformation, from Table 23.
The microscopic equilibrium constant for dehydration step, defined in Scheme 18, calculated as described in Part 6.2.2.4.

*See Part 2.2.5 in Chapter 2.
*See Part 3.2.4 in Chapter 3.
*See Part 4.2.4 in Chapter 4.
*See Part 5.2.4 in Chapter 5.
6.2.2.5 Calculation of the microscopic rate constants.

We now calculate the microscopic rate constants for the dehydration step involved in intramolecular aldol condensation reactions. As is shown in Scheme 18, the dehydration of the ketol is a multistep reaction. What we are interested in for the analysis in terms of Marcus theory is the rate constant for the departure of the hydroxyl group from the reactive conformation of the enolate of the ketol \( K_{\text{micro}}^d \) in Scheme 18. To extract this microscopic rate constant from the observed rate constant, we first need to determine the rate-limiting step for the whole dehydration reaction.

The first step is a hydroxide-catalyzed enolate formation of the ketol at carbon-2. Generally speaking, this step might be a fast pre-equilibrium, or a partially or fully rate-limiting step. We have already examined this problem individually for four dehydration reactions in Chapters 2-5. As was explained in Part 2.2.6.2 in Chapter 2, the hydroxide-catalyzed enolate formation is partially rate-limiting in the dehydration of 3-hydroxy-3-methylcyclopentanone (ketol-1). The hydroxide-catalyzed enolate formation, as was described in Part 3.2.5.2 in Chapter 3, Part 4.2.5.2 in Chapter 4 and Part 5.2.5.2 in Chapter 5, has turned out to be a fast pre-equilibrium, and the
departure of the hydroxyl group from the pre-formed ketol enolate is fully rate-limiting in the dehydration reactions of 3-hydroxy-3-methylcyclohexanone (ketol-2), 3-hydroxy-3-phenylcyclohexanone (ketol-3) and 3-hydroxycyclohexanone (ketol-4).

We can then calculate the microscopic rate constants from the observed rate constants for dehydration reactions. If the hydroxide-catalyzed enolate formation is partially rate-limiting as was the case for the dehydration reaction of ketol-1, we can calculate the microscopic rate constant as follows:

\[ k_2^d = k_{23} \left( 1 + 1/n^d \right) / K_1^d \]

\[ \kappa_{\text{micro}}^d = k_2^d / K_{\text{conf}}^d \]

\[ n^d = k_{-1}^d / k_2^d \]

\( k_{23} \) is the observed second-order rate constant for the base-catalyzed dehydration reaction. \( k_2^d, k_{-1}^d, K_1^d \) and \( K_{\text{conf}}^d \) are defined in Scheme 18. \( \kappa_{\text{micro}}^d \) is the microscopic rate constant for dehydration reaction, which is also defined in Scheme 18.

If the hydroxide-catalyzed enolate formation is a fast pre-equilibrium as was the case for the dehydration reactions of ketol-2, ketol-3 and ketol-4, the calculation of the microscopic rate constant can be simplified as:

\[ k_2^d = k_{23} / K_1^d \]

\[ \kappa_{\text{micro}}^d = k_2^d / K_{\text{conf}}^d \]
The calculated microscopic rate constants for four dehydration reactions are found in Table 25.
Table 25. Calculated Microscopic Rate Constants for the Dehydration Reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$k_{23, b}$ M$^{-1}$s$^{-1}$</th>
<th>$n^d$</th>
<th>$10^2K_1^{d, d}$ M$^{-1}$</th>
<th>$k_2^{d, e}$ s$^{-1}$</th>
<th>$K_{conf}^{d, f}$</th>
<th>$k_{micro}^{d, g}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>0.110$^h$</td>
<td>1.35$^k$</td>
<td>0.0427</td>
<td>449</td>
<td>0.554</td>
<td>770</td>
</tr>
<tr>
<td>RXN-2</td>
<td>0.0195$^d$</td>
<td>&gt;10$^l$</td>
<td>1.51</td>
<td>1.29</td>
<td>0.352</td>
<td>3.66</td>
</tr>
<tr>
<td>RXN-3</td>
<td>0.140$^j$</td>
<td>&gt;10$^m$</td>
<td>3.72</td>
<td>4.00</td>
<td>0.396</td>
<td>10.09</td>
</tr>
<tr>
<td>RXN-4</td>
<td>0.0202$^a$</td>
<td>&gt;10$^o$</td>
<td>1.51</td>
<td>1.33</td>
<td>0.205</td>
<td>6.46</td>
</tr>
</tbody>
</table>

$^a$As defined in **Scheme 18**.

$^b$The observed second-order rate constant for the base-catalyzed dehydration reaction.

$^c$n$^d$ = $k_1^{-d} / k_2^{d}$, $k_1^{d}$ and $k_2^{d}$ are defined in **Scheme 18**.

$^d$As defined in **Scheme 18**, from Table 24.

$^e$Calculated as described in Part 6.2.2.5, defined in **Scheme 18**.

$^f$From Table 23.

$^g$The microscopic rate constant for dehydration reaction, calculated as described in Part 6.2.2.5, defined in **Scheme 18**.

