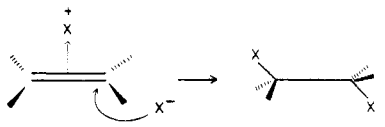
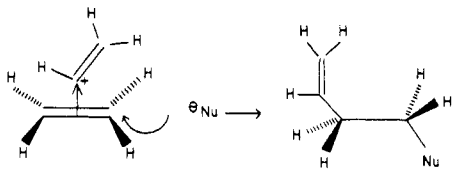
therefore take place at the exocyclic methylene to give derivatives of methylcyclopropane. However, π complexes can also react with nucleophiles by attack at a basal carbon atom, as in the second step in electrophilic addition to olefines; e.g. A corresponding



attack on the π complex corresponding to **1** can give a 3-butenyl derivative; e.g.



There is therefore no need to postulate rearrangement of **1** or **3** to the classical ion (**7**) in order to account for the formation of such products. This represents an example where the π-complex description of nonclassical carbocations is clearly superior to the "dotted line" representation.

Summary and Conclusions

The calculations reported here seem to account in a very satisfactory manner for the experimental evidence concerning the $C_4H_7^+$ system. MINDO/3 predicts both cyclopropylcarbinyl cation (**1**) and a modified form (**3**) of the cyclobutyl cation to be minima on the potential surface and also for the experimental evidence concerning their structures and interconversion. These results indicate once more the value of MINDO/3 in studies of reactions of carbocations and emphasize the inadequacy of other than "state-of-the-art" ab initio methods in this connection. The structures calculated for **1** and **3** are shown to conform to current qualitative ideas concerning molecular structure, and the calculations also account for the isomerization of cyclopropylcarbinyl and cyclobutyl derivatives to 3-buten-1-yl derivatives. This is without any need to postulate prior isomerization of the cyclopropylcarbinyl or cyclobutyl cations to the 3-buten-1-yl cation, which is predicted by MINDO/3 to rearrange without activation to the 3-buten-2-yl cation, as might indeed have been expected on general grounds.

A detailed analysis of the results of the calculations for **1** and **3** has also led to reasonable descriptions of their structures in terms of current qualitative theory. **1** is best represented as a π complex, formed by ethylene as donor and vinyl cation as acceptor, while **3** has a curous "nonclassical" structure which can be interpreted in terms of bonding known to occur in other nonclassical species.

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Registry No. 1, 14973-56-9; **2**, 19067-43-7; **4**, 1015-45-8; **5**, 10437-85-1.

Flash-Photolytic Generation of Acetophenone Enol. The Keto–Enol Equilibrium Constant and pK_a of Acetophenone in Aqueous Solution

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Abstract: Acetophenone enol has been generated by Norrish type II photoelimination of γ-hydroxybutyrophenone, and its rate of ketonization has been measured in dilute aqueous HCl solutions. These data, in combination with the specific rate of acid-catalyzed enolization of acetophenone, give a value of the keto–enol equilibrium constant which is in good agreement with another result based upon enolization and ketonization rate constants measured in NaOH solutions. The average of these determinations gives $pK_E = 7.90 \pm 0.02$. This, when combined with the known acid-dissociation constant of acetophenone enol, leads to $pK_a^K = 18.24 \pm 0.03$ for the acidity constant of acetophenone ionizing as a carbon acid. The present results allow an estimate of the specific rate of proton transfer from H_3O^+ to the β-carbon atom of acetophenone enolate ion, $k = (4.2 \pm 1.2) \times 10^{10}$ M^{-1} s^{-1}, which is so great as to suggest that this reaction occurs through proton transfer down hydrogen-bonded solvent bridges between acid and substrate.

Simple enols have long been of interest because they are essential intermediates in a number of important chemical and biological reactions, and also because they have a fascinating chemistry of their own.[1] Elucidation of this chemistry, however, has been impeded by the thermodynamic instability of simple enols, and also by the speed with which they revert to their keto tautomers.

We have recently shown that these difficulties may be overcome by the use of modern flash-photolytic methods.[2] It is well-known that Norrish type II photoelimination of structurally appropriate carbonyl compounds produces enols,[3] and the subsequent reactions of enols so generated may be monitored by rapid spectroscopic techniques. We have already reported our use of these methods to generate the enols of acetophenone, eq 1,[2a] and acetone[2b] in

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[‡] University of Basel.

