Tetrahedron Vol 45, No 16, pp 4913–4938 1989
Printed in Great Britain

0040-4020/89 $5 00+ 00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 257

STEREOELECTRONIC CONTROL IN THE REACTIONS OF KETONES AND THEIR ENOL(ATE)S

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(*Received in USA* 9 *June* 1988)

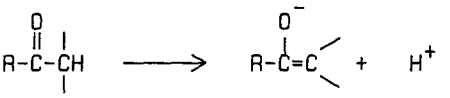
CONTENTS

1. INTRODUCTION

The interconversion of aldehydes and ketones with their enols is one of the most widely investigated reactions in organic chemistry This reaction serves as the prototype for a variety of isomerizations that involve proton transfer between carbon and an electronegative atom, such as aci-nitro and imine–enamine tautomerizations. In addition to the importance of these processes in synthetic chemistry, the reactions of enols and enolates provide an opportunity to examine basic mechanistic principles Since the rate-limiting step in the formation of these species is proton transfer from carbon to oxygen, this reaction is an excellent vehicle for the investigation of structure–reactivity relationships, steric effects, electronic effects, isotope effects, and stereoelectronic effects in simple systems Excellent reviews have appeared that discuss enolization chemistry with regard to some or all of these aspects.[1]

The concept of stereoelectronic control, as originally proposed by Corey and Sneen in 1956,[2] states that loss of a proton from an aldehyde or ketone to produce an enolate ion (eqn 1) or from a protonated carbonyl compound to give an enol (eqn 2) will occur perpendicular to the plane defined by the sp^2 orbitals of the carbonyl carbon (1) The stereoelectronic requirement is due to the need for continuous overlap between the carbon—hydrogen bond that is being broken and the π-orbital of the carbonyl group. This condition can only be satisfied if the C—H bond is per-

pendicular to the CO group Other conformations of the transition state do not allow overlap to occur as efficiently and should be of higher energy The most simple demonstration of this requirement is the drastic conditions necessary for exchange of bridgehead protons of bicyclic ketones such as **2** (2 M K^+ O*t*Bu$^-$, 200°C, two days for 25% exchange of H_1) [3]



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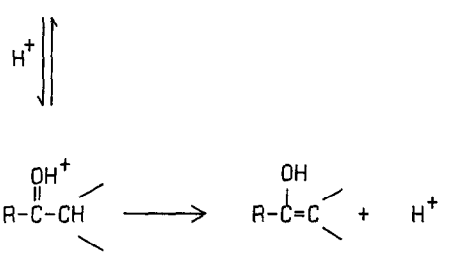

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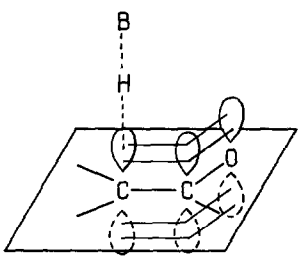
The concept of stereoelectronic control has been extended to encompass halogenations and alkylations of ketones through enolic transition states [4] Similarly, decarboxylations of β-keto acids, retroaldol condensations, hydrolysis of enamines and related reactions should be subject to the same constraints on the geometry of their transition states The majority of the investigations of the effects of stereoelectronic control, however, have dealt with the relative kinetic acidities of two hydrogens bound to the same carbon, where the C—H bond of one of the hydrogens is more nearly aligned than the other with the π-orbital of the carbonyl



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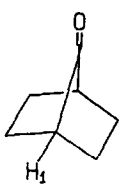

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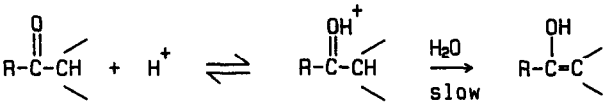
This report will review the application of stereoelectronic principles to the formation and reactions of enols and enolates, both in simple organic systems and in enzymatic processes Other aspects of ketonization/enolization reactions will also be considered, as it is difficult to design systems that isolate the stereoelectronic factor from other effects on the stability of transition states In order to assess the relative contributions of these different factors to the rates of enolization and ketonization, it is necessary first to discuss the mechanism of the reaction and the evidence concerning the nature of the transition state.