$^h$See Part 2.2.5 in Chapter 2.
See Part 3.2.4 in Chapter 3.

See Part 4.2.4 in Chapter 4.

See Part 2.2.6.2 in Chapter 2.

'This means that the departure of the hydroxyl group from the ketol is fully rate-limiting, see Part 3.2.5.2 in Chapter 3.

'This means that the departure of the hydroxyl group from the ketol is fully rate-limiting, see Part 4.2.5.2 in Chapter 4.

See Part 5.2.4 in Chapter 5.

'This means that the departure of the hydroxyl group from the ketol is fully rate-limiting, see Part 5.2.5.2 in Chapter 5.
6.2.2.6 Calculation of the intrinsic barriers in terms of Marcus theory.

The microscopic rate and equilibrium constants are now available for four dehydration reactions involved in intramolecular aldol condensations. We can then calculate the intrinsic barriers for dehydration reactions by using the Marcus equation: \( \Delta G^* = \Delta G^0 \cdot (1 + \Delta G^0 / 4\Delta G^* )^2 \), where \( \Delta G^* \) and \( \Delta G^0 \) refer to the activation energy and the reaction free energy change for the microscopic step, calculated from the microscopic rate and equilibrium constant respectively, and \( \Delta G^* \) is the intrinsic barrier, the activation energy that would be obtained if \( \Delta G^0 \) were zero.

The calculated intrinsic barriers for four dehydration reactions are found in Table 26.
Table 26. Calculated Intrinsic Barriers for the Dehydration Reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$10^3K_{\text{micro}}$</th>
<th>$k_{\text{micro}}$ $^{-1}$</th>
<th>$\Delta G^o$</th>
<th>$\Delta G^*$</th>
<th>$\Delta G^{*,f}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RXN-1</td>
<td>246</td>
<td>770</td>
<td>0.83</td>
<td>13.54</td>
<td>13.12</td>
</tr>
<tr>
<td>RXN-2</td>
<td>1.11</td>
<td>3.66</td>
<td>4.04</td>
<td>16.71</td>
<td>14.62</td>
</tr>
<tr>
<td>RXN-3</td>
<td>6.55</td>
<td>10.09</td>
<td>2.98</td>
<td>16.11</td>
<td>14.58</td>
</tr>
<tr>
<td>RXN-4</td>
<td>0.148</td>
<td>6.46</td>
<td>5.23</td>
<td>16.37</td>
<td>13.63</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$13.99\pm0.74$</td>
</tr>
</tbody>
</table>

*As defined in Scheme 18.

b The microscopic equilibrium constant for dehydration reaction, from Table 24.

c The microscopic rate constant for dehydration reaction, from Table 25.

d The reaction free energy change for the microscopic step, calculated from $K_{\text{micro}}$.  

e The activation energy for the microscopic step, calculated from $k_{\text{micro}}$.

f The calculated intrinsic barrier for dehydration reaction.
6.2.3 Calculation of effective molarity.

The effective molarity\textsuperscript{51} of ketone in intramolecular aldol addition reactions can be calculated from the ratio of rate or equilibrium constants for intra- and inter-molecular reaction. For the intramolecular aldol addition reactions of 2,5-hexanedione (dione-1) and 2,6-heptanedione (dione-2), the self aldol addition of acetone\textsuperscript{16} was used as intermolecular reference. The aldol addition of acetone, acting as carbon nucleophile, and acetophenone\textsuperscript{52} was used as intermolecular reference for the intramolecular aldol addition of 1-phenyl-1,5-hexanedione (dione-3). The aldol addition of acetone, acting as carbon nucleophile, and acetoaldehyde\textsuperscript{16} was used as intermolecular reference for 5-oxohexanal (dione-4). The calculated results for four diones are found in Table 27.
Table 27. The Effective Molarity of Ketones in Intramolecular Aldol Addition Reactions.

<table>
<thead>
<tr>
<th>Ketones</th>
<th>EM&lt;sub&gt;eq&lt;/sub&gt;, * M</th>
<th>EM&lt;sub&gt;rate&lt;/sub&gt;, * M</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,5-hexanедione</td>
<td>257</td>
<td>1.68x10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>2,6-heptanедione</td>
<td>1344</td>
<td>4.03</td>
</tr>
<tr>
<td>1-phenyl-1,5-hexanедione</td>
<td>4074</td>
<td>36.4</td>
</tr>
<tr>
<td>5-oxoхexanal</td>
<td>4368</td>
<td>5.39</td>
</tr>
</tbody>
</table>

*Effective molarity for equilibrium constant.

bEffective molarity for rate constant.

6.3 Conclusions

For the intramolecular aldol addition step, the apparent rate constants ranged from 3.35 x 10<sup>-5</sup> M<sup>-1</sup>s<sup>-1</sup> (dione-1) to 7.34 x 10<sup>-2</sup> M<sup>-1</sup>s<sup>-1</sup> (dione-2), the apparent equilibrium constants from 7.70 (dione-3) to 52.3 (dione-2). However, all the intramolecular aldol addition reactions have similar intrinsic barriers after we carefully introduced all the energetic costs forming the reactive encounter complex. This means that Marcus theory can be usefully applied to the intramolecular aldol addition reactions. For the reaction of 5-oxoхexanal (dione-4), the calculated intrinsic barrier (15.43 kcal/mol) is higher than for the other three reactions. This is because the partitioning factor between
the reproto
tion and intramolecular aldol addition of the enolate of \textit{dione-4} could not be well defined, the estimated value can only be used as an upper limit.