(1) For a recent review, see: Hart, H. *Chem. Rev.* **1979**, *79*, 515–528.
(2) (a) Haspra, P.; Sutter, A.; Wirz, J. *Angew. Chem.* **1979**, *91*, 652–653; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 617–619. (b) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.
(3) McMillan, G. R.; Calvert, J. G.; Pitts, J. N., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 3602–3605. Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168–177. Henne, A.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 435.

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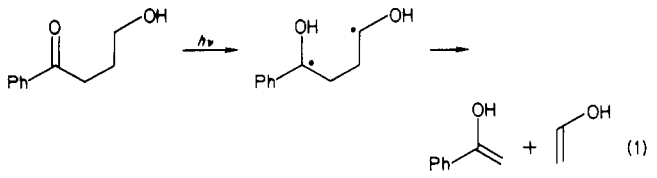
basic solution and our measurements of their rates of ketonization in that medium. In this paper we describe companion experiments



(1)

on acetophenone in aqueous acids. The results of this work, when combined with data we obtained before[2a] plus specific rates of enolization measured here by halogen scavenging, provide the first reliable, absolute value of the keto–enol equilibrium constant for acetophenone in aqueous solution. This results, together with the known acid-dissociation constant of acetophenone enol,[2a] also leads to the first accurate value of the acidity constant of acetophenone ionizing as a carbon acid in a wholly aqueous solvent.

Experimental Section

Materials. γ-Hydroxybutyrophenone was prepared from β-benzoylpropionic acid according to the method of Ward and Sherman[4] as modified by Wagner and Kemppainen.[5] All other materials were best available commercial grades.

Flash Photolysis. The kinetic flash-photolysis system was of conventional design.[6] The excitation flash of 20-μs width at half-height was produced by an electrical discharge of 1000-J energy through two parallel quartz tubes of 16-cm length and 1-cm diameter which were maintained at a reduced air pressure of ca. 6 kPa. A stabilized xenon arc (Osram XBO 250 W/4, Suprasil quartz) was used as a source of monitoring light; this was passed through the 10-cm sample cell and a monochromator with 2-nm resolution and was detected by an EMI 9658 B photomultiplier. The signal from the photomultiplier was captured by a Datalab DL 905 transient recorder, passed to a computer, and analyzed by least-squares fitting to a single exponential. Aqueous solutions of γ-hydroxybutyrophenone (10^{-4} M) were prepared immediately before use and were exposed to no more than two flashes each. The decay kinetics of acetophenone enol (acidic solutions) and enolate ion (basic solutions) were monitored at 270 and 300 nm, respectively. Degassing the samples to less than 0.1 Pa by the freeze–thaw technique had no significant effect on the intensities or decay kinetics of the transient absorptions.

Enolization Kinetics. Rates of enolization of acetophenone in sodium hydroxide solutions were determined through bromine scavenging by monitoring the OBr^- absorbance at λ 330 nm. Measurements were made with a Cary Model 118C spectrometer with the cell compartment thermostated at 25.0 ± 0.05 °C. Initial concentrations of acetophenone were 1×10^{-4} M, those of OBr^- were 3×10^{-3} M, and those of NaOH were $3–9 \times 10^{-2}$ M; under these conditions the reaction is a pseudo-first-order process. Initial absorbances were of the order of 1.0 and final values about 0.9, indicating a bromine:ketone stoichiometry of 3:1. With the spectrometer operating in a zero-suppression mode (A = 0.9–1.0 full scale), good accuracy could be obtained, and the data were found to conform to the first-order rate law precisely. Observed rate constants were evaluated by linear least-squares analysis of the relationship between ln ($A - A_\infty$) and time; replicate values agreed within 1–2% (see Table S2[7]).

Results

Observed first-order rate constants for the ketonization of acetophenone enol were determined in aqueous HCl over the concentration range [HCl] = 0.005–0.040 M; ionic strength was maintained constant at 0.10 M through the addition of NaCl. These data are summarized in Table S1[7] and are displayed in Figure 1. As this figure shows, these rate constants are accurately proportional to acid concentration; least-squares analysis gave the hydronium ion catalytic coefficient $k_{H^+} = (1.25 \pm 0.02) \times 10^3$ M^{-1} s^{-1} and the intercept $k_0 = 1.9 \pm 0.5$ s^{-1}.