2. MECHANISM OF ENOLIZATION

2 1 *General*

Three different pathways are operable in the enolization of carbonyl compounds in aqueous solution, depending on pH (eqns 3–5) (1), initial protonation of the CO group in acid, followed by loss of an α-proton, (2) direct abstraction of a proton from the α-carbon by hydroxide ion to give an enolate ion, followed by protonation of the enolate to generate the enol, and (3) abstraction

of an α-proton by a water molecule, forming an enolate ion that is subsequently protonated to give the enol. The first of these mechanisms is acid-catalyzed and shows an increase in rate with increasing acid concentration in relatively dilute acid solutions In more concentrated solutions ($H_0 < ca\ -4$) the rate diminishes due to a decrease in the availability of water molecules to act as a base for the proton abstraction in the second step and/or to complete the protonation of the CO The rate due to the second mechanism increases with increasing pH because of the requirement for hydroxide ion in the transition state of the reaction The last mechanism involving abstraction of a proton by a water molecule requires the rate of the reaction to be independent of pH, since the rate-limiting step involves only neutral species



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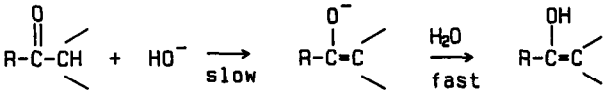

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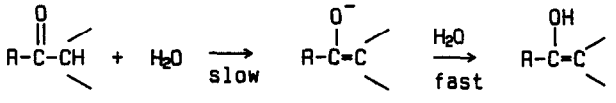

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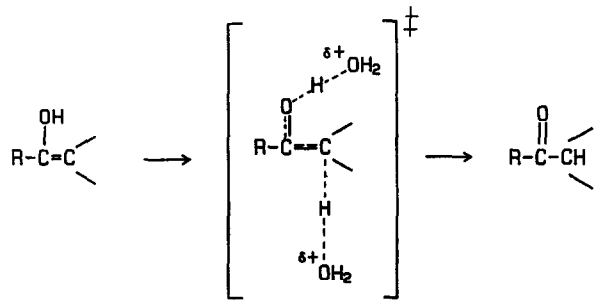
Acid-catalyzed enolization has been known for many years and has been extensively examined for a variety of carbonyl compounds Substantial evidence, including inverse solvent isotope effects,[5] primary hydrogen isotope effects,[5,6] acidity behavior,[7] and the observation of general acid catalysis[8] points to a mechanism in which the first step is a rapid equilibrium protonation of the CO group, followed by a rate-limiting proton transfer to a molecule of solvent Results with the acid-catalyzed hydrolysis of enol ethers as a model system for the ketonization of enols have been interpreted to support the two-step mechanism for acid-catalyzed enolization [8]

More recently, primarily through the work of Kresge,[9] Capon[10] and their collaborators, it has been possible to examine this reaction in the thermodynamically favorable direction, ketonization of the enol These research groups have been able to generate enols in greater than equilibrium concentrations by several techniques, including flash photolysis and rapid hydrolysis of enol precursors Other investigators have used the enzymatic hydrolysis of enol phosphates,[11] as well as flash photolysis[12] to produce unstable enols in aqueous solution In addition, the chemistry of 'hindered' enols has been examined by Rappoport *et al* [13] Although most work on the ketonizations of enols in acid is consistent with the two-step mechanism, Capon *et al* [10c,e] have interpreted their kinetic results with vinyl alcohol (the enol of acetaldehyde) and other enols in terms of a concerted reaction with transfer of the alcoholic proton occurring simultaneously with protonation of the double bond (eqn 6) However, this interpretation has recently been challenged [9d,f]