Compared to the intermolecular aldol addition reaction, the significant difference is that there is a contribution from the entropic cost of bringing a molecule of ketone and an enolate in an encounter complex, and in the intramolecular reactions, an energetic cost for attaining the conformation where the reaction centers are close enough to begin the bond-forming process. When all of the corrections are introduced, we find that the intrinsic barriers for the intramolecular aldol addition reactions, 14.49±0.82 kcal/mol are in excellent agreement with the average value, 13.89±0.80 kcal/mol,\textsuperscript{16} found for the intermolecular aldol addition reactions.

For the dehydration reactions, we similarly observe that the intrinsic barriers for cyclic ketols involved in intramolecular aldol condensations, 13.99±0.74 kcal/mol, are in excellent agreement with the average value, 14.13±0.49 kcal/mol,\textsuperscript{16} found for the dehydration of acyclic ketols involved in the intermolecular aldol condensations.

The equilibrium constant can be calculated by estimating the free energies of formation for the compounds involved.\textsuperscript{33} This implies that the rate constants for intramolecular aldol addition and the subsequent dehydration
reaction could be predicted based on the intrinsic barriers we obtained in this work!
PART II. EQUILIBRIUM CONSTANT DETERMINATION

FOR ACETAL FORMATION REACTIONS
CHAPTER 7. EQUILIBRIUM CONSTANT DETERMINATION
FOR ACETAL FORMATION REACTIONS

7.1 Introduction.

In order to gain a quantitative understanding of the reactions that involve the addition of a nucleophile to a carbonyl group, the equilibrium constants for these reactions must be determined. The acetal formation reaction is a good representative of this kind of reactions. Equilibrium constants for acetal formation can often be determined directly,\textsuperscript{54-60} but for less reactive carbonyl compounds this becomes increasingly difficult. Although there are several independent determinations of the equilibrium constant for acetophenone dimethyl acetal formation,\textsuperscript{55,60} there are no values for compounds much less reactive than acetophenone: p-methoxyacetophenone is the least reactive compound for which an equilibrium constant has been measured directly.\textsuperscript{55} Pfeiffer and Adkins\textsuperscript{61} extended the study of acetal formation to much less reactive compounds by using transacetalization, with formation of triethyl orthoformate from ethyl formate and ethanol as the reference system, although in fact they
didn’t know this equilibrium constant and could only determine relative values. This pioneering work was hampered by the limited means available for analyzing the composition of the equilibrium solutions. In fact, the analyses were based on determination of the amount of ethyl formate in solution by reaction with sodium metal, leading to production of carbon monoxide.

This project combined the idea of transacetalization and modern NMR techniques to extend the study of acetal formation reactions. A ladder of equilibrium constants has been constructed from acetophenone, for which the equilibrium constant for acetal formation has been measured directly in methanol, to methyl formate, for which it has not.

7.2 Results.

7.2.1 Equilibrium constants for transacetalization.

All the transacetalization equilibria were studied in methanol solution, but of greater interest are the equilibrium constants in aqueous solution. The equilibrium constants in aqueous solution were then calculated by using the free energies of transfer for the species involved.

We used acetophenone as our anchor compound, but found that for NMR analysis, the equilibrium constant for transacetalization between acetophenone and trimethyl orthoformate was too far on the side of acetophenone dimethyl
acetal to allow us to measure the equilibrium constant. Accordingly we used pinacolone as a bridge compound; from the work of Pfeiffer and Adkins we knew that pinacolone had a considerably smaller tendency to form an acetal than acetophenone. Both the transacetalization equilibria relating pinacolone and acetophenone, and pinacolone and methyl formate, could be measured conveniently. For benzophenone we expected, based on the results of Pfeiffer and Adkins in ethanol solution, that the acetal formation would be even more difficult than for methyl formate. However, we found that in fact benzophenone is similar to acetophenone in its reactivity. The results of these experiments are found in Table 28.

All the transacetalization reactions were carried out in NMR tubes and the approach to equilibrium was followed by a Gemini-200 NMR spectrometer. For most of the cases, protio methanol was used as solvent to prevent deuterio-protio exchange between methanol and the α-hydrogens of the ketones. For equilibria involving benzophenone and pinacolone, because the relative concentration of pinacolone dimethyl acetal was very low, 15% of deuterio methanol was added to the equilibrium system to give an internal field-lock and to obtain better resolution. All transacetalization equilibria were followed from both directions, and the same equilibrium
constant values were obtained suggesting that the true equilibrium was reached.