This rate constant for the ketonization of acetophenone enol (**1**) is 23 times that for the hydronium ion catalyzed hydrolysis of methyl α-styryl ether (**2**),[8] which is in good agreement with

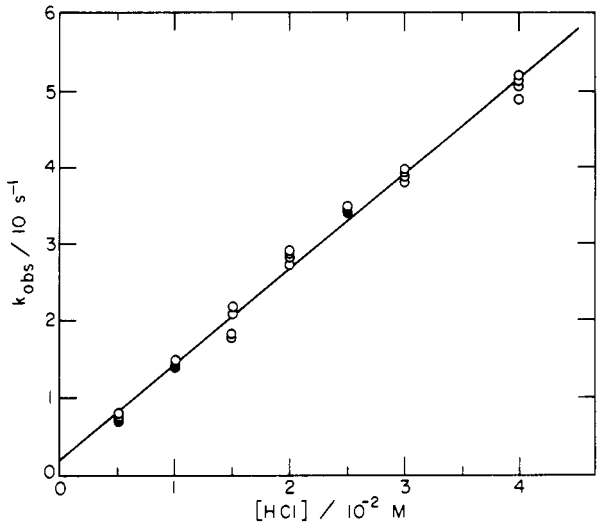
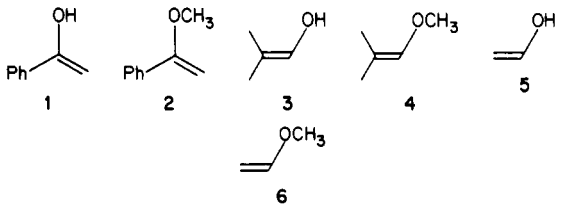


Figure 1. Relationship between the hydrochloric acid concentration and the observed first-order rate constants for the ketonization of acetophenone enol in aqueous solution at 25 °C.

the ca. 20-fold greater reactivity usually found for enols over the corresponding vinyl ethers; e.g., **3**[9] is 23 times more reactive than **4**[10] and **5** is 28 times more reactive than **6**.[11]



First-order specific rates of enolization of acetophenone catalyzed by hydroxide ion were determined over the concentration range [NaOH] = 0.03–0.09 M in solutions whose ionic strength was maintained at 0.10 M through the addition of NaCl. The data so obtained are summarized in Table S2.[7] These observed rate constants proved to be accurately proportional to base concentration, and linear least-squares analysis gave the hydroxide ion catalytic coefficient $k_{HO^-} = 0.249 \pm 0.003$ M^{-1} s^{-1} and a zero intercept $k_0 = -(2.05 \pm 1.70) \times 10^{-4}$ s^{-1}. This result is in good agreement with $k_{HO^-} = 0.244$ M^{-1} s^{-1} reported earlier for an unspecified ionic strength[12] and is consistent with $k_{HO^-} = 0.236$ M^{-1} s^{-1} determined at an ionic strength of 1 M.[13]

Discussion

The equilibrium constant for the isomerization of acetophenone to its enol, eq 2, is equal to the ratio of enolization to ketonization rate constants: $K_E = k^E/k^K$. This equilibrium constant may

(2)

therefore be evaluated from the rate constant for ketonization catalyzed by the hydronium ion determined here, $k_{H^+}{}^K = (1.25 \pm 0.02) \times 10^3$ M^{-1} s^{-1}, and the specific rate of enolization catalyzed by the same species, $k_{H^+}{}^E$. Rates of hydronium ion catalyzed enolization of acetophenones have been measured by halogen scavenging,[14] but the reaction is slow and these measurements were

(4) Ward, H. P.; Sherman, P. D. *J. Am. Chem. Soc.* **1968**, *90*, 3812–3817.
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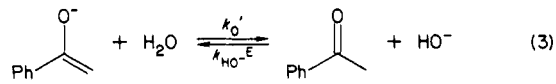
therefore performed in moderately concentrated acids. Determination of a dilute solution rate constant from such data requires extrapolation down an appropriate acidity function. The X function[15] seems to be the best currently available quantity for this purpose,[16] and a recent analysis[14b] of both old[14a] and new[14b] data for acetophenone with this method gives $k_{H^+}^E = (1.63 \pm 0.03) \times 10^{-5}$ M^{-1} s^{-1}.[17] This leads to $K_E = (1.31 \pm 0.03) \times 10^{-8}$, $pK_E = 7.88 \pm 0.01$.

