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Intramolecular Aldol Condensations: Rate and Equilibrium Constants

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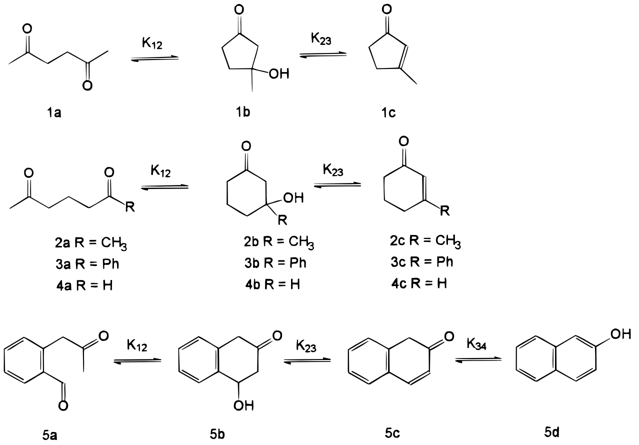
Abstract: Rate and equilibrium constants have been determined for both the aldol addition and the elimination steps in the intramolecular condensation reactions of 2,5-hexanedione, 2,6-heptanedione, 1-phenyl-1,5-hexanedione, and 5-oxohexanal. The overall thermodynamics are similar for cyclization of 2,5-hexanedione and 2,6-heptanedione; conversion of 2,5-hexanedione to the corresponding enone is actually more favorable, but the cyclization of 2,5-hexanedione is 2400 times slower than that of 2,6-heptanedione. As expected on the basis of intermolecular analogs, the addition step is less favorable and slower for 1-phenyl-1,5-hexanedione, and the addition step for 5-oxohexanal is more favorable though similar in rate to that for heptanedione. Detailed analysis of the kinetics and equilibrium for all of these compounds, as well as 2-(2-oxopropyl)benzaldehyde, in terms of Marcus theory, leads to the same intrinsic barriers for the intramolecular reactions as were seen previously for the intermolecular reactions. This means that rate constants for intramolecular aldol reactions should be predictable from the energetics of the reactions and that the effective molarity can be calculated. Methods for estimating thermodynamic quantities for reactants and products of these reactions have been examined.

Introduction

The aldol condensation is of great importance synthetically, but in its intermolecular versions there are often problems caused by production of multiple products, or polymerization.[1] As a consequence, intramolecular aldol reactions, which necessarily have more limited possible products, are generally more useful.[1] We have studied a range of intermolecular aldol condensations[2−10] and have shown that these reactions can be usefully described by Marcus theory.[11] We now investigate intramolecular aldol condensations to inquire whether these reactions can be described by Marcus theory or some extension of it. This entailed what we believe to be the first determination of rate and equilibrium constants for both phases of four intramolecular aldol condensations.

We now report the results of these studies. The results are at first glance paradoxical because for the aldol addition process rate and equilibrium are quite dramatically uncorrelated. This behavior is explicable in terms of Baldwin's rules,[12] and we will present a detailed examination of the energetic basis for this lack of correlation of the overall rate and equilibrium constants.

The reactions studied in this work involved compounds **1**−**4**; we also estimated equilibrium constants for the reactions of compound **5**, for which kinetics were recently reported.



Results

1. Intramolecular Aldol Condensation Reaction of 2,5-Hexanedione. The kinetics of the intramolecular aldol condensation reaction of 2,5-hexanedione were studied with both UV spectroscopy and HPLC analysis. Using HPLC analysis, both the growth of enone, 3-methyl-2-cyclopenten-1-one, and the disappearance of 2,5-hexanedione were followed at the same time. The reaction exhibited simple first-order behavior; that is, no ketol (3-hydroxy-3-methyl-cyclopentanone) was observed during the reaction process at the level of sensitivity required for monitoring dione and enone. The measured rate constants are found in Table 1.

3-Hydroxy-3-methylcyclopentanone was prepared by the reaction of methylmagnesium iodide with 1,3-cyclopentanedione. The kinetics of the hydroxide-catalyzed dehydration of this ketol could be followed by HPLC analysis, leading to both the rate and the equilibrium constants for dehydration. Strictly speaking, the rate constant is for the approach to equilibrium, but this is sufficiently far on the side of the enone that the observed rate constant is essentially that for dehydration.

To determine whether expulsion of hydroxide or proton abstraction was rate limiting for the dehydration process, we

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Table 1. Kinetics of Intramolecular Aldol Condensations[a]

Base-Catalyzed Reactions: 2,5-Hexanedione

$[OH^-]$	$10^6k_1^{obs}$ (s^{-1})	$10^5(k_{12} + k_{21})$ (M^{-1} s^{-1})	K_{12}	$10^3k_2^{obs}$ (s^{-1})	$10^2(k_{23} + k_{32})$ (M^{-1} s^{-1})	K_{23}
0.998[b]	37.5 ± 0.1	3.76 ± 0.01				
0.096[b]	2.82 ± 0.01	2.96 ± 0.01				
0.090[c]	2.47 ± 0.14	2.74 ± 0.16				
0.090[d]	2.47 ± 0.16	2.74 ± 0.16				
0.01[e]				1.01 ± 0.04	10.1 ± 0.4	
0.01[c]				0.980 ± 0.043	9.8 ± 0.4	
0.034[b]				3.91 ± 0.02	11.5 ± 0.06	
0.046[b]				4.80 ± 0.03	10.4 ± 0.07	
0.01[f]						636 ± 0.35
0.1[g]						567 ± 0.35
av		3.35 ± 0.47			11.0 ± 0.7	602 ± 0.49

Base-Catalyzed Reactions: 2,6-Heptanedione

$[OH^-]$	$10^3k_1^{obs}$ (s^{-1})	$10^2(k_{12} + k_{21})$ (M^{-1} s^{-1})	K_{12}	$10^4k_2^{obs}$ (s^{-1})	$10^2(k_{23} + k_{32})$ (M^{-1} s^{-1})	K_{23}
0.010[h]	0.703 ± 0.010	7.03 ± 0.10				
0.010[i]	0.646 ± 0.105	6.46 ± 1.05		2.08 ± 0.15	2.08 ± 0.15	
0.010[j]	0.586 ± 0.237	5.86 ± 2.37		3.62 ± 1.62	3.62 ± 1.62	
0.040[k]	2.95 ± 0.02	7.38 ± 0.04		7.20 ± 0.01	1.80 ± 0.003	
0.150[k]	11.1 ± 0.1	7.40 ± 0.08		29.7 ± 0.1	1.98 ± 0.004	
0.01[l,m]				2.52 ± 0.27	2.52 ± 0.27[o]	61.4
0.10[l,m]						52.3
av		7.34 ± 0.13			1.87 ± 0.10	

Base-Catalyzed Reactions: 1-Phenyl-1,5-hexanedione

$[OH^-]$	$10^4k_1^{obs}$ (s^{-1})	$10^2(k_{12} + k_{21})$ (M^{-1} s^{-1})	K_{12}	$10^3k_2^{obs}$ (s^{-1})	$(k_{23} + k_{32})$ (M^{-1} s^{-1})	K_{23}
0.010[o]	1.70 ± 0.35	1.70 ± 0.35				
0.010[p]	1.31 ± 0.23	1.31 ± 0.23				
0.010[q]			7.30 ± 0.4			930 ± 70
0.180[r]	25.2 ± 0.1	1.40 ± 0.006				
0.580[r]	81.0 ± 0.5	1.40 ± 0.009				
0.010[s]	1.30 ± 0.21	1.30 ± 0.21		1.32 ± 0.20	0.132 ± 0.020	
0.010[t]				1.49 ± 0.18	0.149 ± 0.018	
0.010[u]				1.27 ± 0.08	0.127 ± 0.008	
0.027[v]				3.88 ± 0.02	0.145 ± 0.001	
0.036[v]				4.86 ± 0.02	0.135 ± 0.001	
0.010[w]			8.5 ± 0.5			1000 ± 100
av		1.37 ± 0.023	7.7 ± 0.7		0.140 ± 0.006	950 ± 50

Base-Catalyzed Reactions: 2-Oxohexananal

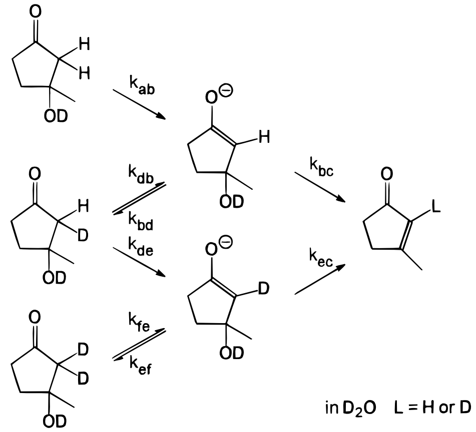
$[OH^-]$	$10^4k_1^{obs}$ (s^{-1})	$10^2(k_{12} + k_{21})$ (M^{-1} s^{-1})	K_{12}	$10^2k_2^{obs}$ (s^{-1})	$(k_{23} + k_{32})$ (M^{-1} s^{-1})	K_{23}
0.011[x]	3.61 ± 0.03	6.92 ± 0.06		2.47 ± 0.02		
0.018[x]	6.15 ± 0.04	7.21 ± 0.05		2.43 ± 0.01		
0.024[x]	8.18 ± 0.07	7.19 ± 0.16		2.54 ± 0.02		
0.010[y]				2.52 ± 0.20		
0.010[z]				2.44 ± 0.24		
0.010[aa]						4.51 ± 0.01
av		7.12 ± 0.16		2.46 ± 0.05		

Acid-Catalyzed reaction 2,6-Heptanedione[ab]

$10^5(k_{23} + k_{32})$ (M^{-1} s^{-1})	K_{23}
4.17 ± 0.78[q]	58.6

[a] In aqueous solution at 25 °C, ionic strength 1.0 M (KCl). UV absorbance or HPLC peak height−time data were fitted to $y = a_1 + a_2 \exp(-a_3t)$ or $y = a_1 + a_2 \exp(-a_3t) + a_4 \exp(-a_5t)$ by nonlinear least squares. a_3 and a_5 correspond to the pseudo-first-order rate constants; the second-order rate constants are calculated as $a_3/[OH^-]$ or $a_5/[OH^-]$. These will be identified with λ_i derived from the appropriate reaction scheme. Standard deviations for the parameters were calculated by the least-squares procedure. Average values are weighted means. [b] The growth of **1c** was followed by UV spectrophotometry at 232 nm. [c] The growth of **1c** was followed by HPLC monitoring absorbance at 232 nm. [d] The disappearance of **1a** was followed by HPLC monitoring absorbance at 265 nm. [e] The growth or disappearance of **1b** was followed by HPLC monitoring absorbance at 271 nm. [f] The equilibrium constant, for reactions starting with **1a**, was determined by measuring the final concentrations by HPLC, as described under Experimental Section. [g] The equilibrium constant, for reactions starting with **1c**, was determined by measuring the final concentrations by HPLC, as described under Experimental Section. [h] The disappearance of **2a** was followed by HPLC monitoring absorbance at 271 nm. [i] The change in concentration of **2b** was followed by HPLC monitoring absorbance at 271 nm. [j] The appearance of **2c** was followed by HPLC monitoring absorbance at 240 nm. [k] The appearance of **2c** was followed by UV monitoring absorbance at 240 nm. [l] Followed by HPLC analysis on quenched samples. **2c** was followed at 240 nm; both **2a** and **2b** were followed at 271 nm. [m] The initial concentration of **2c** was 5.29×10^{-3} M; only hydration/dehydration could be followed. [n] The initial concentration of **2c** was 0.5 M; both equilibrium constants could be determined. [o] The disappearance of **3a** was followed by HPLC monitoring absorbance at 246 nm. [p] The appearance of **3c** was followed by HPLC monitoring absorbance at 289 nm. [q] The equilibrium concentration of **3b** was measured by HPLC monitoring absorbance at 205 nm. [r] The appearance of **3c** was followed by UV monitoring absorbance at 289 nm. [s] The appearance and then disappearance of **3a** were followed by HPLC monitoring absorbance at 246 nm. [t] The disappearance of **3b** was followed by HPLC monitoring absorbance at 205 nm. [u] The appearance of **3c** was followed by HPLC monitoring absorbance at 289 nm. [v] The appearance of **3a** was followed by UV monitoring absorbance at 289 nm. [w] Final concentrations of **3a**, **3b**, and **3c** were determined by HPLC analysis monitoring absorbance at 246, 205, and 289 nm, respectively. [x] The appearance of **4c** was followed by UV monitoring absorbance at 240 nm. [y] The appearance of **4b** was followed by HPLC monitoring absorbance at 271 nm. [z] The disappearance of **4c** was followed by HPLC monitoring absorbance at 240 nm. [aa] Final concentrations of **4b** and **4c** were determined by HPLC analysis monitoring absorbance at 271 and 240 nm, respectively. [ab] Reaction carried out in 1.0 M HCl, following the growth of **1b** by HPLC analysis monitoring absorbance at 271 nm. For the equilibrium constant the **1c** concentration was determined by HPLC analysis monitoring absorbance at 240 nm.