Table 28. Transacetalization Equilibrium Constants in Methanol, Dodecane and Water

<table>
<thead>
<tr>
<th>Equation</th>
<th>$K_f^b$</th>
<th>$K_r^b$</th>
<th>$K_a^b$</th>
<th>$K_d^c$</th>
<th>$K_w^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>115.9±5.6</td>
<td>113.3±7.3</td>
<td>114.6±6.5</td>
<td>108.6</td>
<td>115.6</td>
</tr>
<tr>
<td>[2]</td>
<td>55.5±2.5</td>
<td>46.5±2.3</td>
<td>51.0±2.4</td>
<td>35.6</td>
<td>59.1</td>
</tr>
<tr>
<td>[3]</td>
<td>6.1±0.1</td>
<td>5.3±0.4</td>
<td>5.7±0.3</td>
<td>34.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*For transacetalization equilibrium:

\[
\text{Ketone-1} + \text{Acetal-2} \rightleftharpoons \text{Ketone-2} + \text{Acetal-1}
\]

[1] PhCOMe + Me$_2$CC(OMe)$_2$Me = Me$_3$CCCOMe + PhC(OMe)$_2$Me

[2] PhCOPh + Me$_2$CC(OMe)$_2$Me = Me$_3$CCCOMe + PhC(OMe)$_2$Ph

[3] Me$_3$CCCOMe + HC(OMe)$_3$ = HCOOMe + Me$_3$CC(OMe)$_2$Me

The equilibrium constant was defined as: $K = \frac{[\text{Ketone-2}][\text{Acetal-1}]}{[\text{Ketone-1}][\text{Acetal-2}]}$. The activity coefficient ratio did not differ significantly from unity. This was confirmed by experiments showing that the equilibrium constant was concentration-independent and that dilution of a system at equilibrium did not change the apparent value of the equilibrium constant.

$K_a$ is the equilibrium constant in methanol and was measured by $^1$H-NMR. $K_a$ is the average of $K_f$ and $K_r$, which were
obtained from reactions run in the forward and reverse directions, respectively.

$K_d$ and $K_r$ stand for equilibrium constants in dodecane and water, respectively, and were calculated by the use of free energies of transfer from Table.29.

The $^1$H-NMR spectrum of a solution at equilibrium between acetophenone and pinacolone, starting with pinacolone and acetophenone dimethyl acetal, is found in Figure 24. Based on the integrated signals from the methyl groups in acetophenone, pinacolone and acetophenone dimethyl acetal, and the t-butyl group in pinacolone dimethyl acetal, the equilibrium constant was obtained.

Figure 25 is the $^1$H-NMR spectrum of a solution at equilibrium between pinacolone and methyl formate, starting with pinacolone and trimethyl orthoformate. The transacetalization equilibrium constant was obtained based on the integrated signals from the formyl hydrogen in methyl formate, the methine hydrogen in trimethyl orthoformate, and the t-butyl groups in pinacolone and its dimethyl acetal.

The whole $^1$H-NMR spectrum of a solution at equilibrium between pinacolone and benzophenone, starting with pinacolone and benzophenone dimethyl acetal, is found in Figure 26. To evaluate the transacetalization equilibrium constant, two regions of interest were expanded for analysis.
Figure 27 is the expansion of Figure 26 around 7-8 ppm. Based on the \(^1\)H-NMR spectra of pure benzophenone and its dimethyl acetal, the group of peaks between 7.70-7.80 ppm was assigned to four hydrogens in benzophenone and the group of peaks between 7.16-7.30 ppm was assigned to six hydrogens in benzophenone dimethyl acetal. The ratio of benzophenone dimethyl acetal and benzophenone was calculated from the integrations for these peaks.

The expansion of Figure 26 around 1 ppm is found in Figure 28. Because the equilibrium concentration of pinacolone dimethyl acetal was very low, the integrations from the \(^13\)C-satellite of the t-butyl group in pinacolone and the t-butyl group in its dimethyl acetal used to calculate the concentration ratio for pinacolone and its dimethyl acetal.
Figure 24. $^1$H-NMR spectrum of a solution at equilibrium for the transacetalization reaction:

$$C_6H_5COMe + Me_3CC(OMe)_2Me = C_6H_5C(OMe)_2Me + Me_3CCOMe,$$

starting from the right side.
Figure 25. $^1$H-NMR spectrum of a solution at equilibrium for the transacetalization reaction:

$\text{Me}_3\text{CCOME} + \text{HC(O)}\text{Me}_3 = \text{Me}_3\text{CC(O)}\text{Me}_2\text{Me} + \text{HCOOME}$, starting from the left side.
Figure 26. The whole $^1$H-NMR spectrum of a solution at equilibrium for the transacetalization reaction: $(C_6H_5)_2CO + Me_3CC(OMe)_2Me = (C_6H_5)_2C(OMe)_2 + Me_3CCOMe$, starting from the right side.
Figure 27. The expansion of Figure 26 around 7-8 ppm.

4H IN \((C_6H_5)_2CO\)

5H IN \((C_6H_5)_2C(OH)Me\)
Figure 28. The expansion of Figure 26 around 1 ppm.
7.2.2 The determination of the free energies of transfer.