Another completely independent estimate of this equilibrium constant may be obtained from measurements made in basic solution. In our previous study of the ketonization of acetophenone enol in basic solutions,[2a] we were able to determine the rate constant for ketonization through carbon protonation of the enolate ion by a water molecule, eq 3; that work was done at ambient



(3)

temperature, but we have now repeated the experiments at 25 °C and have obtained $k_0' = (7.22 \pm 0.20) \times 10^3$ s^{-1}.[18] The reverse of this reaction is hydroxide ion catalyzed enolization of acetophenone, the specific rate constant of which we have determined in the present study to be $k_{HO^-}^E = 0.249 \pm 0.003$ M^{-1} s^{-1}. The ratio of these rate constants is equal to the equilibrium constant for this reaction, which in turn is equal to the self-ionization constant of water divided by the keto–enol equilibrium constant for acetophenone and the acidity constant of acetophenone enol: $k_0'/k_{HO^-}^E = K_w/(K_E K_a^E)$. We have previously determined the latter to be $K_a^E = (4.57 \pm 0.26) \times 10^{-11}$ for wholly aqueous solution,[2a] and a combination of this with k_0' and $k_{HO^-}^E$ plus the known value of K_w[19] leads to $K_E = (1.20 \pm 0.07) \times 10^{-8}$, $pK_E = 7.92 \pm 0.03$.

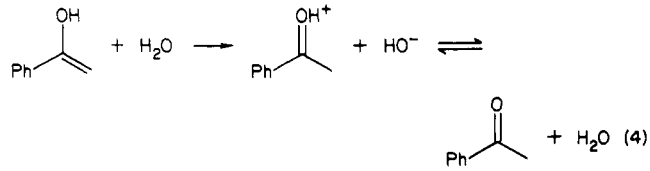
This result is in excellent agreement with the value obtained in acidic solutions; the average of the two, $K_E = (1.25 \pm 0.06) \times 10^{-8}$, $pK_E = 7.90 \pm 0.02$, is the best estimate of this constant for aqueous solution at 25 °C.[21]

This value is quite different from results obtained for the keto–enol equilibrium constant of acetophenone measured by the classic halogen titration method, $pK_E = 3.46$[22] and 4.72.[23] That method, however, is known to present difficulties when enol contents become very low.[24] Estimates somewhat closer to our result are provided by several approximate methods which have been developed recently. For example, $pK_E = 6.7 \pm 1.0$ from a thermodynamic cycle containing an unknown quantity estimated by using a free energy relationship,[25] and $pK_E = 6.6$ on the assumption that rates of ketonization of enols are equal to rates of hydrolysis of the corresponding methyl enol ethers;[26] the latter was once a seemingly reasonable assumption but is now known to be not entirely correct (vide supra). Another of these recently developed methods requires an estimate of a rate constant believed to be encounter controlled and gives $pK_E = 8.15 \pm 0.30$.[14c] Although these newer methods provide values which are in good to moderate agreement with our result, it must be remembered that they rely on extraempirical assumptions. Our result, on the other hand, is based completely on experimentally determined quantitites and is, in that sense, an absolute value.

The good agreement between our result and the last of the approximate values mentioned above means that the estimate of the rate constant which this method uses is essentially correct. Our result allows this rate constant, that for the encounter-controlled reaction of bromine with acetophenone enol, to be fixed more precisely. Thus, we now obtain $k = (2.8 \pm 0.2) \times 10^9$ M^{-1} s^{-1}, as opposed to the estimate made before, $k = 5 \times 10^9$ M^{-1} s^{-1}, which was considered to be good only to within a factor of 2.[14c]