Scheme 1



also studied the kinetics in D_2O. The kinetics showed two exponential phases with rate constants 0.196 and 0.0268 M^{-1} s^{-1}; this behavior can be interpreted in terms of the mechanism shown in Scheme 1.[13] This mechanism actually predicts three exponentials, but two are likely to have very similar rate constants and hence be unresolvable. Assuming that the enolates are steady state intermediates, we can carry out a rigorous solution of the kinetic equations, which leads to three non-zero potentially observable rate constants:

$$\lambda_1 = k_{ab}$$

$$\lambda_2 = k_{db} + [k_{db}k_{bc}/(k_{bc} + k_{bd})]$$

$$\lambda_3 = k_{fe}k_{ec}/(k_{ec} + \mathrm{k}_{ef})$$

To extract the partitioning ratio, $n = (k_{-3}/k_4)$, as defined in Scheme 2, applicable to reaction in H_2O, we must estimate the various kinetic isotope effects using the analysis shown in Scheme 2. We will assume that the primary kinetic isotope effect on k_3 is the same as the value determined for acetone, $k_H/k_D = 7.24$.[14,15] On the basis of Hine's findings for enolization of acetone,[15] we will assume that all secondary deuterium kinetic isotope effects are negligible, i.e. $k_H/k_D = 1$. Following Schowen's analysis of solvent deuterium isotope effects,[16] we will assume that the solvent isotope effect on neutral enolization is negligible. The equilibrium solvent deuterium isotope effect on the ionization of the enol will be assumed to be the same as that for phenol:[17] enols and phenols have similar pK_a values.[18] For the reaction of hydroxide with the enol to give enolate this is $K_{H/D} = 0.57$, which will also be the value for the reaction of hydroxide with the keto tautomer to give enolate. The neutral elimination of water from a ketol to give an enone should have a solvent deuterium isotope effect of approximately 1, again following Schowen's analysis of solvent deuterium isotope effects.[16] This implies that the solvent equilibrium isotope effect for loss of hydroxide from the enolate will be $0.57^{-1} = 1.74$. The equilibrium free energy change for the microscopic rate-determining step for enolization is small (vide infra), and thus the transition state will be central; by the formula derived for the quartic model for Marcus theory,[19,20] $\chi = 0.463$. Loss of one solvating water, $\phi = 0.70$, will cause the equilibrium isotope effect for the actual deprotonation to be 0.82. Thus, the expected solvent deuterium kinetic isotope effect is $0.82^{\chi} = 0.91$ for the microscopic rate-determining step and $0.70 \times 0.91 = 0.64$ for the observable reaction; for the reverse step the isotope effect is 1.10. Experimentally, for acetone the solvent kinetic isotope effect for deprotonation is 0.68;[21] we will use this value, but take reassurance from the similarity of the estimated value. The equilibrium free energy change for the rate-determining step in elimination is small (vide infra), and thus the transition state will also be central, $\chi = 0.507$. Since the microscopic elimination step leads to a partially desolvated hydroxide, which has not yet gained the third hydrogen bonding water, $\phi = 0.70$, the equilibrium solvent isotope effect will be 1.20. Thus, the expected solvent deuterium kinetic isotope effect is $1.20^{\chi} = 1.10$. The primary kinetic isotope effect (1°KIE) for reprotonation of the enolate will, in terms of the above analysis, be determined by

$$K_{H/D} = (k)_{H/D}/(k_{-1})_{H/D} = 0.68 \times 7.24/0.91 \times (1°\mathrm{KIE}\ k_{-3}) = 0.57$$

The value so calculated is 7.85.

We can now write each rate constant in terms of the aqueous solution value and the appropriate isotope effects:

$$k_{ab} = 0.68^{-1} \times 1 \times 1 \times k_3 = 1.47k_3$$

$$k_{db} = 0.68^{-1} \times 1 \times 1 \times k_3 = 1.47k_3$$

$$k_{de} = 0.68^{-1} \times 7.24^{-1} \times 1 \times k_3 = 0.203k_3$$

$$k_{fe} = 0.68^{-1} \times 7.24^{-1} \times 1 \times k_3 = 0.203k_3$$

$$k_{bd} = 0.91^{-1} \times 7.85^{-1} \times 1 \times k_{-3} = 0.140k_{-3}$$

$$k_{ef} = 0.91^{-1} \times 7.85^{-1} \times 1 \times k_{-3} = 0.140k_{-3}$$

$$k_{bc} = 1.10^{-1} \times 1 \times 1 \times k_4 = 0.91k_4$$

$$k_{ec} = (1 \times 10^{-1}) \times 1 \times 1 \times k_4 = 0.91k_4$$

From the kinetics experiments we have the following quantities:

$$\begin{array}{ll} k_3/(n + 1) = 0.110 & \text{from kinetics in } H_2O \\ \left.\begin{array}{l} k_{ab} = 1.46k_3 = 0.196 \quad \text{if } \lambda_1 \text{ dominates} \\ k_{db} + k_{de}\, k_{bc}/(k_{bd} + k_{bc}) = 1.46k_3 + 0.203k_3/ \\ \quad (0.153n + 1) = 0.196 \quad \text{if } \lambda_2 \text{ dominates} \\ k_{fe}k_{ed}/(k_{ef} + k_{ed}) = 0.203k_3/(0.140k_{-3}/ \\ \quad 0.91k_4 + 1) = 0.203k_3/(0.153n + 1) = 0.0268 \end{array}\right\} & \text{from kinetics in } D_2O \end{array}$$

These are not quite consistent, though the deviations are not large. Two unresolvable exponential terms contribute to the fast observed process; these terms are expected to have

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[13] We use the following notation for rate constants. k_{12} etc. are observable rate constants expressed in terms of the total species present, except for 2-oxohexanal, where we correct for aldehyde hydration to make rate constants more directly comparable. k_1 etc. are microscopic rate constants for reactions in water, expressed in terms of the individual reactive species. k_{ab} etc. are microscopic rate constants for reactions in D_2O, expressed in terms of the individual reactive species and taking account of isotopic substitution.

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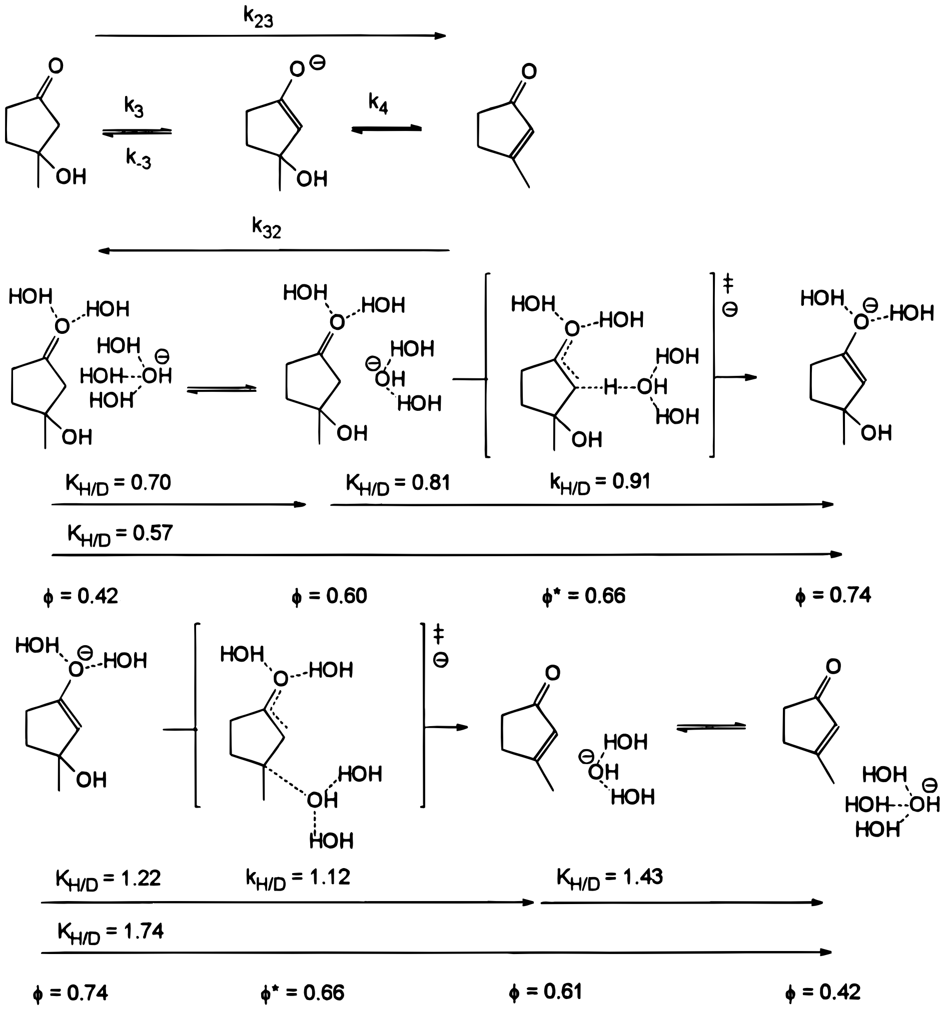
Scheme 2



comparable amplitudes, so the observed "rate constant" will be an average of λ_1 and λ_2. If we assume that the observed "rate constant" is in fact the average, we would have

$$1.56k_3 + 0.108k_3/(0.167n + 1) = 0.196$$

The fast process is not well defined by the data, since it corresponds only to a faster initial rise in absorbance than would be defined by the later data. Using only the slow process and the rate constant for reaction in water, we obtained $k_3 = 0.137$ and $n = 0.245$. This leads to a rate constant for the fast process of 0.200 if λ_1 dominates or 0.226 if λ_2 dominates. Thus, the results are self-consistent if the fast process reflects λ_1. By independent estimation we obtained $k_3 = 0.41$, a factor of 3 larger; this value of k_3 implies $n = 2.7$. Estimation of rate constants is unlikely to lead to results which are correct to better than a factor of 2 or 3, so the agreement is adequate. We conclude that $k_3 = 0.137$ and $n = 0.245$.

Because no 2,5-hexanedione was detected directly at the end of reaction, we developed a DNPH[22] approach to determine the equilibrium concentration of 2,5-hexanedione. By converting the 2,5-hexanedione 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 for the dione derivative and thus to much better HPLC resolution. Using this DNPH approach, the overall equilibrium constants were determined both starting with 2,5-hexanedione and starting with enone. The measured values are found in Table 2.

Table 2. Overall Equilibrium Constants for Intramolecular Aldol Condensation of 2,5-Hexanedione[a]

starting point		equilibrium point		
10^4-[enone]	10^4-[2,5-hexanedione]	10^4-[enone][b]	10^7-[2,5-hexanedione][c]	10^3K_{13}
9.60	0	9.58	1.68	5.70
0	7.40	7.40	1.17	6.32
			av	6.03 ± 0.31

[a] In 1.0 M NaOH aqueous solution at 25 °C. K_{13} = [enone]/[2,5-hexanedione]. [b] Determined by HPLC analysis, measuring absorbance at 232 nm. [c] Determined by the DNPH approach, analyzing by HPLC, and measuring absorbance at 360 nm.

2. Intramolecular Aldol Reaction of 2,6-Heptanedione. The kinetics of the intramolecular aldol condensation reaction of 2,6-heptanedione were studied using HPLC analysis. The growth of 3-methyl-2-cyclohexen-1-one (enone), the disappearance of 2,6-heptanedione, and the change in the concentration of 3-hydroxy-3-methyl-cyclohexanone (ketol) were followed at the same time. The reaction exhibited two-phase kinetic behavior, and the ketol intially accumulated and then decreased to the equilibrium level. The measured rate constants are found in Table 1.

The kinetics and equilibrium of the base-catalyzed hydration reaction of the enone were also studied using HPLC analysis. By following the growth of ketol we obtained the rate constant for approach to equilibrium. In the present case, this rate constant is essentially the rate constant for the dehydration of

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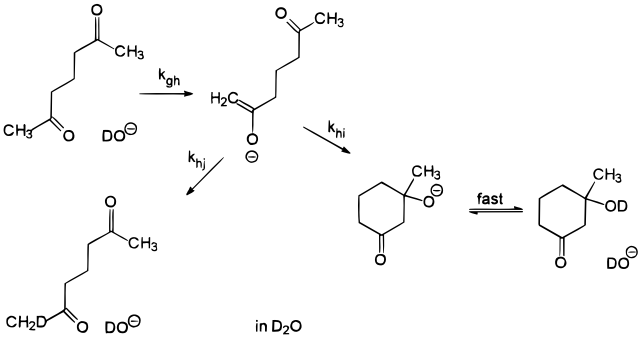
(22) DNPH: 2,4-dinitrophenylhydrazone.

Scheme 3



the ketol (k_{23}). The value so obtained was consistent with the value obtained from the second phase of the reaction starting with 2,6-heptanedione. The measured rate and equilibrium constants are found in Table 1.