As we stated above, the equilibrium constants in water are of greater interest. Once we obtained the transacetalization equilibrium constants in methanol, the transacetalization equilibrium constants in water can be calculated by using the free energies of transfer for the compounds involved.

The free energies of transfer from methanol to water were then determined by measuring the partition constants from methanol to water. To measure the partition constants from methanol to water, we used the approach of Toullec et al.,\textsuperscript{35} that is, using dodecane as an intermediate solvent, not miscible with either water or methanol. The measured partition constants and the calculated free energies of transfer are found in Table 29.

In the case of the acetals and orthoformate, 0.1 M aqueous NaOH solution was used as water phase to inhibit the hydrolysis of the test compounds. pH = 7.0 buffer solution was used as water phase for methyl formate for analogous reasons.

Once we obtained the free energies of transfer, we can then calculate the transacetalization equilibrium constants in water and in dodecane from those in methanol. These equilibrium constants are found in Table 28.
<table>
<thead>
<tr>
<th>Compounds</th>
<th>$P_{d-w}$</th>
<th>$\Delta G_{d-w}$, kJ/mol</th>
<th>$P_{d-m}$</th>
<th>$\Delta G_{d-m}$, kJ/mol</th>
<th>$\Delta G_{m-w}$, kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCOPh$^b$</td>
<td>0.383±0.005</td>
<td>2.38</td>
<td>(1.253±0.074)$\times10^{-3}$</td>
<td>16.56</td>
<td>18.93</td>
</tr>
<tr>
<td>PhC(OMe)$_2$Ph$^c$</td>
<td>1.630±0.035</td>
<td>-1.21</td>
<td>(6.651±0.508)$\times10^{-5}$</td>
<td>23.83</td>
<td>22.62</td>
</tr>
<tr>
<td>Me$_3$CCOMe$^b$</td>
<td>0.259±0.020</td>
<td>3.35</td>
<td>0.155±0.016</td>
<td>4.62</td>
<td>7.97</td>
</tr>
<tr>
<td>Me$_3$CC(OMe)$_2$Me$^d$</td>
<td>1.58±0.21</td>
<td>-1.13</td>
<td>(4.89±0.20)$\times10^{-3}$</td>
<td>13.18</td>
<td>12.05</td>
</tr>
<tr>
<td>HCOOMe$^d$</td>
<td>0.16±0.04</td>
<td>4.54</td>
<td>2.94±0.06</td>
<td>-2.67</td>
<td>1.87</td>
</tr>
<tr>
<td>HC(OMe)$_3$ $^d$</td>
<td>0.16±0.01</td>
<td>4.54</td>
<td>2.19±0.23</td>
<td>-1.94</td>
<td>2.60</td>
</tr>
</tbody>
</table>

$^a$ $P_{d-w}$ and $P_{d-m}$ are the partition constants from methanol to dodecane and those from dodecane to water. $\Delta G_{d-w}$, $\Delta G_{d-m}$ and $\Delta G_{m-w}$ are the free energies of transfer from methanol to dodecane, from dodecane to water, and from methanol to water, respectively. Both the partition constants and the free energies of transfer are based on the mole concentration. In the determination of partition constants, activity coefficients were assumed to be unity and this was confirmed by the observation that the measured values were concentration-independent.
*Measured directly by UV.

*Acid-catalyzed hydrolysis to benzophenone, followed by UV analysis.

*Measured directly by $^1$H-NMR.
7.2.3 Equilibrium constants for acetal formation reactions.

So far we have already obtained three transacetalization equilibrium constants in methanol, in dodecane and in water respectively, which construct a ladder of equilibrium constants for acetal formation reactions. By combining the known equilibrium constant for acetal formation from acetophenone\(^{55}\) with the equilibrium constants for transacetalization that we determined, we could calculate equilibrium constants for acetal formation from benzophenone, pinacolone and methyl formate. These calculations are summarized in Table 30.

**Table 30. Equilibrium Constants for Acetal Formation Reactions in Dodecane, Methanol and Water\(^a\)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(10^6K_d)</th>
<th>(10^6K_m)</th>
<th>(10^6K_w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCOMe(^b)</td>
<td>328.0</td>
<td>632.0</td>
<td>43.8</td>
</tr>
<tr>
<td>PhCOPh(^c)</td>
<td>107.0</td>
<td>281.0</td>
<td>22.4</td>
</tr>
<tr>
<td>Me(_3)COCMe(^e)</td>
<td>3.02</td>
<td>5.51</td>
<td>0.379</td>
</tr>
<tr>
<td>HCOOMe(^f)</td>
<td>0.0869</td>
<td>0.968</td>
<td>0.257</td>
</tr>
</tbody>
</table>

\(^a\)\(K_d\), \(K_m\) and \(K_w\) are equilibrium constants for acetal formation reactions with respect to mole fraction in dodecane, methanol and water respectively.
The values for acetophenone were from the literature. The calculated by combining transacetalization equilibrium constants from Table 28 and the equilibrium constant for acetal formation from acetophenone.