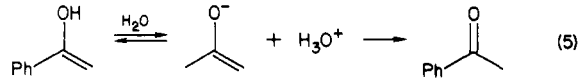
The keto–enol equilibrium constant determined here may be combined with the acid-dissociation constant of acetophenone enol, which we measured before,[2a] to give the acidity constant of the ketone ionizing as a carbon acid. The result, $K_a^K = K_E K_a^E = (5.74 \pm 0.42) \times 10^{-19}$, $pK_a = 18.24 \pm 0.03$,[21] is somewhat less than the value we reported earlier,[2a] but that result was based upon a keto–enol equilibrium constant[23] which is now superseded by the present work. Our present result does agree with an early estimate made by using rate–equilibrium relationships, $pK_a^K = 19.2 \pm 1.0$,[27] but it is significantly different from $pK_a^K = 15.8 \pm 1.0$[23] based upon an indirectly estimated pK_a^E[28] and a value of K_E measured by halogen titration.[23] The present result shows acetophenone to be a considerably stronger acid in water than it is in dimethyl sulfoxide solution, for which $pK_a^K = 24.7$ has recently been determined;[29] this is to be expected on the basis of the solvent effect on the stability of the enolate ion product of this ionization reaction.

It is interesting that the present measurements of the rate of ketonization of acetophenone enol in acid solutions show a significant uncatalyzed term or "water" reaction: the relationship between k_{obsd} and [HCl] extrapolates to the intercept $k_0 = 1.9 \pm 0.5$ s^{-1} at zero acid concentration (see Figure 1). This term could, in principle, represent reaction by two different stepwise routes: (1) carbon protonation of the enol by water to give oxygen-protonated acetophenone plus hydroxide ion followed by conversion of these products to acetophenone and water, eq 4,



(4)

or (2) ionization of the enol to enolate ion and a solvated proton followed by ketonization of enolate by the latter, eq 5.



(5)

In acid solutions the latter reaction will show an overall zero-order dependence upon $[H_3O^+]$, for H_3O^+ is produced in the equilibrium forming the enolate ion and is then consumed in the subsequent carbon-protonation step. The specific rate of reaction by the route of eq 4, however, must be very much slower than the observed value of k_0, inasmuch as k_{H^+} for ketonization of the enol is only 1250 M^{-1} s^{-1}: simple application of the Brønsted relation with an exponent of one-half predicts a rate constant for this route of the order of 10^{-4} s^{-1}. All of k_0 may thus be assigned to reaction by the route of eq 5. The observed rate constant for this process is equal to $K_a^E k_{H^+}'$, where k_{H^+}' is the specific rate of the second step, carbon protonation of enolate by H_3O^+. Since K_a^E is known, k_{H^+}' may be evaluated as $k_0/K_a^E = (4.2 \pm 1.2) \times 10^{10}$ M^{-1} s^{-1}.

(14) (a) Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791–2798. (b) Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2952–2959. (c) Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401.

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(16) Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M. F. *Can. J. Chem.* **1983**, *61*, 249–256.

(17) A value of 1.22×10^{-5} M^{-1} s^{-1} is estimated for this rate constant in ref 14c on the basis of the unverified assumption that the acidity dependence of this reaction is the same as that of the enolization of acetone.

(18) This is the average of four measurements in 0.10 M NaOH at 25.0 ± 0.2 °C.

(19) Taken as 1.59×10^{-14} M^2 at ionic strength = 0.10 M on the basis of activity coefficients recommended by Bates.[20]

(20) Bates, R. B. "Determination of pH. Theory and Practise"; Wiley: New York, 1973; p 49.

(21) This equilibrium constant is made up of quantities measured at, or, in the case of $[H^+]$, calculated for, an ionic strength of 0.10 M; it is therefore a *concentration quotient* which refers specifically to ionic strength = 0.10 M.

(22) Gero, A. *J. Org. Chem.* **1954**, *19*, 1960–1970.

(23) Novak, M.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 2494–2498.

(24) See, e.g.: Hine, J. "Structural Effects on Equlibria in Organic Chemistry"; John Wiley: New York, 1975; pp 279–280.

(25) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1979**, *57*, 240–248.

(26) Guthrie, P. J. *Can. J. Chem.* **1979**, *57*, 797–802.