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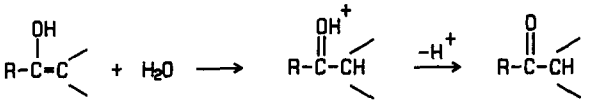
The question of concertedness in enolization has been discussed in some detail by Toullec in a recent review [1d] Several investigators have found a third-order term in the general acid-catalyzed component of enolization [14] This term has been interpreted as being due to concerted catalysis by two molecules of the general acid [14c] However, strong arguments against extending the concerted mechanism to enolization catalyzed by hydronium ion, with water acting as the general base, have been presented [1d,14c] In order for proton transfer between the OH group of the transition state and water to be thermodynamically favorable, it is necessary for the acidity of the OH group to be greater than that for hydronium ion Since fully formed hydroxycarbonium ions are only slightly more acidic than the hydronium ion, it is unlikely that this condition will be satisfied in the transition state for ketonization [1d,e]

Base-catalyzed enolization has been examined in both the enolization and ketonization directions and there is little controversy about the reaction mechanism Large primary isotope effects[10c,15] and the occurrence of general base catalysis[9d,e,10c,16] are consistent with a simple proton abstraction from the α-carbon to generate the enolate ion, which may subsequently be protonated to give the enol if the pH of the solution is lower than the pK_a of the enol. Generally pK_as of simple enols are in the range of 10 to 12 [1e,9]

Investigation of pH-independent enolization is hampered by the sluggishness of the reaction, but recent work on the ketonization of enols has allowed this process to be examined in this direction [9,10] *A priori*, three mechanisms are reasonable for the reaction in neutral solution (1) direct protonation of the enol by water to give a hydroxycarbonium ion, either with concerted proton transfer of the enolic proton to another water molecule or simply through H-bonding by water at that site (eqn 7), (2) ionization to the enolate ion, followed by protonation of the enolate by hydronium ion (eqn 8), or (3) a concerted proton transfer from the enolic oxygen to the α-carbon of the product ketone, possibly through one or more intervening water molecules (eqn 9)



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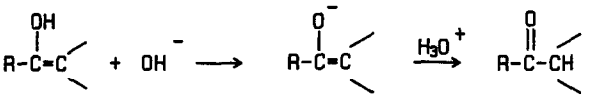

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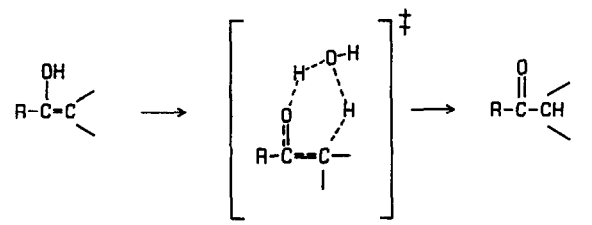


(9)

Direct protonation of the enol by water can be most easily ruled out since the pH-independent reaction generally has a half-life of seconds to minutes,[9,10c,e] whereas the corresponding hydrolysis of enol ethers under these conditions is too slow to be observed Since addition of a proton to enol ethers is generally only 20–70 times slower than proton addition to the corresponding enols,[9d,10e] protonation by water should be observable with enol ethers if that reaction is occurring with enols Although a concerted mechanism for the uncatalyzed reaction has been proposed by Capon *et al* [10e] on the basis of a rate ratio for hydroxypropadiene/vinyl alcohol of 74 for the base-catalyzed reaction and 0 6 for the uncatalyzed reaction, Chiang *et al* [9a] have argued, on the basis of free energy relationships that a stepwise mechanism (eqn 8) is most consistent with the available data

2 2 *Nature of the transition state*

The position of the transition state along the reaction coordinate is an important consideration in the evaluation of the magnitude of the stereoelectronic effect in enolization/ketonization reactions The stereoelectronic theory postulates that delocalization of the electron pair of the C—H bond with the π-orbital of the CO is an important factor in the transition state Thus, a very early transition state (in the enolization direction), in which there is little bond cleavage and little possibility for delocalization of the electrons, would be inconsistent with a large stereoelectronic effect Similarly, as will be discussed later, a very late transition state is also inconsistent with a large stereoelectronic effect for the discrimination of two different α-hydrogens