7.3 Discussion

Our method for determining transacetalization equilibrium constants should be general. The main limitations are the limited dynamic range of NMR analysis and the problem of overlap between the peaks used for analysis and other peaks from species in solution. The former problem forces us to use integration of a peak from a minor species relative to a $^{13}$C satellite of a peak from a major species. With more intermediate compounds, and more steps to the ladder, this could be overcome. The latter problem will restrict application to more elaborate structures but will become less important as higher field NMR instruments become more available.

We were distressed to find that our results did not bear out those of Pfeiffer and Adkins. The discrepancy is shown in Figure 29, which contrasts the results from the two methods. To allow a direct comparison we calculated equilibrium constants for transacetalization involving methyl formate/trimethyl orthoformate as the reference reaction. Admittedly Pfeiffer and Adkins worked in ethanol
with triethylorthoformate and diethyl acetics, but the discrepancies seem too large for the relatively modest effects expected for replacement of methyl by ethyl. Adkins and Adams found very similar equilibrium constants for acetal formation from acetaldehyde and methanol, ethanol, propanol, or
butanol.\textsuperscript{54} We are forced to conclude that there were systematic errors in the work of Pfeiffer and Adkins.\textsuperscript{61} The problem doubtless lies in their analytical procedure, the conversion of ethyl formate to carbon monoxide by the action of sodium on the ethanol solution. An investigation of the kinetics of this reaction found that there is a smooth decomposition of ethyl formate under the influence of ethoxide ion in ethanol, which leads to a temperature-dependent equilibrium with carbon monoxide.\textsuperscript{62} Methyl formate is produced industrially by the reaction of carbon monoxide with methanol and a catalytic amount of sodium methoxide at 70°C and 20-200 bar.\textsuperscript{63} An unavoidable conclusion is that the set of transacetalization equilibrium constants reported by Pfeiffer and Adkins\textsuperscript{64} must be considered unreliable, and should be redetermined.

Pfeiffer and Adkins\textsuperscript{61} found that acetal formation from benzophenone was much more difficult than from acetophenone (see Figure 29). This seemed reasonable from the assumption that two conjugated phenyl groups would favor the carbonyl group relative to acetal more effectively than one. From this perspective the observation that the equilibrium constants for acetalization of benzophenone and acetophenone are quite similar seems most surprising. This is, however, general agreement, both from theoretical calculations,\textsuperscript{64-65} and from experimental investigations,\textsuperscript{66-67} that the benzene rings in
benzophenone are twisted substantially away from coplanarity with the carbonyl. The exact angle in solution is not yet well established, with estimates varying from 26.2° "to 36°," and the angle in the solid, a twist angle of 33° with respect to the plane of the carbonyl," may well be influenced by packing. Benzophenone adopts a nonplanar conformation in order to relieve nonbonded interactions of the ortho hydrogens. As a consequence the conjugative stabilization in benzophenone need not be greater than in acetophenone. Thus it should not be surprising that benzophenone and acetophenone have similar equilibrium constants for acetal formation.

What are the prospects for extension of this transacetalization procedure? We have examined the question of whether transacetalization equilibrium constants could be measured for other, less reactive esters by similar experiments. It seems probable that it will be possible, but only if a suitable ladder can be constructed, because transacetalization equilibrium constants must be in the range from 0.01 to 100, in order to be practical for NMR analysis. By the use of hindered ketones (which might react very slowly) and esters with electron-withdrawing groups it should be possible to do this. On the other hand, extension to amides appears unlikely, because of the need for acid catalysis of the transacetalization reaction. Acid, except at very low concentrations (high pH values), would protonate the amine,
pulling the alcoholysis of the amide or amide acetal to completion. At very low acid concentrations, transacetalization would be very slow, and substantial concentrations of amine would need to be present to maintain the concentration of amide.

7.4 Experimental

7.4.1 Materials

1 M methanolic HCl solution was made by adding 0.7 mL of acetyl chloride to 10 mL of methanol at 0°C. All reagents were from BDH or Aldrich and were used without further purification except as follows:

1) Acetophenone, pinacolone, methyl formate and trimethyl orthoformate were purified by distillation.

2) The dimethyl acetals of acetophenone, pinacolone and benzophenone were synthesized by acid-catalyzed reaction of the ketone with trimethyl orthoformate in methanol, and purified by distillation (acetophenone and pinacolone dimethyl acetals) or by recrystallization from methanol (benzophenone dimethyl acetal).

3) Methanol was dried by reaction with magnesium followed by distillation under nitrogen. The water concentration was checked by Karl Fischer titration using a Metrohm 684KF Coulometer; the value found was 68 µg/mL.
7.4.2 Partition constant determination.

For each compound a stock solution was prepared (volumetric flask) in solvent in which it is less soluble. This stock solution (4-7 mL) was mixed with the other partition solvent (7-4 mL) in a volumetric tube with a standard taper stopper, shaken vigorously for 10 min., transferred into a centrifuge tube, and sealed using foil and parafilm. It was then placed in a constant temperature bath set at 25°C and left overnight. Finally the two partition phases were separated carefully by centrifugation and the relative concentrations of the two phases were measured by UV or ¹H-NMR. In the determination of partition constants of benzophenone or its dimethyl acetal between dodecane and water and of pinacolone dimethyl aceta, the test compound was introduced in dodecane instead of in water because of the large difference in limiting solubilities. Also in these cases the partition systems were stirred overnight at 25°C instead of just shaken for 10 min to make sure that partition equilibrium was reached.