To establish the nature of the rate-determining step for the aldol addition process, an experiment was carried out in D_2O, starting with the dione. By quenching after partial reaction and measuring the ratio of deuterium incorporation into the starting material to formation of ketol, we could determine the ratio of k_{hj} to k_{hi} in D_2O, $k_{hj}/k_{hi} - 0.182$, as defined in Scheme 3; this scheme applies to early stages of reaction. Now we must convert the ratio in D_2O to one in H_2O, by estimating the isotope effects. This will be done using the analysis shown in Scheme 4. The primary isotope effect on reprotonation will be assumed to be the same as for reprotonation of the ketol, i.e. 7.85. The solvent isotope effect on reprotonation will also be assumed to be the same as for reprotonation of the ketol, i.e. 0.91. The solvent isotope effect on the aldol addition is more problematic. We do not know how many waters solvate the carbonyl oxygen and, thus, how many will solvate the initially formed alkoxide anion. On the basis of Schowen's treatment of solvent isotope effects, we expect that the equilibrium solvent isotope effect for the neutral aldol addition reaction will be 1.0. The equilibrium isotope effect for the reaction of hydroxide with dione to give enolate will be 0.57, and the equilibrium isotope effect for the reaction of ketol anion with water to give ketol and hydroxide will be 1.0 (conversion of one RO^- to another with similar pK_a). Thus, the equilibrium isotope effect for the microscopic cyclization step will be 1.74, and the kinetic isotope effect for the forward reaction will be 1.28 (using $\chi = 0.44$, based on $\Delta G° = -8.89$, $\Delta G^* = 13.85$).

Now we have

$$k_{hj} = 0.91^{-1} \times 7.85^{-1} \times 1.0k_{-1} = 0.140k_{-1}$$

$$k_{hi} = 1.26^{-1} \times 1.0 \times 1.0k_2 = 0.79k_2$$

$$k_{hj}/k_{hi} = 0.177n = 0.182$$

$$n = (k_{-1}/k_2) = 1.03$$

Thus, in H_2O, k_{-1} and k_2 have very similar values and both steps are partially rate limiting. As we will see below, independent estimation of k_1 leads to a value of $k_1 = 0.200$, which implies $n = 1.72$.

3. Acid-Catalyzed Hydration Reaction of 2,6-Heptanedione. To check the value for the hydration−dehydration equilibrium constant (K_{23}), the hydration reaction of enone was also studied under acidic conditions using HPLC analysis. In acid we expected,[9,10,23−25] and found in this case, that retro-aldol reaction is much slower than hydration−dehydration. The equilibrium constant obtained in this experiment was consistent with that obtained from the base-catalyzed hydration reaction of enone. In the course of this determination, the rate constant for the acid-catalyzed dehydration of ketol (k_{23}) was also obtained by following the growth of ketol. The measured rate and equilibrium constants are found in Table 1.

4. Intramolecular Aldol Reaction of 1-Phenyl-1,5-hexanedione. The kinetics of the intramolecular aldol condensation reaction of 1-phenyl-1,5-hexanedione were studied using both UV and HPLC analysis. The growth of 3-phenyl-2-cyclohexen-1-one (enone) could be conveniently followed by UV. Both the growth of enone and the disappearance of 1-phenyl-1,5-hexanedione could be followed at the same time by HPLC and both showed simple, single-exponential kinetic behavior. The measured rate constants are found in Table 1. Although the ketol was not detected during regular analyses, careful amplification of the data for a sample at equilibrium permitted the determination of the amount of ketol at equilibrium. 3-Hydroxy-3-phenylcyclohexanone was independently prepared and subjected to the same reaction conditions; reaction was followed by UV and HPLC analysis. The growth of enone, whether followed by UV or HPLC, and the disappearance of ketol, followed by HPLC, both showed essentially single-exponential behavior. However, the dione concentration, monitored by HPLC, first increased and then decreased, following a two-exponential integrated rate law. It was not practical to carry out kinetics experiments starting with the enone, but equilibrium constants were determined for a solution starting with enone and the same values were obtained.

To determine whether expulsion of hydroxide or proton abstraction was rate limiting for the dehydration process, we also studied the kinetics in D_2O. The kinetics showed two exponential phases governed by second-order rate constants 0.622 and 0.101 M^{-1} s^{-1}. This behavior can be interpreted in terms of the mechanism shown in Scheme 5. For this mechanism only one proton undergoes ready exchange. This reflects the conformational control of the phenyl which has a strong preference for being equatorial (MM3 calculations say that having phenyl equatorial is favored by 1.46 kcal/mol) so that exchange of the second protium would be much slower than the first. For this mechanism, a kinetic derivation, assuming that the enolate is a steady state intermediate, leads to

$$\lambda_1 = k_{lm}$$

$$\lambda_2 = k_{om}k_{mn}/(k_{mn} + k_{mo}) = k_{om}/(1 + k_{mo}/k_{mn})$$

We have already estimated the various kinetic isotope effects in the analysis of the dehydration of 3-hydroxy-3-methylcyclopentanone. These kinetic isotope effects should be the same for the analogous processes for 3-hydroxy-3-phenylcyclohexanone. With the isotope effects so estimated, we obtain

$$\lambda_1 = 1.47k_3 = 0.622$$

$$\lambda_2 = 1.47k_3/(1 + 0.154n) = 0.101$$

which leads to $k_3 = 0.423$, $n = (k_{-3}/k_4) = 33$. There is thus a strong prediction that k_4 is the rate determining step for the

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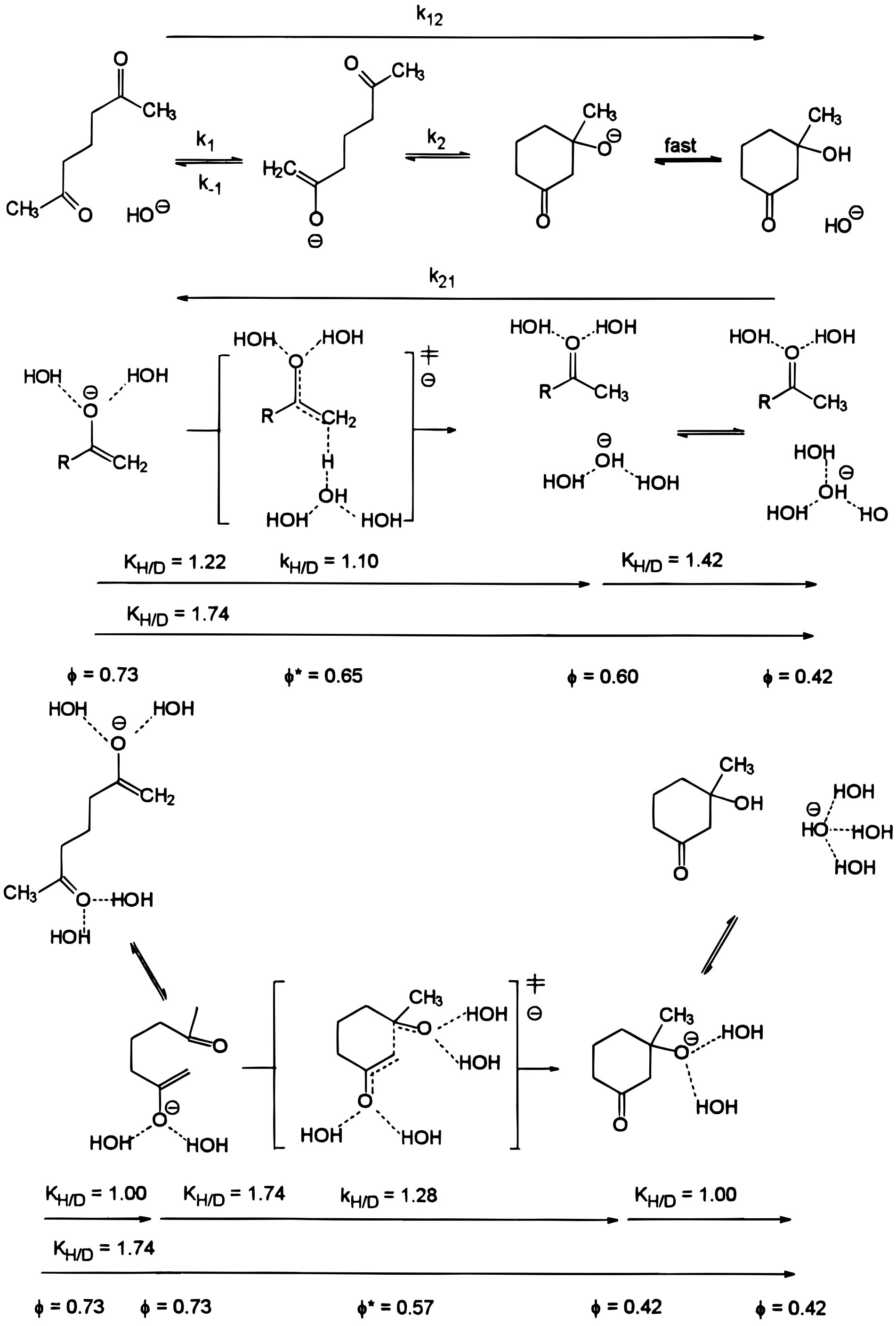
(23) Noyce, D. S.; Pryor, W. A.; King, P. A. *J. Am. Chem. Soc.* **1959**, *81*, 5423.

(24) Jensen, J. L.; Carre, D. J. *J. Org. Chem.* **1974**, *39*, 2103.

(25) Kim, Y. K.; Hatfield, J. D. *J. Chem. Eng. Data* **1985**, *30*, 149.

Scheme 4



reaction in water. Independent estimation of k_3 leads to a value of 2.3 M^{-1} s^{-1}, a factor of 2.5 larger, which would imply a value of $n = 16$. This is in adequate agreement and confirms the conclusion that dehydration rather than enolate formation is rate limiting.

5. Intramolecular Aldol Reaction of 5-Oxohexanal. The kinetics of the intramolecular aldol condensation reaction of 5-oxohexanal were studied using UV analysis. The growth of 2-cyclohexen-1-one (enone) exhibited two-phase kinetic behavior. For this system where the first step is essentially irreversible, the two exponentials have a particularly simple form: For a system following the kinetic pattern

$$A_1 \xrightarrow{k_{12}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3$$

it may readily be shown[26] that one apparent rate constant is equal to k_{12} and the other is equal to $k_{23} + k_{32}$. The measured rate constants are found in Table 1. An additional complication for this system comes from hydration of the aldehyde in the dione. By NMR analysis the equilibrium constant K_h = [hydrate]/[aldehyde] was found to be 1.11. k_{12} can be corrected for hydration by multiplying the apparent value by $(1 + K_h)$. Analysis of this system in terms of the mechanism in Scheme 6 showed that hydration can be treated as a processs lowering the concentration of aldehyde, but not adding any complexity to the kinetics, because the enolates of aldehyde and hydrate interconvert much more slowly than they reprotonate on carbon or (for the aldehyde) cyclize. The rate constant for HO^--

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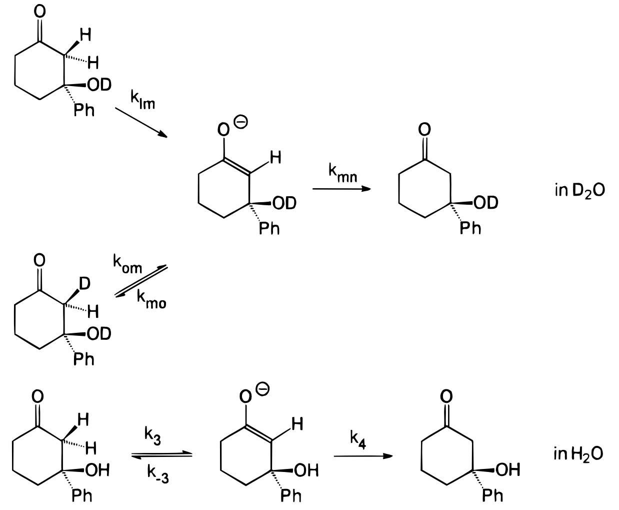
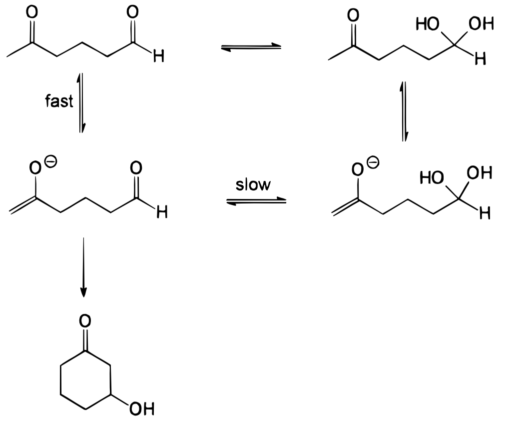
[26] Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism,* 3rd ed.; Wiley: New York, 1981.