Brønsted values for the base-catalyzed enolization of a variety of ketones have been determined Values of $\beta > 0\ 5$ (e g 0 88 for carboxylate catalysis[16a] and 0 73 for substituted pyridine catalysis[17]) for the enolization of acetone have been interpreted in terms of a product-like transition state [1d] Since carboxylic acids and pyridinium ions are substantially more acidic than simple ketones (pK_a of acetone is 19 2[9b]) this result is in agreement with what would be expected from considerations based on the Hammond postulate Similarly, Brønsted α values of 0 37 for the protonation of isobutyrophenone enolate by a series of carboxylic acids[9e] and 0 23 for the protonation of acetaldehyde enolate by carboxylic acids[10c] are consistent with an enolate-like transition state. Measurements of the variation of the isotope effect as a function of the pK_a difference between the base and the ketone[15] are also in accord with a transition state that involves a proton that is more than half-transferred in the transition state Thus, both primary kinetic isotope effects and Brønsted relations argue for an enolate ion-like transition state in this reaction

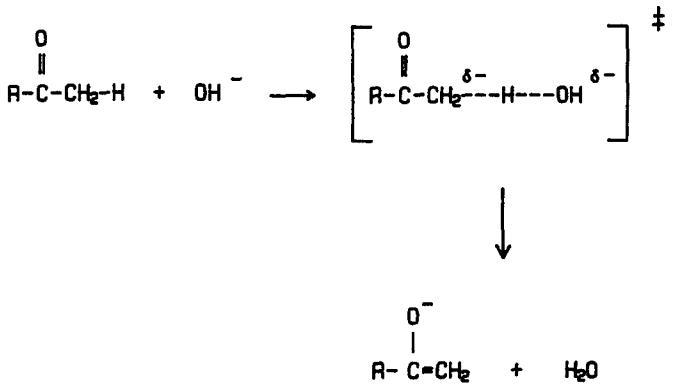
Similar arguments concerning the position of the transition state along the reaction coordinate for the acid-catalyzed process lead to the conclusion that the transition state is located earlier on the reaction coordinate for the acid-catalyzed reaction than for the base-catalyzed one Assuming conservation of bond order at hydrogen, the Brønsted α value of 0 55 for carboxylic acid-catalyzed enolization of acetone[16a] can be converted to a β value of 0 45 for proton abstraction from the protonated ketone, suggesting a transition state in which the proton is approximately half-transferred A Brønsted α of 0 58 for protonation of the enol of isobutyrophenone[9a] is also consistent with this model Furthermore, the large values of primary isotope effects observed in acid-catalyzed enolization of ketones indicate a transition state in which proton transfer is nearly half completed

It should be noted that the above arguments are concerned with the position of the proton in the transition state An early transition state is one in which there is very little proton transfer from the (protonated) ketone to the base, a late transition state has almost complete proton transfer to the base However, the extent of reaction (reaction coordinate) cannot always be described by only one variable When there is more than one structural change during a reaction these changes may not occur in parallel Thus, a transition state that is characterized by substantial proton transfer might only have a minimal change in the overall geometry of the molecule While Brønsted values and primary isotope effects might be good probes for the extent of proton transfer, the conclusions drawn from these studies may not be applicable to other reaction progress variable(s), such as heavy-atom reorganization

Bernasconi[18a] has discussed at some length the possibility of 'transition state imbalance' in connection with carbanion-forming reactions He has suggested that "whenever resonance is involved as a reactant or product stabilizing factor in a reaction, this factor will develop late [in the product] or be lost early [in the reactant] " Application of this principle to the enolization of ketones leads to the expectation that resonance stabilization of the transition state is not as large as is indicated from measures of proton transfer as a probe for electron delocalization in the transition state A better probe for the extent of resonance stabilization at the transition state would be a Brønsted coefficient based upon structural changes in the ketone

Chiang *et al* [9f] have carried out such an analysis for proton transfer to hydroxide ion from acetaldehyde, acetone and acetophenone, using experimentally determined pK_as (eqn 10) They

found a linear Brønsted plot with an α value of 0 38, compared to Brønsted βs for variation of the base of 0.53 (isobutyraldehyde with aryl oxide anions[19]), 0.88 (acetone with carboxylate ions[16a]), and 0 66 (acetone with tertiary amines[20]). This result was interpreted in terms of a model in which proton transfer is more advanced than in charge delocalization into the CO group at the transition state Since the effect of the *R* group on the stability of the enolate ion is probably primarily due to stabilization of the double bond, the low sensitivity of the reaction to changes in *R* reflects little double bond formation and, thus, relatively little delocalization of the charge into the CO