In the case of acetics, 0.1 M aqueous NaOH solution was used as the water phase to inhibit acetal hydrolysis. pH 7 buffer (from BDH, contains 5.775 g/L of Na₂HPO₄ and 3.538 g/L of KH₂PO₄) was used as the water phase for methyl formate for analogous reasons. Usually the relative concentration was
measured directly except that benzophenone dimethyl acetal was first hydrolysed to benzophenone.

In the UV determination of benzophenone and its dimethyl acetal, samples of the two partition phases were usually diluted in a common solvent: methanol and a 0.1 M HClO₄ solution in 90% methanol:10% water were used for benzophenone and its dimethyl acetal, respectively. For pinacolone, however, the samples of the two partition phases were diluted in the corresponding solvent and then analysed using the appropriate molar extinction coefficients: \( \lambda = 288 \text{ nm}, \log{\varepsilon} = 1.32 \) in dodecane (this work); \( \lambda = 278 \text{ nm}, \log{\varepsilon} = 1.48 \) in water; and \( \lambda = 282 \text{ nm}, \log{\varepsilon} = 1.40 \) in methanol.⁶⁹

In the \(^1\text{H-NMR}\) determination of methyl formate, methyl orthoformate, and pinacolone dimethyl acetal, 0.35 mL of the dodecane or methanol phase was added to 0.35 mL of CDCl₃ containing methyl acetate as internal reference, and 0.35 mL of the water phase was added to 0.35 mL D₂O containing methyl acetate as internal reference for methyl formate determination and sodium acetate for the other cases. In the determination of the partition constant of pinacolone dimethyl acetal between dodecane and water, the relative concentration in the water phase was obtained by the use of \(^13\text{C-satellite}\) of the methyl group in sodium acetate as reference because the concentration of pinacolone dimethyl acetal was very low.
7.4.3 Transacetalization equilibrium constant determination.

To an NMR tube were added the appropriate amount of each reactant, 0.38 mL of 1 M methanolic HCl solution and enough methanol to give a total volume of 1.5 mL. Then the NMR tube was sealed using a torch and put into the constant temperature bath at 25°C. The transacetalization equilibrium reactions were carried out in the NMR tube and the approach to equilibrium was followed by $^1$H-NMR using a Gemini-200. Relative concentrations of all species at equilibrium were measured by the NMR integrations. For most of the cases, protio methanol was used to prevent the deuterio-proton exchange between CD$_3$OD and CH$_3$COR and consequently an external deuterium lock was used. However, for the equilibrium starting with pinacolone and benzophenone dimethyl acetal, because the relative equilibrium concentration of the pinacolone dimethyl acetal was very low, 15% of CD$_3$OD was added to the system after equilibrium was reached, in order to give an internal lock. Analysis was carried out by measuring the ratio of the $^{13}$C-satellite of the tert-butyl group in pinacolone and the peak of tert-butyl group in its dimethyl acetal.

Some typical initial concentrations of the reactants for both directions are listed as follows:
\[ \text{Me}_3\text{CCOME} + \text{HC(OMe)}_3 = \text{Me}_3\text{CC(OMe)}_2\text{Me} + \text{HCOOMe} \]

\[
\begin{array}{cccc}
1.01 \text{ M} & 2.01 \text{ M} & 0 \text{ M} & 0 \text{ M} \\
0 \text{ M} & 0 \text{ M} & 0.5 \text{ M} & 1.5 \text{ M} \\
\end{array}
\]

\[ \text{PhCOMe} + \text{Me}_3\text{CC(OMe)}_2\text{Me} = \text{PhC(OMe)}_2\text{Me} + \text{Me}_3\text{CCOME} \]

\[
\begin{array}{cccc}
1.01 \text{ M} & 1.01 \text{ M} & 0 \text{ M} & 0 \text{ M} \\
0 \text{ M} & 0 \text{ M} & 1.48 \text{ M} & 1.01 \text{ M} \\
\end{array}
\]

\[ \text{PhCOPh} + \text{Me}_3\text{CC(OMe)}_2\text{Me} = \text{PhC(OMe)}_2\text{Ph} + \text{Me}_3\text{CCOME} \]

\[
\begin{array}{cccc}
0.10 \text{ M} & 0.20 \text{ M} & 0 \text{ M} & 0 \text{ M} \\
0 \text{ M} & 0 \text{ M} & 0.11 \text{ M} & 0.22 \text{ M} \\
\end{array}
\]
Appendix 1. Kinetic Derivation

for two phase kinetics.