Scheme 5



Scheme 6



catalyzed dehydration of acetaldehyde is 8 × 10^4 M^{-1} s^{-1} (calculated from the rate constant for hydroxide-catalyzed hydration[27] and the equilibrium constant for hydration[28]), while the rate constant for reprotonation of acetone enolate is 5.01 × 10^4 s^{-1}.[29] Thus, in 0.01 M NaOH solution, reprotonation is approximately 100 times faster than dehydration. Reaction starting with 2-cyclohexen-1-one permitted determination of the equilibrium constant for hydration of the enone and the rate of approach to hydration equilibrium. The values so determined were in good agreement with those determined starting with 5-oxohexanal. The estimated value for the rate of deprotonation of 5-oxohexanal is 0.10 M^{-1} s^{-1}, while the observed value for k_{12} is 0.071 M^{-1} s^{-1}. These values are very similar, so that k_{12} may represent rate-limiting deprotonation. The estimated value for 5-oxohexanal is based on a perturbation of the rate constant for acetone, so it should be fairly good.

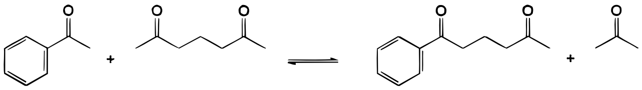
Average values for the rate and equilibrium constants for the aldol condensations of 2,5-hexanedione, 2,6-heptanedione, 1-phenyl-1,5-hexanedione, and 5-oxohexanal are found in Table 3.

6. Intramolecular Aldol Reaction of 3-(2-Formylphenyl)-2-propanone. This compound has been studied by Richard et al.,[30] who found that the rate constant for the cyclization of the enolate ion was 1.6 × 10^6 s^{-1}. The subsequent elimination process was fast and was followed by an irreversible tautomerization to 2-naphthoxide.

7. Estimation of Thermodynamic Quantities for Compounds Discussed in This Paper. Free energies of formation of the starting dicarbonyl compounds, ketols, and enones were estimated, in many cases by disproportionation reactions. For various disproportionation reactions (in which the number of each Benson group contribution was unchanged in the disproportionation), the free energy change was calculated from the enthalpy change, taken to be the change in MM3 strain energy, and the entropy change, calculated from the MM3 entropies. In other cases free energies of formation in aqueous solution were calculated from measured or estimated values of the enthalpy of formation and entropy in the gas phase and the free energy of transfer. Free energies of transfer measured in this work are found in Table 4.

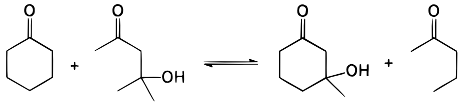
a. 2,5-Heptanedione and 2,6-Heptanedione. ΔH_f(g) and $S°$ were calculated by MM3; ΔG_t was the experimental value. For acetone and acetophenone there are literature values.[31]

b. 1-Phenyl-1,5-hexanedione. The free energy of formation was calculated by means of the disproportionation reaction



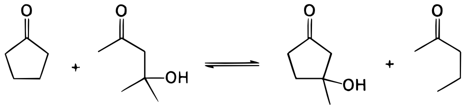
for which we assume $\Delta G° = 0.0$.

c. 3-Hydroxy-3-methylcyclohexanone. $\Delta G_f°$(aq) was calculated from that of heptanedione using the experimental equilibrium constant for aldol cyclization: −66.03 kcal/mol. A value was also calculated by means of the disproportionation reaction



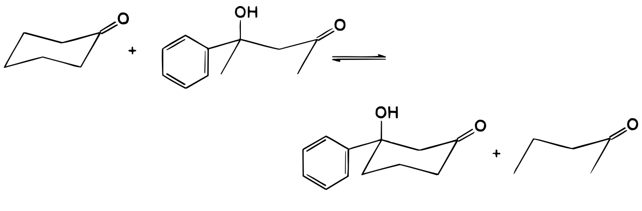
The value so obtained was −66.53 kcal/mol, in excellent agreement.

d. 3-Hydroxy-3-methylcyclopentanone. $\Delta G_f°$(aq) was calculated as described for 3-hydroxy-3-methylcyclohexanone, −67.32 kcal/mol, and also estimated in an analogous way using the disproportionation reaction



The value so obtained was −68.99 kcal/mol, which is within 1.6 kcal of the value derived from equilibrium. The agreement is useful if not wonderful.

e. 3-Hydroxy-3-phenylcyclohexanone. $\Delta G_f°$(aq) was calculated by means of the disproportionation reaction



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[27] Bell, R. P.; Rand, M. H.; Wynne-Jones, K. M. A. *Trans. Faraday Soc.* **1956**, *52*, 1093−1102.

[28] Kurz, J. *J. Am. Chem. Soc.* **1967**, *89*, 3524−3528.

[29] Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460−462.

[30] Nagorski, R. W.; Mizerski, T.; Richard, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 4718−4719.

[31] Guthrie, J. P. *Can. J. Chem.* **1992**, *70*, 1042−1054.

Table 3. Summary of Rate and Equilibrium Constants for Base-Catalyzed Inter- and Intramolecular Aldol Condensation Reactions[a]

10^4k_{12} (M^{-1} s^{-1})	10^4k_{21} (M^{-1} s^{-1})	10^4k_{23} (M^{-1} s^{-1})	10^4k_{32} (M^{-1} s^{-1})	K_{12}	K_{23}
		a. 2,5-Hexanedione			
0.305 ± 0.043	0.0305 ± 0.005	1100 ± 70	1.82 ± 0.19	10.0 ± 0.9[b]	602 ± 49
		b. 2,6-Heptanedione			
720 ± 13	13.8 ± 1.1	184 ± 10	3.20 ± 0.31	52.3 ± 4.0	57.4 ± 4.7[c,d]
		c. 1-Phenyl-1,5-hexanedione			
121.3 ± 2.4	15.8 ± 1.3	1400 ± 60	1.47 ± 0.10	7.7 ± 0.7	950 ± 50
		d. 2-Oxohexanal			
712 ± 16	0.0057	202.2 ± 1.6	44.8 ± 0.37	1.3×10^{5}[d,e]	4.51 ± 0.01

[a] All in aqueous solution at 25 °C. Unless otherwise noted, rate constants are calculated from data in Table 1, using $k_{12} = (k_{12} + k_{21})/(1 + 1/K_{12})$ and $k_{21} = (k_{12} + k_{21})/(1 + K_{12})$. [b] Calculated from K_{23} and K_{13} (Table 2). [c] Average of values from Table 1 for both acidic and basic conditions. [d] Calculated using estimated $\Delta G_f°$ values for 5-oxohexanal and 3-hydroxycyclohexanone.

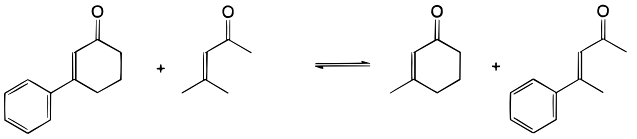
Table 4. Free Energy of Transfer Determinations

compound	$P_{d\to w}$[a]	S_d[b] (M)	S_w[c] (M)	P[d] (atm)	$\Delta G°_{g\to w}$[e] (kcal)
3-methyl-2-cyclopentenone	4.27	1.23	5.25	2.00×10^{-3}	−4.67
2,5-hexanedione	23.58	0.29	6.84	1.27×10^{-3}	−5.09
3-methyl-2-cyclohexenone			1.32	8.66×10^{-4}	−4.35
2,6-heptanedione	14.50	0.18	2.61	2.58×10^{-4}	−5.47

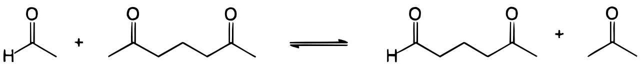
[a] Partition constant from dodecane to water [$I = 1.0$M (KCl)], based on the molar concentration at 25 °C. [b] Limiting solubility in dodecane at 25 °C directly measured by HPLC. [c] Theoretical limiting solubility in water [$I = 1.0$M (KCl)] at 25 °C calculated from the corresponding $P_{d\to w}$ and S_d except that S_w of 3-methyl-2-cyclohexen-1-one was directly measured by UV analysis of a saturated solution. [d] Vapor pressure at 25 °C, obtained by extrapolation of literature bp at different pressures.[69] [e] Free energy of transfer at 25 °C from gas (1 atm) to aqueous solution [1 M, $I = 1.0$ M (KCl)].

f. 4-Phenyl-3-penten-2-one. $\Delta G_f°$(aq) was calculated from the values for acetone and acetophenone using the experimental equilibrium constant for aldol condensation.

g. 3-Phenyl-2-cyclohexenone. $\Delta G_f°$(aq) was calculated by means of the disproportionation reaction

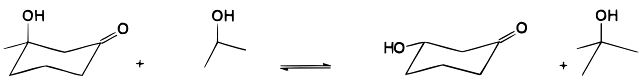


h. 5-Oxohexanal. $\Delta G_f°$(aq) is available for 2,6-heptanedione (estimated above), acetaldehyde (carbonyl form), and acetone.[31] $\Delta G_f°$(aq) was calculated by means of the disproportionation reaction



for which we assume $\Delta G° = 0.0$.

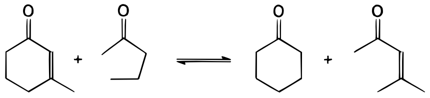
i. 3-Hydroxycyclohexanone. $\Delta G_f°$(aq) has been estimated for 3-hydroxy-3-methylcyclohexanone; values for 2-propanol and 2-methyl-2-propanal are available.[31] $\Delta G_f°$(aq) was calculated by means of the disproportionation reaction



j. 2-Cyclohexenone. $\Delta G_f°$(aq) was calculated from $\Delta G_f°$(aq) for 3-methylcyclohexenone using the difference in group contributions ($[C_dH(C)] - [C_d(C)_2] - [CH_3(C_d)]$).[31]

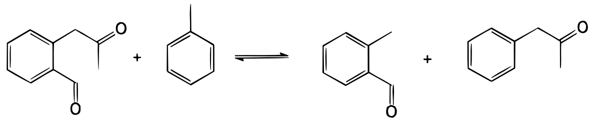
k. 3-Methylcyclopentenone. $\Delta G_f°$(aq) was calculated from $\Delta G_f°$(aq) for 2,6-hexanedione and water, using $\Delta G°$ calculated from the equilibrium constants for aldol addition and dehydration. The value so calculated was −14.42 kcal/mol. No disproportionation calculation is possible because necessary parameters for MM3 are not available.

l. 3-Methylcyclohexenone. $\Delta G_f°$(aq) was calculated from $\Delta G_f°$(aq) for 2,6-heptanedione and water, using $\Delta G°$ calculated from the equilibrium constants for aldol addition and dehydration. The value so calculated was −11.72 kcal/mol. It was also estimated from the disproportionation reaction



All $\Delta G_f°$(aq) were available except that for 3-methylcyclopentenone, for which $\Delta G_f°$(aq) was calculated to be −14.40. The agreement is not as good as would be wished and suggests that the MM3 parameters for enones, which are based on very few compounds,[32] are not adequate for this calculation.

m. 2-(2-Oxopropyl)benzaldehyde. $\Delta G_f°$(aq) was calculated from the disproportionation reaction



using the $\Delta G_f°$(aq) for toluene, a value for *o*-tolualdehyde estimated using ΔH_f(g), and $S°$ calculated by MM3 and ΔG_t calculated by group additivity. MM3 gives a good estimate of ΔH_f(g) and $S°$ for benzaldehyde. For 1-phenyl-2-propanone we used the experimental value of ΔH_f(g), $S°$ calculated by MM3, and a value for ΔG_t calculated from solubility and vapor pressure. The solubility was estimated[33] from the value of log P,[34] and the vapor pressure was estimated[35] using a value of ΔH_{vap} calculated[35] from vapor pressure data from Beilstein[36] and $\Delta C_{P,vap}$ estimated by group additivity.[37]

n. 4-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-one. $\Delta G_f°$(aq) was calculated from the disproportionation reaction

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(32) Allinger, N. L.; Rodriguez, S.; Chen, K. *J. Mol. Struct. (THEOCHEM)* **1992**, *260*, 161−178.

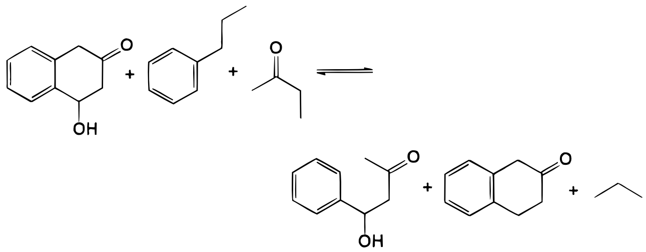
(33) Hansch, C.; Quinlan, J. E.; Lawrence, G. L. *J. Org. Chem.* **1968**, *33*, 347−350.

(34) Leo, A.; Hansch, C. H.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525.

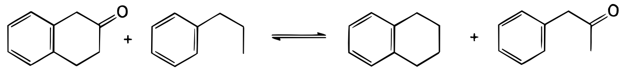
(35) Guthrie, J. P. *Can. J. Chem.* **1986**, *64*, 635−640.

(36) *Beilstein Handbuch der organischen Chemie*: 7, IV, 687; 7, III, 1037,; 7, II, 233; 7, I, 161; 7, H, 303.