(10)

A similar analysis was carried out by a comparison of the rates and equilibrium constants for the ionization of acetaldehyde and isobutyraldehyde [9f] Although isobutyraldehyde is a stronger acid than acetaldehyde by greater than 10-fold, the rate constant for proton transfer to hydroxide ion is almost 10-fold greater for acetaldehyde Chiang *et al* [9f] concluded that these results are also a manifestation of transition state imbalance Methyl group stabilization of the double bond in the final state is important, whereas in the transition state the negative charge is localized on the carbon and is destablized by the electron-donating methyl groups Although steric effects of the methyl groups of isobutyraldehyde in the transition state were ignored in this analysis, the model agrees with the conclusions from the analysis of the results with acetone, acetophenone and acetaldehyde, where steric effects should be minimal

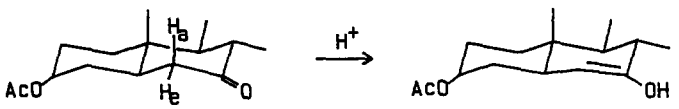
Cox *et al* [7a] have measured the rates of acid-catalyzed enolization of substituted acetophenones and the corresponding basicities of the ketones On the basis of the substituent dependence of these constants, they concluded that "between 50% and 70% of the positive charge present in the protonated ketone is still present in the transition state for enolization " This conclusion, based upon variation in the structure of the reactant, is similar to the one reached by Pruszynski *et al* [9e] in their study of the general acid-catalyzed ketonization of isobutyrophenone enol. The observed Brønsted α value of 0 58 for this reaction, based upon variation of the acid, also suggests a transition state with slightly greater than 50% of the positive charge on the ketone. The agreement between the progress along the reaction coordinate measured by these two probes is consistent with a transition state having little or no charge imbalance for the acid-catalyzed reaction

3. STEREOELECTRONIC CONTROL IN SIMPLE KETONES

3 1. *Axial* vs *equatorial reaction in cyclohexanones*

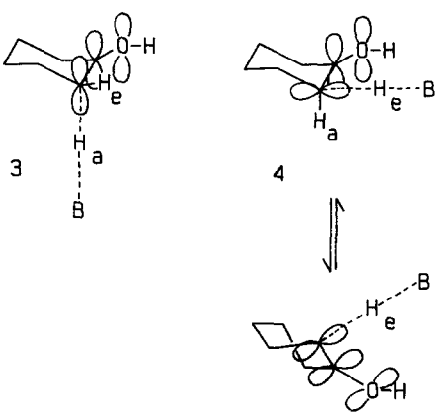
The concept of stereoelectronic control in the enolization of ketone was originally proposed in 1956 by Corey and Sneen[2] to account for the preferred loss of the axial hydrogen in the acid-catalyzed enolization of 3β-acetoxycholestan-7-one to the corresponding Δ^6-en-7-ol (eqn 11). In chloroform with HBr as a catalyst, the axial hydrogen is lost 1.2 times more rapidly than the equatorial hydrogen. For the reverse reaction, ketonization of the enol by HBr, protonation occurs

preferentially at the axial position by a factor of 1 5-fold. Corey and Sneen assumed that gain or loss of an axial hydrogen should be subject to steric retardation relative to reaction at the equatorial position They concluded that there must be a strong measure of stereoelectronic control favoring axial reaction to overcome the steric preference for equatorial reaction They estimated that, with a correction for steric effects, this stereoelectronic factor is about 12-fold (HBr as catalyst) to 50-fold (HOAc as catalyst) This stereoelectronic preference was postulated to be due to the requirement for continuous overlap between the C—H bond that is being broken and the π-orbital of the CO group This constraint may be met easily for the axial C—H bond (shown for a simple cyclohexanone in **3**), but is impossible to satisfy for the equatorial hydrogen in the normal chair form (**4**). Alternatively, the equatorial hydrogen is correctly aligned for enolization in the higher energy boat or twist-boat conformations (**5**) The difference in rates for the axial and equatorial hydrogens then represents the difference in the energies of the transition states **3** and **5**