For a reaction path:

\[
\text{Dione} \overset{k_{12}}{\underset{k_{21}}{\rightarrow}} \text{Ketol} \overset{k_{23}}{\underset{k_{32}}{\rightarrow}} \text{Enone}
\]

the reaction will show two phase kinetics mathematically, no matter whether we start with dione, ketol or enone. The concentration \(A\) of dione, ketol or enone as a function of time \(t\) can be expressed by a double exponential equation: \(A = A_1 + A_2 \times \exp(-A_3 \times t) + A_4 \times \exp (-A_5 \times t)\). The general solution for this double exponential equation is available in the literature\(^{18}\) as:

\[
A_3 = \frac{(p + q)}{2}
\]

\[
A_5 = \frac{(p - q)}{2}
\]

where \(p = k_{12} + k_{21} + k_{23} + k_{32}\) and \(q = (p^2 - 4(k_{12}k_{23} + k_{21}k_{32} + k_{12}k_{32}))^{0.5}\).
1) For reaction starting with \textbf{dione-2} (see Part 3.2.1 in Chapter 3), since
\[ k_{12} \gg k_{21} \text{ and } k_{23} \gg k_{32}, \]
then we have:
\[ p = k_{12} + k_{23} \text{ and } q = ((k_{12} + k_{23})^2 - 4 k_{12}k_{23})^{0.5} = k_{12} - k_{23}, \]
(because \( k_{12} > k_{23} \)), so that \( A3 = k_{12} \) and \( A5 = k_{23} \).

2) For reaction starting with \textbf{dione-4} (see Part 5.2.1 in Chapter 5), since
\[ k_{12} \gg k_{21} \text{ and } k_{12} > k_{23} + k_{32}, \]
then we have:
\[ p = k_{12} + k_{23} + k_{32} \text{ and } q = ((k_{12} + k_{23} + k_{32})^2 - 4 (k_{12}k_{23} + k_{12}k_{32}))^{0.5} = k_{12} - (k_{23} + k_{32}), \]
so that \( A3 = k_{12} \) and \( A5 = k_{23} + k_{32} \).

1. The standard deviation for the observed activation energy.

The standard deviation for the observed activation energy is given by $\sigma(\Delta G^o) = \left| \frac{\partial \Delta G^o}{\partial k} \right| \sigma(k) = \left| -\frac{RT}{k} \right| \sigma(k)$, where $k$ is the observed rate constant and $\sigma(k)$ is the standard deviation for the observed rate constant. For the dehydration of ketol-2, $k = k_2 = 1.95 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}$ and $\sigma(k) = 3.0 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ (See Table 8 on Page 61). Thus the standard deviation for the observed activation energy $\sigma(\Delta G^o) = \left( (1.99 \times 10^{-3} \times 298) / (1.95 \times 10^{-2}) \right) \times 3.0 \times 10^{-3} = 0.09 \text{ kcal/mol}$.

2. The standard deviation for the estimated activation energy.

The activation energy was estimated by using Guthrie's model\textsuperscript{16} based on the Marcus equation: $\Delta G^o = \Delta G^e (1 + \Delta G^o/4\Delta G^e)^2$. The intrinsic barrier for the deprotonation of a ketone by hydroxide has been estimated as $10.70 \pm 0.14$
kcal/mol. The standard deviation for the estimated activation energy is given by 
\[ \sigma(\Delta G^*) = \left[ \left( \frac{\partial \Delta G^*}{\partial \Delta G^*} \right)^2 \sigma(\Delta G^*)^2 + \left( \frac{\partial \Delta G^*}{\partial \Delta G^*} \right)^2 \sigma(\Delta G^*)^2 \right]^{0.5} = \left[ (1 - \frac{\Delta G^*}{4 \Delta G^*})^2 \sigma(\Delta G^*)^2 + (0.5 + \frac{\Delta G^*/8 \Delta G^*}{\sigma(\Delta G^*)})^2 \sigma(\Delta G^*)^2 \right]^{0.5} \]. For the dehydration of ketol-2, the reaction free energy change within the encounter complex was 
\[ \Delta G^* = -6.66 \pm 0.41 \text{ kcal/mol (assuming an error for pKa estimation of 0.3 pKa units), and thus the standard deviation for the estimated activation energy is} \sigma(\Delta G^*) = \left[ (1 - \frac{-6.66}{(4 \times 10.70)})^2 \times 0.14^2 + (0.5 - \frac{-6.66}{(8 \times 10.70)})^2 \times 0.41^2 \right]^{0.5} = 0.22 \text{ kcal/mol.} \]
Appendix 3. MM3 Calculations.

MM3 calculations were carried out using the MM3(89) program\textsuperscript{70} as supplied by Quantum Chemistry Program Exchange (QCPE), Indiana University, Bloomington, Indiana. In order to treat enols it was necessary to supply a parameter for torsion about a H-O-C(sp\textsuperscript{2})-C(sp\textsuperscript{3}) bond. We used $V_1=V_2=V_3=0.0$: this should have no effect on relative energies of different conformations of the enols, so long as the equilibrium dihedral angle is the same in each conformation compared. The enols are planar and the enolic OH is not close to other groups. The parameters were updated from the original values supplied with MM3(89) to use the values given in subsequent papers for conjugated hydrocarbons,\textsuperscript{71} hydrocarbons,\textsuperscript{70,72} enones,\textsuperscript{73} aldehydes and ketones,\textsuperscript{74} and alkenes.\textsuperscript{75}
References


(53) Guthrie, J. P. unpublished results.