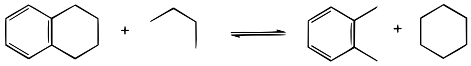
(37) Guthrie, J. P.; Taylor, K. F. *Can. J. Chem.* **1984**, *62*, 363−372.



using $\Delta G_f°$(aq) for butanone, propane, and propylbenzene,[31] a value for 4-hydroxy-4-phenyl-2-butanone calculated from the values for acetone and benzaldehyde[31] and the equilibrium constant for aldol addition,[8] and a value for 2-tetralone estimated by means of the disproportionation reaction

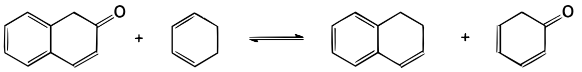


using values of $\Delta G_f°$(aq) for propylbenzene[31] and 1-phenyl-2-propanone and a value for tetralin estimated using the disproportionation



with values of $\Delta G_f°$(aq) for butane, *o*-xylene, and cyclohexane.[31]

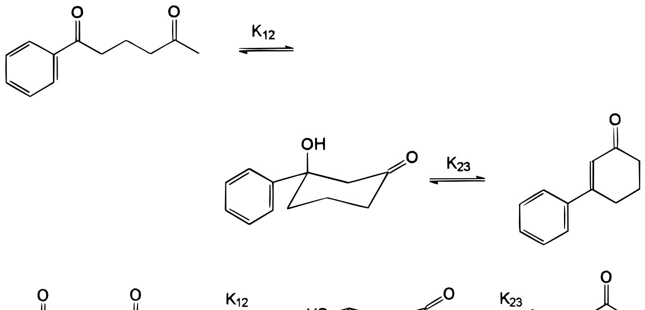
o. 1,2-Dihydronaphthalen-2-one. $\Delta G_f°$(aq) was calculated from the disproportionation reaction

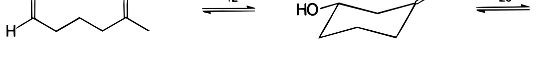


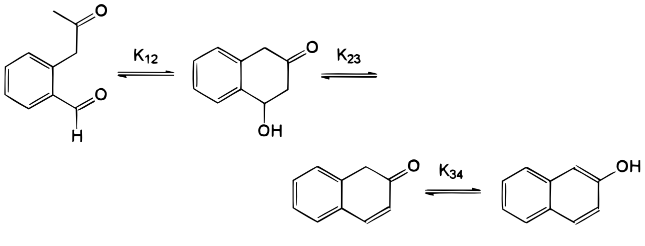
using $\Delta G_f°$(aq) for cyclohexadiene calculated from the experimental $\Delta H_f°$(g), $S°$ calculated using MM3, and ΔG_t estimated by group additivity;[31,38] $\Delta G_f°$(aq) for dihydronaphthalene calculated form the experimental $\Delta H_f°$(g), $S°$ calculated using MM3, and ΔG_t estimated by group additivity;[31] and $\Delta G_f°$(aq) for 2,4-cyclohexadienone calculated from K for tautomerization of phenol to the keto form.[39]

All of the thermodynamic quantities are contained in Table 5. The equilibrium constants used in these calculations are given in Table 6. The results of MM3 calculations used to estimate $\Delta G_{\text{disproportionation}}$ are found in Table 7.

We can now calculate the equilibrium constants for the reactions studied.







For 1-phenyl-1,5-hexanedione, log K_{12}(calcd) = −1.23, log K_{12}(exptl) = 0.89, log K_{23}(calcd) = 2.97, and log K_{23}(exptl) = 2.98. For 5-oxohexanal, log K_{12}(calcd) = 4.89, (no experimental value), log K_{23}(calcd) = 3.13, log K_{23}(exptl) = 0.65. For the cases where the answer is known, the estimation procedures are within an order of magnitude (rms error 1.09), so we can expect that the value estimated for log K_{12} for 5-oxohexanal will be similarly reliable.

For reactions starting with 2-(2-oxopropyl)benzaldehyde, the estimated values are probably less reliable, because we have less complete matching in the disproportionation reactions: the values obtained were log K_{12}(calcd) = 5.19; log K_{23}(calcd) = 6.48; log K_{34}(calcd) = 5.25. We see that this reaction is highly irreversible at each stage.

8. Marcus Analysis of the Intramolecular Aldol Reactions. The detailed mechanism of the reaction is believed to be as shown in Scheme 7. To analyze the aldol condensations in terms of Marcus theory, we will need equilibrium constants for each step in this scheme. 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 diketone into the conformation in which 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 in which the hydroxyl which is to leave to form the enone is perpendicular to the plane of the enolate.

The pK_a values for the diketones were estimated starting with acetone, for which the pK_a is 19.27.[40] The enol content (for enolization to the methyl groups) is assumed to be the same as for acetone. The pK_a of the enol is assumed to respond to polar substituents with the same ρ^* as an alcohol.[41] (This seems reasonable and the effect is small; there are to date no accurate pK_a values for enols with nonconjugating electron-withdrawing groups.) For PhCO and HCO we used σ^* values from Perrin et al.,[42] corrected for added CH_2's using the falloff factor of 0.4 recommended by Perrin et al. For 5-oxohexanal, one should really allow for hydration of the aldehyde, but this would only reduce σ^* from $0.4 \times 0.4 \times 0.63$ for $CH_2CH_2CH_2CHO$ to an estimated $0.4 \times 0.4 \times 0.50$ for $CH_2CH_2CH_2CH(OH)_2$, and the calculation would be much more complicated because of reciprocal effects of enolization upon formation of the hydrate. The perturbation appears small enough to be neglected. For 2-(2-oxopropyl)benzaldehyde we used σ^* for $CH_2CH_2CH_2CHO$ estimated from the value for CH_2CHO[42] as a model for the effect of the aldehyde and σ^* for $PhCH_2$ as a model for the effect of the benzene ring. For all of the monomethyl ketones a correction for the decreased number of enolizable methyls was made. The pK_a of the ketol hydroxyl is assumed to be the same as that of diacetone alcohol, which we have estimated previously.[11] For **3a** we corrected for the effect of the phenyl by using the difference in the pK_a values reported for benzyl alcohol and ethanol;[41] for **4a** we corrected for the effect of replacing CH_3 by H by using the difference in the pK_a values reported for *tert*-butyl alcohol and 2-propanol.[41] Values so estimated are found in Table 8.

The reactive conformations of the enolates were assumed to be the 3,4-eclipsed conformation of **1a** enolate and the

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[38] Hine, J.; Mookerjee, P. K. *J. Org. Chem.* **1975**, *40*, 292−298.

[39] Capponi, M.; Gut, I.; Wirz, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 344−345.

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[42] Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK$_a$ Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981.

Table 5. Thermodynamic Quantities for Compounds Discussed in This Paper[a]

a. Compounds for which ΔG_f(aq) Has Not Previously Been Reported

compound	ΔH_f(g)	$S°$(g)	ΔG_f(g)[b]	ΔG_t	ΔG_f(aq)
1,3-cyclohexadiene	25.38 ± 0.22	73.18[c]	43.22	1.44[d]	44.66
2,5-hexanedione	−94.96[c]	98.09[c]	−60.64	−5.31[e]	−65.95
2,6-heptanedione	−99.72[c]	105.66[c]	−57.94	−5.74[e]	−63.69
3-phenyl-2-propanone	−24.07	100.78[c]	3.37	−3.88[f]	−0.51
1,2-dihydronaphthalene	30.62[g]	88.19[c]	54.91	−0.40[d]	54.51
2-naphthol	−7.15[h]	90.14[c]	14.56	−5.94[d]	8.62

b. Compounds for which ΔG_f(aq) Has Been Reported[i]

compound	ΔG_f(aq)	compound	ΔG_f(aq)
H_2O	−56.69 ± 0.01[j]	2-pentanone	−34.49 ± 0.27
acetaldehyde	−32.97 ± 0.18	phenol	−12.60 ± 0.25
propane	−1.97 ± 0.18	cyclohexane	10.63 ± 0.23
acetone	−38.48 ± 0.21	cyclohexanone	−23.77 ± 0.52
2-propanol	−44.41 ± 0.18	mesityl oxide	−18.95 ± 0.29
butane	0.00 ± 0.21	toluene	30.26 ± 0.20
2-butanone	−36.74 ± 0.23	*o*-xylene	30.18 ± 0.30
tert-butyl alcohol	−45.12 ± 0.23	acetophenone	−2.22 ± 0.41

c. Compounds for which ΔG_f(aq) Was Calculated in This Work

compound	ΔG_f(aq)
2,4-cyclohexadienone	5.16[k]
cyclohexenone	−11.90[l]
diacetone alcohol	−75.04[m]
5-oxohexanal	−58.18[n]
3-hydroxycyclohexanone	−64.32[o]
3-hydroxy-3-methylcyclopentanone	−67.32[p]
3-methylcyclopentenone	−14.42[q]
3-hydroxy-3-methylcyclohexanone	−66.03[r]
3-methylcyclohexenone	−11.72[s]
o-tolualdehyde	4.32[t]
propylbenzene	34.17 ± 0.23[u]
2-phenyl-2-propanol	−7.34 ± 0.38[v]
4-hydroxy-4-phenyl-2-butanone	−36.89[w]
4-phenyl-3-penten-2-one	19.49[x]
tetralin	40.01[y]
2-tetralone	5.78[z]
4-hydroxy-2-tetralone	−32.05[aa]
1,2-dihydro-2-naphthalenone	15.80[bb]
2-(2-oxopropyl)benzaldehyde	−25.09[cc]
1-phenyl-1,5-hexanedione	−27.43[dd]

[a] All at 25 °C; enthalpies and free energies are in kcal/mol, entropies are in cal/deg/mol, standard states are the ideal gas at 1 atm and 1 M aqueous solution with an infinitely dilute reference state. Unless otherwise noted, enthalpies of formation are from ref 70, entropies are from ref 71, free energies of formation in the gas phase are calculated from the corresponding enthalpies of formation and the standard entropies, and free energies of formation in aqueous solution are calculated from the corresponding free energies of formation in the gas and free energies of transfer. [b] Free energy of transfer from the gas at 1 atm to 1 M aqueous solution. [c] Calculated using MM3. [d] Estimated by group additivity.[31] [e] This work. [f] Calculated from the solubility and vapor pressure at 25 °C. The solubility was calculated from the water/octanol partition constant[34] using the published linear free energy relation between log(solubility) and log(P).[33] The vapor pressure was estimated from literature boiling point data[36] by a method we have reported[35] using a value for the enthalpy of vaporization estimated from the boiling point data[35] and a value for the heat capacity of vaporization estimated by additivity.[37] [g] Calculated from the enthalpy of formation for the liquid[70] and a heat of vaporization calculated[35] from the boiling point data.[72] [h] Reference 73. [i] Values from ref 31 unless otherwise noted. [j] Reference 74. [k] Calculated from the free energy of formation of phenol and the equilibrium constant for tautomerization.[75] [l] Estimated by Benson group additivity,[53] with the entropy and ring strain corrections based on MM3 calculations, and the free energy of transfer by group additivity.[31] [m] Calculated from the free energy of formation of acetone and the equilibrium constant for aldol addition (Table 6). [n] Estimated by a disproportionation calculation, using the free energies of formation of acetaldehyde, acetone, and 2,6-heptanedione. [o] Estimated by a disproportionation calculation, using the free energies of 3-hydroxy-3-methylcyclohexanone, isopropyl alcohol, and *tert*-butyl alcohol, with corrections from the differences in strain energy and entropy calculated by MM3. [p] Calculated from the free energy of formation of 2,5-hexanedione and the equilibrium constant for aldol cyclization, K_{12}, measured in this work. [q] Calculated from the free energy of formation of 2,5-hexanedione and the equilibrium constant for aldol condensation, K_{13}, measured in this work. [r] Calculated from the free energy of formation of 2,6-heptanedione and the equilibrium constant for aldol cyclization, K_{12}, measured in this work. [s] Calculated from the free energy of formation of 2,6-heptanedione and the equilibrium constant for aldol condensation, K_{13}, measured in this work. [t] Estimated using enthalpy of formation and entropy values from MM3, and a free energy of transfer estimated by group additivity.[31] [u] Reference 31. [v] Reference 2. [w] Calculated from the energy of formation of benzalacetone and the equilibrium constant for its hydration (Table 6). [x] Calculated from the free energies of formation of acetone, acetophenone, and water and the equilibrium constant for aldol condensation, K_{13}, from Table 6. [y] Estimated using a disproportionation reaction from the free energies of formation of butane, o-xylene, and cyclohexane, with corrections for changes in strain energy and entropy based on MM3 calculations. [z] Estimated using a disproportionation reaction from the free energies of formation of propylbenzene, tetralin, and 1-phenyl-2-propanone, with corrections for changes in strain eanergy and entropy based on MM3 calculations. [aa] Estimated using a disproportionation reaction from the free energies of formation of propylbenzene, butanone, β-tetralone, 4-hydroxy-4-phenyl-2-butanone, and propane, with corrections for changes in strain energy and entropy based on MM3 calculations. [bb] Estimated using a disproportionation reaction from the free energies of formation of 1,2-dihydronaphthalene, 2,4-cyclohexadienone, and 1,3-cyclohexadiene, with corrections for changes in strain energy and entropy based on MM3 calculations. [cc] Estimated using a disproportionation reaction from the free energies of formation of toluene, *o*-tolualdehyde, and 1-phenyl-2-propanone, with corrections for changes in strain energy and entropy based on MM3 calculations. [dd] Estimated using a disproportionation reaction from the free energies of formation of acetophenone, 2,6-heptanedione, and acetone, with corrections for changes in strain energy and entropy based on MM3 calculations.