(11)

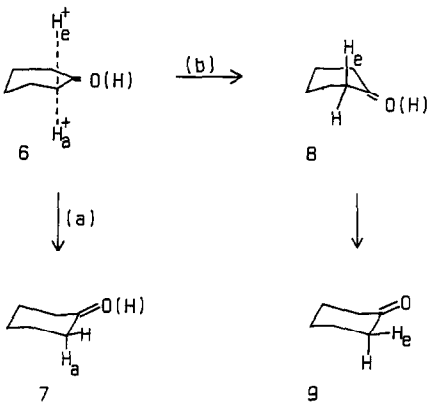
Although this theory is attractive and has been widely accepted, the assumption that there are significant steric effects that must be overcome for axial proton gain or loss has been challenged by Bordwell and Scamehorn [21a] They showed that axial substituents (phenyl or methyl) at the 4-position of cyclohexanones do not cause a large reduction in the rate of enolization at C-2 The lack of a significant rate retardation by these axial substituents casts doubt on the importance of stereoelectronic control in simple cyclohexanones Recent work by Spencer's group[21b] with substituted *trans*-decalones confirms that the effect of an axial methyl on the rate of abstraction of *syn*-axial protons α to a CO group is small (*ca* 5-fold) On the other hand, extensive work by Zimmerman *et al* [1f] on somewhat different systems has shown that the kinetic protonation of enols is subject to significant steric effects Zimmerman has concluded that " steric hindrance to approach of the proton donor is a major factor in controlling from which face a proton is delivered to the α-carbon "[1f] Although steric effects on the protonation of enols and deprotonation of ketones are clearly important, it appears that steric effects were somewhat overestimated by Corey and Sneen, leading to an inflated value for the stereoelectronic effect in simple cyclohexanones



Subsequent kinetic investigations of enolizations of cyclohexanones confirm the conclusion that stereoelectronic effects in these systems are small There is a preference for axial reaction in both

acidic and basic solutions, but the observed discriminations are generally relatively small Metzger and Casadevall[22] found that the axial hydrogens of *trans*-2-decalone exchange 2–3-fold faster than the equatorial protons at both positions α to the carbonyl in acetic acid/sulfuric acid solution Similarly, Trimitsis and Van Dam[23] showed that the axial protons in 4-*t*-butylcyclohexanone exchange more rapidly than the equatorial protons in alkaline DMSO/water ($k_{ax}/k_{eq} = 5\ 5$)

The small discriminations observed in these reactions have been explained by House[4] in terms of a very late transition state that resembles the enol(ate) (eqn 12) Since the principle of microscopic reversibility requires that the discrimination between axial and equatorial protonation of the enol be the same as that between loss of the axial and equatorial protons of the ketone, the problem can be analyzed by consideration of the two possible modes of attack of an electrophile on an enol (**6**). Attack at both sides of the enol to produce a geometry that allows orbital overlap is possible, with path (a) leading to axial orientation of the incoming proton (**7**) and a chair form of the ring, and path (b) giving equatorial attack, leading to a twist boat form (**8**) If the transition state is enol-like (**6**), then energy differences between the two pathways should be small, with the only significant difference due to steric interactions between the axial C-4 hydrogen and H_a, as is observed

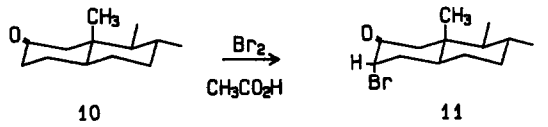


(12)

An alternative explanation for the lack of a large discrimination in basic solution is suggested by the transition state model for enolization presented by Chiang *et al* [9f] If charge delocalization is not of major importance in the transition state, then the lack of a strong stereoelectronic preference for enolization of simple cyclohexanones might be explained without recourse to a late transition state In a transition state with little charge delocalization, resonance would be unimportant and the transition state would not be required to have the partial C—H bond parallel to the π-orbitals of the CO Probably the most reasonable explanation, however, is that, whether the proton is almost completely transferred (as in base-catalyzed enolization) or about half-transferred (in acid-catalyzed enolization), the geometry of the transition state resembles the enol Thus, both a 'chair-like' and a 'twist-boat-like' transition state have similar energies Since the twist-boat conformation for cyclohexanone is only about 3 kcal mol^{-1} less stable than the chair form in cyclohexanone,[24] small deviations in the geometry of the transition state from the enol(ate) might not be significant.