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This is a very large rate constant. Its size shows that the activating effect which a negatively charged oxygen substituent exerts upon electrophilic attack of H_3O^+ on carbon–carbon double bonds is very powerful indeed. This activation is many orders of magnitude greater than that of a nonionized hydroxyl group, as shown by the ratio $k_{H^+}'/k_{H^+} = (3.3 \pm 0.9) \times 10^7$.

Although this ratio is very large, it is nevertheless an order of magnitude smaller than those we have observed for other enolate ion–enol pairs.[9,30] This suggests that in this case k_H' is reduced because the enolate reaction here might be a diffusion-controlled process, an idea reinforced by the very large value of this rate constant. This rate constant is, in fact, so great as to imply that proton transfer occurs via hydrogen-bonded solvent bridges between the substrate and H_3O^+. Such a Grotthuss chain mechanism is the accepted mode of proton transfer between oxygen and nitrogen acids and bases in aqueous solution,[31] but it has heretofore been generally believed that such solvent bridges do not play a role in proton transfers involving carbon.[32]

It is possible, on the other hand, that the uncatalyzed term observed here is due to reaction by a non-diffusive process, for example, a concerted cyclic proton switch down a chain of water molecules which moves H^+ directly from enol oxygen to the β-carbon atom in a single reaction step. Another possibility which retains the general stepwise character of eq 5, but yet avoids diffusive encounter, involves ionization of the enol and then protonation on carbon of the enolate ion by the solvated proton before these ions, once formed, can diffuse apart; a "one-encounter" mechanism of this kind has been proposed for the corresponding uncatalyzed term in the ketonization of acetone enol.[33]

Acknowledgment. We are grateful to Professor William P. Jencks for pointing out the possibility of a one-encounter mechanism and to the Natural Sciences and Engineering Research Council, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Swiss National Science Foundation (Project No. 2,470-82), and the Ciba Stiftung for their financial support of this work.

Registry No. Acetophenone enol, 4383-15-7; acetophenone, 98-86-2; acetophenone enolate ion, 34172-40-2; γ-hydroxybutyrophenone, 39755-03-8.

Supplementary Material Available: Tables of rates of ketonization and bromination of acetophenone (2 pages). Ordering information is given on any current masthead page.

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(32) See, e.g.: Albery, W. J. "Proton Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 289–290.
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Proton NMR Investigation of the Rate and Mechanism of Heme Rotation in Sperm Whale Myoglobin: Evidence for Intramolecular Reorientation about a Heme Twofold Axis

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Abstract: The characterization of the initial product upon reacting apomyoglobin with hemin is shown to be the holoprotein with the hemin 1:1 rotationally disordered about the α-γ-meso axis. Determination of the rate of equilibrium of the disordered state as a function of pH and hemin 2,4 substituents has shown that the rate is highly pH dependent with a minimum near neutral pH and that the relative rates at any pH depend critically on the 2,4 substituent; the slowest rate is observed for native hemin (2,4-vinyl), the fastest for deuterohemin (2,4-hydrogen), and intermediate for mesohemin (2,4-ethyl). Competitive reconstitution for two different hemins reveals that the forward rate is independent of the 2,4 substituent, and hemin replacement reactions yield the relative binding constants for the various hemes. These two sets of data yield the relative dissociation rates for the various hemes which are shown to be semiquantitatively the same as the heme reorientation rates, indicating that disruption of the heme cavity is the rate-determining step in the reorientation. However, competition experiments between heme reorientation and heme replacements reveal that reorientation occurs faster than replacement, dictating that the reorientation occurs by an intramolecular mechanism, i.e., without leaving a "protein cage".

Both the equilibrium structure and the mechanism of formation of myoglobin from heme and apoprotein have long been considered to be well understood. X-ray studies[2,3] have revealed a highly folded protein with a unique orientation of the heme and optical stopped-flow studies.[4,5] had indicated a single bimolecular reaction between heme and apoprotein which yielded the native holoprotein within 1 ms.

Both of these views have recently been shown to be untenable on the basis of high-resolution ^1H NMR data on sperm whale myoglobin.[6,7] First, the solution ^1H NMR spectrum clearly shows that there are two slowly interconverting protein forms in solution at equilibrium which differ in the orientation of the heme by a 180° rotation about the α-γ-meso axis[6,8] (Figure 1). The dominant (~90%) component has the same heme orientation as found

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