Table 6. Equilibrium Constants Used in This Work[a]

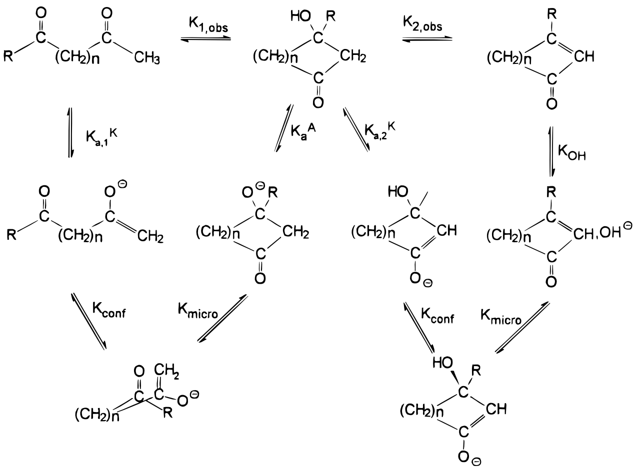
	K	ΔG	ΔG_{prod}
benzalacetone + water = 4-hydroxy-4-phenyl-2-butanone	0.04[b]	1.18	−36.89
acetone + acetophenone = 4-phenyl-3-penten-2-one + water	2.72×10^{-3} [c]	3.50	19.49
2,5-hexanedione = 3-hydroxy-3-methylcyclopentanone	10.02[d]	−1.37	−67.32
2,5-hexanedione = 3-methylcyclopentenone + water	6025[d]	−5.16	−14.42
2,6-heptanedione = 3-hydroxy-3-methylcyclohexanone	52.3[d]	−2.34	−66.03
2,6-heptanedione = 3-methylcyclohexenone + water	2818[d]	−4.72	−11.72
acetone + acetone = diacetone alcohol	0.039[e]	1.92	−75.04

[a] All in aqueous solution at 25 °C. [b] Reference 8. [c] Reference 10. [d] This work. [e] Reference 76.

Table 7. Results of MM3 Calculations for Compounds Discussed in This Work

	MM3 results					
compound	steric energy	strain energy	$S°$	n_C	n_H	n_O
propane	2.02	−0.01	64.42	3	8	
2-propanol	3.66	0.01	73.41	3	8	1
2-butanone	1.78	−0.41	93.81	4	8	1
butane	3.09	0.00	71.90	4	10	
tert-butyl alcohol	5.38	0.00	77.91	4	10	1
3-penten-2-one	2.33	−2.06	83.20	5	8	1
cyclopentanone	15.28	5.65	75.17	5	8	1
2-pentanone	2.87	0.02	86.31	5	10	1
cyclohexenone	3.26	−2.70	79.52	6	8	1
3-methylcyclopentenone	8.98	−0.57	80.08	6	8	1
cyclohexanone	7.93	2.74	79.41	6	10	1
mesityl oxide	6.45	1.18	96.03	6	10	1
5-oxohexanal	4.92	1.35	99.99	6	10	2
enol, equilibrium conformation	7.13					
enol, reactive conformation	8.51					
hexanedione	2.54	−0.07	97.59	6	10	2
enol, equilibrium conformation	4.71					
enol, reactive conformation	12.38					
3-hydroxy-3-methylcyclopentanone	19.15	4.99	88.78	6	10	2
enol, equilibrium conformation	15.63					
enol, reactive conformation	15.98					
cyclohexane	8.04	1.69	71.29	6	12	
3-hydroxycyclohexanone	9.91	3.09	87.17	6	12	2
enol, equilibrium conformation	7.44					
enol, reactive conformation	8.38					
3-methylcyclohexenone	3.94	−1.16	85.36	7	10	1
2,6-heptanedione	4.51	0.83	105.66	7	12	2
enol, equilibrium conformation	7.30					
enol, reactive conformation	9.23					
3-hydroxy-3-methylcyclohexanone	12.28	2.58	93.36	7	12	2
enol, equilibrium conformation	8.63					
enol, reactive conformation	9.25					
o-tolualdehyde	5.15	−0.05	85.66	8	8	1
o-xylene	7.35	0.33	88.12	8	10	0
3-phenyl-2-propanone	5.63	−1.19	100.78	9	10	1
propylbenzene	6.17	−0.41	93.81	9	12	0
2-phenyl-2-propanol	6.86	−0.48	98.30	9	12	1
2-tetralone	8.77	1.18	95.43	10	6	1
2-(2-oxopropyl)benzaldehyde	7.45	1.42	111.63	10	10	2
enol, equilibrium conformation	9.16	1.37				
enol, reactive conformation	8.95	0.56				
4-hydroxy-2-tetralone	10.14	0.92	102.38	10	6	2
enol, equilibrium conformation	10.71	−1.74				
enol, reactive conformation	10.76					
tetralin	8.75	1.53	88.55	10	8	0
4-phenyl-3-penten-2-one	10.21	3.25	122.23	10	12	1
phenylcyclohexenone	7.87	0.10	105.59	10	12	1
4-hydroxy-4-phenyl-2-butanone	8.40	0.43	113.60	10	12	2
1-phenyl-1,5-hexanedione	6.08	−1.27	125.85	12	14	2
enol, equilibrium conformation	9.00					
enol, reactive conformation	9.79					
hydroxyphenylcyclohexanone	14.72	4.22	112.46	12	14	2
enol, equilibrium conformation	10.58					
enol, reactive conformation	11.13					

Scheme 7



conformations of the enolates of **2a, 3a**, and **4a** with the enolate and acetyl, benzoyl, or formyl in what is equivalent to a 1,3-diaxial interaction. For the enolate of **5a**, the lowest energy conformation has the CH_2 of the enolate in van der Waals contact with the carbonyl carbon. These conformations can convert to the ketol anion products simply by bond rotation accompanied by bond formation (see Scheme 8). Both the 3,4-eclipsed and 3,4-staggered conformations of **1a** enolate have the nucleophilic carbon and the carbonyl carbon in van der Waals contact, but for the eclipsed conformation the carbon−carbon vector is closer to being orthogonal to the planes of both π-systems and thus should be better suited to reaction. The equilibrium constant for the conformational shift from the preferred, extended conformation to the reactive conformation was calculated using the difference in MM3 steric energies for the two conformations.

The carbon pK_a values for the ketols were estimated starting from the corresponding unsubstituted cycloalkanone, correcting for the effect of the hydroxyl by adding the difference in pK_a between 4-hydroxy-2-butanone and 2-butanone.[11] pK_a values for cyclopentanone and 2-butanone were estimated from the enol contents[18] assuming the enol had the pK_a of cyclohexanone enol.[18] For **3b** we started with the value for **2b** and corrected for the effect of the phenyl using $\Delta pK_a = -1.32 \times 0.4 \times 0.27$. For **4b** we corrected the value for **2b** using using $\Delta pK_a = -1.32 \times 0.4 \times 0.4 \times 0.49$. For **5b** we corrected the value for **2b** using $\Delta pK_a = -1.32 \times 0.27$.

The equilibrium constants for conversion of the equilibrium conformation of the enolate to the conformation with the hydroxyl leaving group perpendicular to the plane of the enolate were estimated from the differences 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. The energies calculated in this way lead to the values in Table 8.

By including all of the pre-equilibria, we can now correct the observed rate constants to give the microscopic rate constants for the rate-determining steps of the two phases of the condensations. These values are also given in Table 8.

From the rate and equilibrium constants for the microscopic steps we could calculate the intrinsic barriers for the steps.

Table 8. Microscopic Rate and Equilibrium Constants[a]

a. Aldol Addition Step

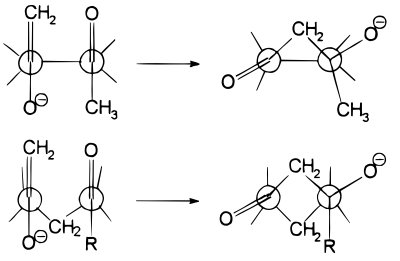
compound	K_{obs}[b]	pK_a^{K}[c]	pK_a^{A}[d]	K_{conf}[e]	K_{micro}[f]	$\Delta G°$[g]	k_{obs}[h]	k_{micro}[i]	ΔG^*[j]	$\tilde{G}$[k]
1a	10.0	18.94[l]	16.21[l]	2.4×10^{-6}[m]	1.1×10^{9}	−12.76	3.1×10^{-5}	5.5×10^{5}	9.20	15.15
2a	52.3	19.14[l]	16.21[l]	0.039[m]	1.6×10^{6}	−8.89	0.0734	2.1×10^{5}	9.77	14.11
3a	7.7	19.39[l]	15.86[l]	0.26[m]	9.9×10^{4}	−6.82	0.0124	1.3×10^{4}	11.82	15.04
4a	3.1×10^{4}	19.44[l]	15.94[l]	0.098[m]	1.0×10^{9}	−13.30	0.0712	7.0×10^{5}	9.46	14.98
5a	1.2×10^{5}[n]	18.89[l]	15.86[l]	1.	1.3×10^{8}	−12.75		1.6×10^{6}[o]	8.97	13.97
										av 14.65 ± 0.56

b. Elimination Step

compound	K_{obs}[p]	pK_a^{K}	K_{OH}[q]	K_{conf}[r]	K_{micro}[f]	$\Delta G°$[g]	k_{obs}[h]	k_{micro}[i]	ΔG^*[j]	$\tilde{G}$[k]
1b	602	17.84[l]	1×10^{-7}	0.586[m]	0.732	0.18	0.11	257	13.19	14.07
2b	55.0	16.28[l]	1×10^{-7}	0.361[m]	0.00306	3.43	0.0195	10.5	16.05	14.29
3b	950	16.12[l]	1×10^{-7}	0.396[m]	0.0326	2.03	0.140	36.4	15.16	14.28
4b	4.51	16.18[l]	1×10^{-7}	0.205[m]	0.000339	4.74	0.0202	14.7	15.85	13.38
										av 14.01 ± 0.42

[a] All in aqueous solution at 25 °C. The reaction systems are described in Scheme 6. [b] Observed overall equilibrium constant for the aldol addition step; values from Table 3. [c] pK_a of the ketone which reacts as carbon nucleophile. [d] pK_a of the ketol OH. [e] Equilibrium constant for conversion of the equilibrium conformation of the enolate of the starting material to the conformation which is ready to react: see text. [f] Equilibrium constant for the microscopic rate determining step; calculated using pK_a^K, pK_a^A, K_{conf}, and statistical corrections for the number of potential enolic carbons. [g] The free energy change corresponding to K_{micro}, needed for the Marcus analysis. [h] Observed apparent rate constant, second order (cyclizations). [i] Rate constant for the microscopic rate determining step within the encounter complex or reactive conformation; calculated using pK_a^K, K_{conf}, statistical corrections for the number of potential enolic carbons, and a partitioning ratio, (k_{-1}/k_2), calculated either from the results of experiments in D_2O or from k_{obs} and and estimated value for $k_{deprotonation}$. [j] The corresponding free energy of activation for k_{micro}, needed for the Marcus analysis. [k] The intrinsic barrier for this reaction. [l] Estimated as described in the text. [m] Calculated from the differences in MM3 steric energy between the reactive conformation and the most stable conformation of the enolate. [n] Calculated from estimated $\Delta G°_f$ values for starting material and product. [o] Reference 30. [p] Observed overall equilibrium constant for the equilibrium step. [q] Equilibrium constant for partial desolvation of hydroxide by loss of one hydrogen bonded water.[11] [r] Reference 77.

Scheme 8



An analogous intermolecular reaction for comparison is the self-condensation of acetone.[11] The significant difference is that there is a contribution from the entropic cost of bringing together a molecule of acetone and an acetone enolate in an encounter complex and, in the intramolecular reactions, an energetic cost for attaining the conformation in which the reaction centers are close enough to begin the bond-forming process. When all of these corrections are introduced, we find that the intrinsic barriers for the intramolecular reactions are in excellent agreement with the average value, 13.89 ± 0.80,[11] found for intermolecular reactions.

For the elimination reactions we similarly observe that the intrinsic barriers for the intramolecular reactions are in excellent agreement with the average value, 14.13 ± 0.49,[11] found for the dehydration of acyclic aldols.

Discussion

The results reported above constitute the first examples of detailed kinetic and thermodynamic analysis of intramolecular aldol condensations. These reactions constitute a clear example of Baldwin's rules:[12,43,44] the cyclization of 2,5-hexanedione, though actually more favorable (dione to enone) than the cyclization of 2,6-heptanedione, is 2400-fold slower. We have demonstrated that this rate effect is completely explicable in terms of the energetics of the reactions and the Marcus intrinsic barrier which applies to the analogous intermolecular reactions. This implies that the rate constant for any such reaction could be predicted. A further implication of this result, if it proves to be general, is that effective molarities[45] can be calculated from thermodynamics (which can, at least in principle, be estimated from structures) for equilibrium processes and from thermodynamics and the appropriate intrinsic barrier for kinetic processes. We intend to test the generality of this conclusion in various systems.

The application of Baldwin's rules[12,43,44,46] to the intramolecular aldol reaction requires comment. As Baldwin made clear,[46] these reactions are *exo-trig* as far as the carbonyl that suffers nucleophilic attack is concerned, but *enolendo-trig* as far as the nucleophilic center is concerned, and thus should be referred to as (*enolendo-trig*)-*exo-trig*. This matters, because *exo-trig* reactions are allowed for both 5- and 6-membered rings, while *endo-trig* reactions are allowed for 6-membered rings but not for 5-membered rings. Thus, we are dealing with a reaction for which Baldwin's rules are expected to apply with their full rigor, and our conclusions should apply to *endo-trig* reactions in general.

Our goal in this work was to find a way to account, quantitatively, for the effect of intramolecularity on the rates of aldol addition reactions. We hoped that this could be done by some simple extension of Marcus theory. Our hypothesis was that the strain energy of the conformation which was about to begin the intramolecular bond-forming process would prove to be the analog of the work term for intermolecular reactions. The difficulty was to define such conformations in a simple and unambiguous fashion. We first attempted to find conformations for the enolates of 2,5-hexanedione and 2,6-heptanedione with the C−C distance corresponding to van der Waals contact

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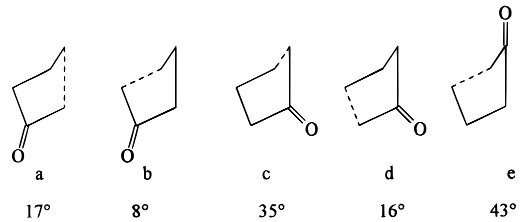
Scheme 9. Envelope Conformations for Cyclopentanone, Showing the Possible Relations of the Carbonyl to the Bond That Would Cleave in a Retro-aldol Reaction of 3-Hydroxy-3-methylcyclopentanone[a]



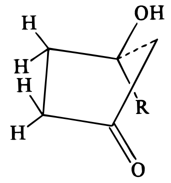
[a] To simplify the pictures, the CH_3 and O^- present at the beginning of a retro-aldol reaction have been omitted.

and approach angles of either 90° or 105°,[47,48] but all such conformations had prohibitively high energy. To force such conformations in MM3, we assigned special atom types to the atoms constrained to be in contact, with a "bond length" equal to the sum of the van der Waals radii, and preferred angles of 90 or 105°. Calculations were carried out with a range of values for both stretching and bending force constants. Angles close to the "preferred" values could only be obtained if stiff bending force constants were used, and this imposed high strain energies, e.g. 40 kcal for a 5° deviation. Total strain energies from the MM3 calculations included contributions from the unphysical stretch and bend force constants used to constrain the conformation. These contributions were subtracted to leave the strain due only to the interactions present in the imposed conformation. With softer force constants strain energies were less, but the angular deviations were large. Even with deviations of 37° the cost was 10 kcal. Strain energies were higher if the assumed attack angle was 105° rather than 90°. This led to the conclusion that the reaction cannot take place by first attaining a conformation with optimal attack angles and then initiating bond formation.

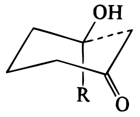
We next looked for conformations from which reaction could take place by simple concerted bond rotations accompanied by bond formation leading from starting materials to products. This corresponds to a conformation of the enolate of 2,5-hexanedione with $COCH_3$ and $C(O^-){=}CH_2$ eclipsed and to a conformation of the enolate of 2,6-heptanedione with $COCH_3$ and $C(O^-){=}CH_2$ in what is in effect a "1,3-diaxial" arrangement.

The model we have used for the intramolecular aldol additions or reversions corresponds in a simple way to the requirements that the C−C bond which forms in the cyclization, or which would break in the retro-aldol cleavage, must be approximately orthogonal to the plane of the carbonyl in the product. In a planar cyclopentanone ring no ring bond would be perpendicular to the exocyclic carbonyl. In the preferred twist conformation of cyclopentanone[49] the C−C bond which would cleave in a retro-aldol reaction makes an angle of 11° to the plane of the carbonyl. If we examine the possible envelope conformations of cyclopentanone, we find that there are five cases to be considered, with the bond to plane angles shown in Scheme 9. The best conformations are clearly c and e. Conformation e has the disadvantage of requiring the CH_3 and OH of the ketol to be eclipsed by the hydrogens of an adjoining CH_2, while this interaction can be partly staggered in c.

In conformation c, although the bond angles are far from the stereoelectronic ideal, the bond that is made/broken is at least not in the plane of the carbonyl. Thus, stereoelectronic requirements seem to dictate that this be the conformation of the immediate product and hence that the enolate which is to cyclize must do so from a conformation with the two CH_2's eclipsed.



A 6-membered ring aldol compound in a chair conformation has the C−C bond which breaks in a retro-aldol approximately orthogonal to the plane of the carbonyl group. The equilibrium angle between this C−C bond and the plane of the carbonyl is 47°.



The picture that we present partially contradicts the Dunitz−Burgi[47,48] hypothesis of a preferred or obligatory trajectory. It is not clear how strict the constraints upon angle of approach should be. Crystallography can tell the preferred angle but not the energetic rigor of the preference. Calculations suggest[50] (as would intuition) that in the bond-forming direction, the preference is small for large reaction distances and much greater as reaction proceeds and the new bond approaches its equilibrium length.

Thus, the contradiction may be more apparent than real. In the initial stages of reaction, our model deviates severely from the Dunitz−Burgi trajectory, but the energy cost of this deviation is likely to be small. In the later stages of bond forming, where the cost would be higher, the deviation is less, because addition leads to a new tetrahedral carbon, with close to ideal bond angles.

A common interpretation of Baldwin's rules is that they result from the strain implicit in following an obligatory Dunitz−Burgi trajectory.[12] Our atttempts to follow this logic showed that this is not a satisfactory picture. A starting conformation with the reacting atoms at the "obligatory" approach angle but not yet beginning to bond is of very high energy in these systems.

If instead Baldwin's rules arise from the need to achieve a conformation from which reaction can take place by a simple rotation and bond reorganization, then a simple and predictively useful picture is obtained. The success of our approach suggests that this is indeed the fundamental origin of these widely used rules.

Both processes (aldol addition and dehydration) in these reactions are multistep, and there might be a concern that the rate-determining step would not always be the C−C bond-making process. To allay this concern, we have constructed detailed reaction coordinate diagrams, shown in Figures 1−5. It is possible to make very plausible estimates of the rate constants for each of the subsidiary processes. The concern is very justified because for hexanedione the dehydration step may have rate-limiting proton transfer, and for the aldol additions of heptanedione, phenylhexanedione, and oxohexanal the proton transfer rate constant is sufficiently similar to the observed overall rate constant that one cannot be sure. In the cases of **1a**, **2a**, and **3b** we have performed kinetics experiments in D_2O

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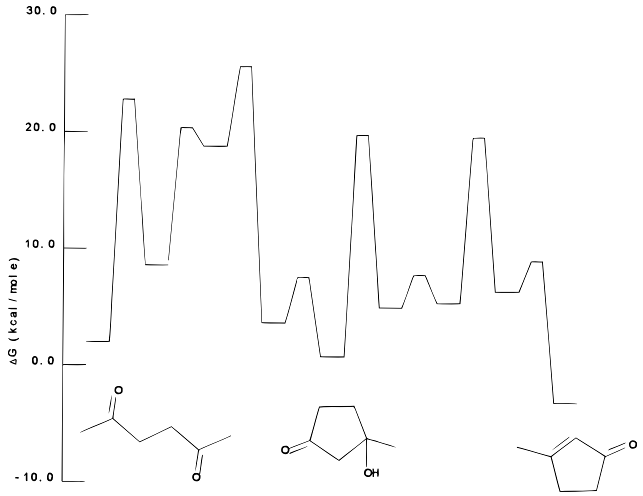

Figure 1. Reaction coordinate diagram for the aldol condensation of 2,5-hexanedione. The steps shown are as follows: ketone to enolate; enolate to reactive conformation (rate constant in the thermodynamically favored direction assumed to have $k = 10^{11}$ s^{-1}); reactive conformation to ketol alkoxide; ketol alkoxide to ketol (assumed to have $k = 10^{10}$ s^{-1}); ketol to enolate; enolate to reactive conformation (rate constant in the thermodynamically favored direction assumed to have $k = 10^{11}$ s^{-1}); reactive conformation to encounter complex with hydroxide; diffusional separation of hydroxide (assumed to have $k = 10^{11}$ s^{-1}).

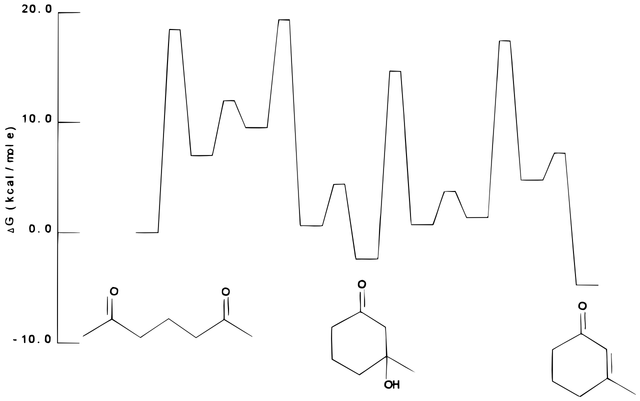

Figure 2. Reaction coordinate diagram for the aldol condensation of 2,6-heptanedione. See legend to Figure 1.

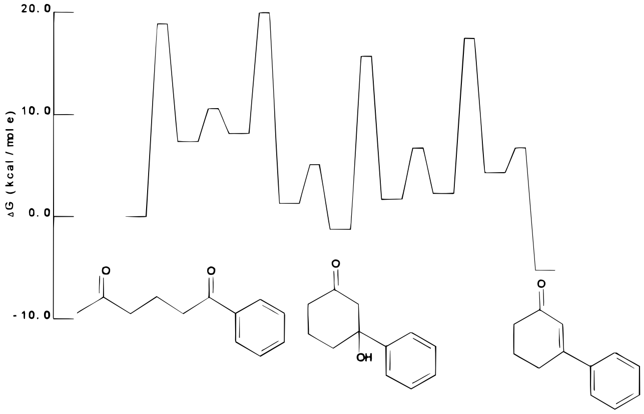

Figure 3. Reaction coordinate diagram for the aldol condensation of 1-phenyl-1,5-hexanedione. See legend to Figure 1.

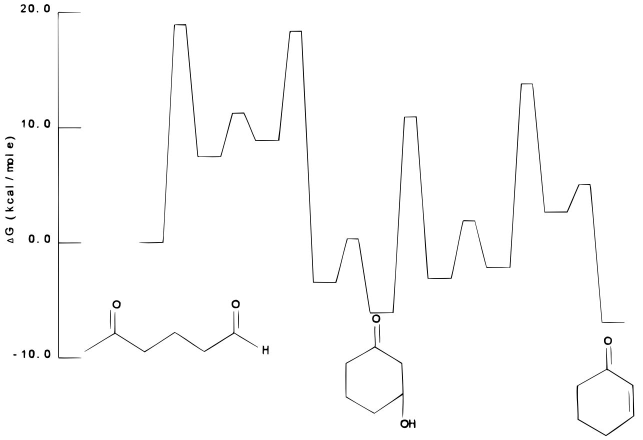

Figure 4. Reaction coordinate diagram for the aldol condensation of 5-oxohexanal. See legend to Figure 1.

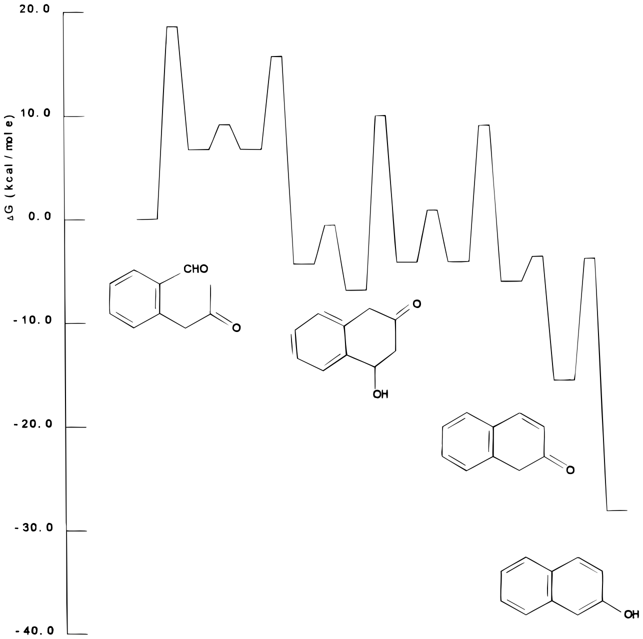

Figure 5. Reaction coordinate diagram for the aldol condensation of 2-(2-oxopropyl)benzaldehyde. See legend to Figure 1.

which confirm that proton transfer is partially rate limiting and allow extraction of the desired rate constant.

We have estimated the rate constants for enolate-forming reactions for all of the compounds considered. For the acyclic dicarbonyl compounds, the rate constants for hydroxide-catalyzed enolization of a methyl ketone were estimated starting from the known rate constants for acetone[51] and the estimated pK_a. The rate constant was taken as

$$\log k = \log k_{\text{acetone}} + (\text{d} \log k/\text{d} \log K)\Delta \log K$$

For the ketols, the rate of hydroxide-catalyzed enolate formation was estimated using the Marcus relation previously reported.[11] For both steps we may estimate the partitioning ratio, k_{-1}/k_2 or k_{-3}/k_4, from the observed rate constant and the estimated rate constant for proton abstraction. For the dehydration reactions of the ketols from hexanedione and phenylhexanedione these values are large enough that aldol addition is clearly rate limiting. For the intramolecular aldol addition of heptanedione the two rate constants are comparable, as was confirmed by an experiment in D_2O.

For the intramolecular aldol addition of **4a** the two rate constants are also comparable, but an experiment in D_2O to measure the rate ratio is not practical because of the lack of a reporter group like the methyl in **2a**/**2b** which would allow facile determination of the amount of **4b** formed.

Since estimates of k are unlikely to be better than within a factor of 2, we cannot have much confidence in the partitioning

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ratio for **4a**. However in the intermolecular analog, the rate constants for aldol addition of the enolate of acetone to acetone or acetaldehyde are similar, which suggests that in fact the observed rate constant may reflect at least partially rate-limiting C−C bond formation. Furthermore, the observed rate constant leads to a value of the intrinsic barrier, $\tilde{G}$, consistent with the other intrinsic barriers calculated. If the rate-determining step were in fact deprotonation, then by using the average $\tilde{G}$ value for aldol addition one would calculate a rate constant only 5-fold faster than the value we have used. Recently Koch et al.[52] reported a study of the aldol cyclization of 7-aryl-5-oxoheptanal, including an evaluation of the rate constant for carbon−carbon bond formation from the enolate. From their data we can calculate a rate constant for this step of $1.6 \times 10^5\ \mathrm{s}^{-1}$, which is similar to the value of $7 \times 10^4\ \mathrm{s}^{-1}$ calculated for the corresponding step for 5-oxohexanal using the observed rate constant and the estimated rate constant for deprotonation.

Estimation of ΔG_f(aq). For some time we have been concerned with the problem of estimating $\Delta G°_f$ and K_{eq} from molecular structure.[2,31] The systems discussed in this work provide an incentive and opportunity to apply these techniques to multifunctional compounds. Although estimation by group additivity[31,53] or molecular mechanics[32,49,54,55] is straightforward and generally reliable for monofunctional compounds, the problem is much more difficult for molecules with more than one potentially interacting functional group. It is clear that there are important effects on solvation of molecules from such interactions.[38,56] We tried various approaches and discovered that errors of over 3 kcal/mol were all too likely unless the following guidelines were employed:

In disproportionation reactions all important interactions between functional groups must be matched in both starting materials and products. If an interaction perturbs ΔG_t, it will surely perturb $\Delta G_{\mathrm{disproportionation}}$.

A molecular mechanics calculation can only be as good as the parameters involved in it—if they are not solidly based, the results will be unreliable. This applied to calculations involving enones. The published parameters are based on few compounds and must be regarded as preliminary.

Conclusions

1. Marcus theory can be applied to intramolecular aldol additions, leading to essentially the same intrinsic barrier as for intermolecular aldol additions.

2. It appears that effective molarities for rates of reaction can be calculated by thermodynamic estimation combined with Marcus theory, once appropriate parameters have been evaluated.

Experimental Section

Materials. 2,5-Hexanedione (98%), 3-methyl-2-cyclopenten-1-one (97%), and 3-methyl-2-cyclohexen-1-one (98%) were obtained from Aldrich; diacetone alcohol (97%) was from BDH and 2,4-dinitrophenylhydrazine (DNP) from Eastman. 2-Cyclohexen-1-one (enone-4, 98%) was from Aldrich and diacetone alcohol (97%) from BDH. All compounds were used as supplied but were checked by ^{1}H NMR and HPLC before being used in this work.

2,6-Heptanedione was synthesized from formaldehyde and diketene by published procedures.[57] Recrystallization from *n*-hexane gave pure 2,6-heptanedione (judged by HPLC): ^{1}H NMR (200 MHz, CDCl$_3$) δ (TMS) 1.78−1.92 (2H, quintet) CCH$_2$C, 2.14 (6H,s) CH$_3$CO, 2.45−2.52 (4H,t) CH$_2$CO.

2,5-Hexanedione Bis(2,4-dinitrophenylhydrazone) (Bis-DNPH). DNP solution (150 mL) was prepared by a standard method.[58] 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; 3.25g (100%) of yellow solid was obtained after filtration. Recrystallization from pyridine gave pure bis-DNPH (judged by HPLC): MS, *m/e* 474 (M$^+$, 5%); mp 259 °C, UV (CHCl$_3$) $\lambda_{\max}$ 367 nm (4.64). Literature:[59] mp 260 °C,[60] UV (CHCl$_3$) $\lambda_{\max}$ 362 nm (4.64).

3-Hydroxy-3-methylcyclopentanone was synthesized following a literature procedure[61] used 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-cyclopentanedione (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) and then water (10 mL). The ether layer was separated, the residue was extracted by ether (4 × 150 mL), and the combined ether extracts were dried over anhydrous MgSO$_4$. 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): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.51 (s, 3 H), 1.73 (s, 1 H), 1.84−2.50 (m, 6 H); MS, *m/z* 114 (M$^+$, 30%), 96 (100%). Literature[62] data for ketol-1: ^{1}H NMR (CDCl$_3$) δ 1.50 (s, 3 H), 1.90−2.60 (m, 7 H); MS, *m/z* 114 (M$^+$, 27%), 96 (100%).

1-Phenyl-1,5-hexanedione was synthesized by published procedures.[63] The product from the reaction was found to be pure (judged by HPLC), and the structure was confirmed by NMR: ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.05 (quintet, 2 H, CH$_2$*CH$_2$*CH2), 2.19 (s, 3 H, CH$_3$), 2.60 (t, 2 H, *CH$_2$*COCH$_3$), 3.05 (t, 2 H, *CH$_2$*COPh), 7.4−8.0 (m, 5 H, aromatic H); UV (H$_2$O) $\lambda_{\max}$ 246 nm (log ϵ = 3.96).

3-Hydroxy-3-phenylcyclohexanone (ketol-3) and 3-phenyl-2-cyclohexen-1-one (enone-3) were prepared following Woods's procedure,[61] by reaction of phenylmagnesium bromide with cyclohexadienone.

Recrystallization from ether gave pure 3-hydroxy-3-phenylcyclohexanone (judged by HPLC): ^{1}H NMR (300 MHz, CDCl$_3$) δ 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); ^{13}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−^{13}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).

1-Methylcyclopentene. 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, and 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

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extracts were dried over anhydrous Na_2SO_4. Distillation gave pure 1-methylcyclopentene (6.79 g, 34.8%) at 71 °C: ^1H 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: 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 (about 1 h). Excess ozone was purged from the reaction mixture with oxygen for 15 min and 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 Na_2HPO_4 (2.0 g, 14.1 mmol) at 0 °C under vigorous stirring. The function of Na_2HPO_4 is to destroy any acids in the reaction mixture and to prevent the formation of the dimethyl acetal of the desired aldehyde. The acetal was reported as the major product for this reduction method in the absence of Na_2HPO_4.[64] The reaction mixture was then stirred vigorously at 0 °C for 55 min. The byproduct, thiourea *S*-dioxide, and phosphates were filtered, and the methanol in the filtrate was removed by rotary evaporation. The 5-oxohexanal was extracted by CH_2Cl_2 (3 × 20 mL), and the CH_2Cl_2 was then removed by rotary evaporation. Distillation gave pure 5-oxohexanal: bp 90 °C at 3 Torr (0.41 g, 38.4%); ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1 H, CHO), 2.42−2.52 (m, 4 H, CH_2 CO), 2.11 (s, 3 H, CH_3), 1.86 (quintet, 2 H, CH_2 CH_2 CH_2). Lit:[65] ^1H NMR ($CDCl_3$) δ 9.86 (s, CHO), 2.70 (broad t, CH_2), 2.36 (s, CH_3), 1.8 (m, CH_2).

Methods. Reactions were carried out in a constant temperature bath at 25 °C, quenched by the addition of phosphoric acid to pH 7, and followed by HPLC on the quenched samples. HPLC analysis was carried out using a C18 Radial-Pak column, with suitable mixtures of acetonitrile in water as the eluting solvent. For reactions involving **1a**−**c** various solvent mixtures with 3−20% acetontrile were used; for **2a**−**c**, 5% acetonitrile was used; for **3a**−**c**, 35% acetonitrile was used; and for **4b**−**c**, 5% acetonitrile was used. Calibrations were carried out using suitable stock solution of the pure compounds except that diacetone alcohol was used as model compound for 3-hydroxy-3-methylcyclopentanone and 3-hydroxy-3-methylcyclohexanone.

Ozonolyses were carried out using a Hankin type S model 13 ozone generator; we thank Dr. S. Sharma for the use of this apparatus.

Kinetics. The reactions were carried out in a constant temperature bath at 25 °C, quenched by the addition of phosphoric acid (for alkaline conditions) or sodium phosphate (for acidic conditions), and followed by HPLC analysis of the quenched. 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 nonlinear least squares procedure to calculate the rate constants.

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. For the determination of the equilibrium concentrations of **3a** and **3b**, 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 stage and make the amplification of HPLC chromatograms easy.

For the kinetics involving **3b** in D_2O, we started with 4.01×10^{-5} M of ketol-3 in 0.010 M NaOD with ionic strength 1.0 M (KCl). The growth of the product, **3c**, was followed by UV at 289 nm. The UV absorbance−time data were fitted to a double-exponential equation by a nonlinear least-squares procedure.

Equilibrium Constant for Cyclization of 2,5-Hexanedione. The equilibrium concentration of enone was determined in the same way as for a kinetics experiment. The equilibrium concentration of 2,5-hexanedione was determined using the DNPH approach as follows: The reaction mixture was quenched by addition of phosphoric acid. To 100 mL of that quenched solution was added 200 mL of ca. 2×10^{-3} M DNP solution in 2 M hydrochloric acid. The mixture was stirred for 2 h at room temperature and extracted with $CHCl_3$ (3 × 50 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 in the concentrated $CHCl_3$ solution was determined by HPLC: eluent, 35% H_2O/75% CH_3CN; detector, Waters 490, 360 nm. The integration was used for quantitative analysis. The equilibrium concentration of 2,5-hexanedione was obtained by calibration using a known mixture with similar composition to the equilibrium reaction mixture. When this known solution was carried through the same procedure, the average overall recovery of 2,5-hexanedione as its bis-DNPH was 67% by HPLC analysis.

Equilibrium Constant for Cyclization of 2,6-Heptanedione. The concentration of 2,6-heptanedione in equilibrium with 3-methyl-2-cyclohexenone could be determined by direct HPLC analysis.

Equilibrium Constant for Hydration of 5-Oxohexanal. A 0.010 M solution of NaOD in D_2O with ionic strength 1.0 M (KCl) was placed in a Neslab Exacal EX300 constant temperaure 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 to give a solution 5.11×10^{-2} M in 5-oxohexanal. The reaction was then quenched by the addition of potassium dihydrogen phosphate after 50 s. Finally, the quenched reaction mixture was analyzed by ^1H NMR.

Determination of Free Energies of Transfer. In the determination of partition constant, the stock solution of the test compound in one solvent was stirred with another solvent at 25 °C overnight. For the determination of limiting solubility, the pure compound to be studied was stirred with the solvent at 25 °C overnight. Then the two phases were separated carefully by centrifugation, and the absolute concentrations were usually measured by HPLC: column, C_{18}; eluent, 80% water/20% CH_3CN. For the limiting solubility of 3-methyl-2-cyclohexen-1-one in water, the saturated aqueous solution was diluted with ethanol and the concentration was determined by UV ($\lambda = 234$ nm, $\log \epsilon = 4.08$[66]).

Molecular mechanics calculations were carried out using the MM3-(89)[54] program as obtained from QCPE. To treat enols, it was necessary to supply a parameter for torsion about a H−O−C(sp^2)−C(sp^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 about this bond 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,[67] hydrocarbons,[54,55] enones,[32] aldehydes and ketones,[49] and alkenes.[68] The results of MM3 calculations used in this paper are found in Table 6.

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