The concept of stereoelectronic control has been extended to encompass halogenations and alkylations of ketones through enolic transition states, although steric effects appear to be significant in these reactions [4] The bromination of 19-methyl-2-keto-steroids (**10**) at C-3 produces the stereoelectronically favored axial bromide (eqn 13),[25a] whereas reaction of a 19-methyl-3-keto-steroid gives the equatorial isomer (eqn 14) [25b–e] Presumably, the steric interactions between the entering bromine and the 19-methyl group for attack on the enol of **12** at C-2 are severe enough to cause approach of the nucleophile to be equatorial Alkylations of enolates are also subject to steric hindrance as well as to stereoelectronic considerations Treatment of the enolate ions of 1-methyl-

2-decalones (**14**) with ethyl iodide gives very different stereochemical results depending on the nature of the substituent at C-10 (eqn 15) [25f] For $R = CH_3$, steric hindrance to axial attack is severe giving equatorial approach of the electrophile, whereas for $R = H$, axial attack is favored



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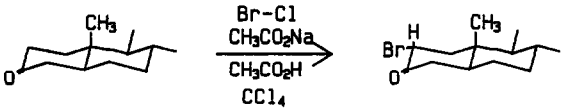

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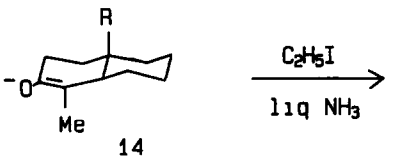

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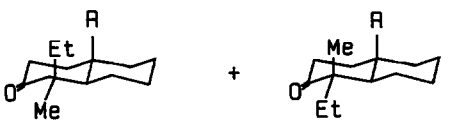
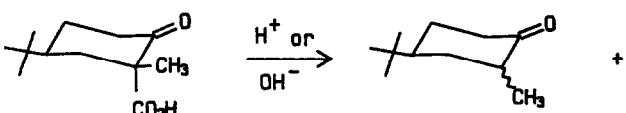


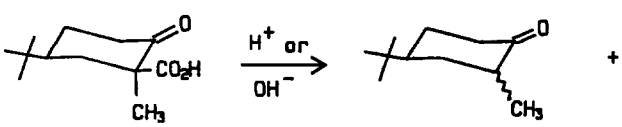
15 16 (15)

R = H	> 95%	< 5%
Me	< 5%	> 95%

A reaction analogous to the enolization of ketones, and which should be subject to stereoelectronic control, is the decarboxylation of β-ketoacids [26] The effect of stereoelectronic control on these reactions has been investigated for the decarboxylations of the two epimers of 5-*t*-butyl-1-methyl-2-oxocyclohexanecarboxylic acid in both acidic and basic solutions (eqns 16 and 17) [26a] If stereoelectronic control is a significant factor in the decarboxylation, the epimer with the axial carboxyl group (**17**) should be more reactive than the epimer with the equatorial carboxyl group (**19**) In fact, the isomer with the *equatorial* carboxyl (**19**) is more reactive by a factor of 3-fold in acid and a factor of 15- to 20-fold in base, in apparent conflict with stereoelectronic principles

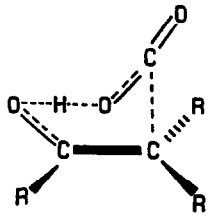


17 18 (16)



19 18 (17)

These results can be accommodated within the framework of the need for continuous overlap by an examination of the nature of the transition states for decarboxylation. The transition state for the decarboxylation of the unionized acids has a 6-membered ring in which the newly forming O—H bond is nearly in the same plane as the original C—C=O system (**20**) [26b,c] Continuous overlap of the incipient *p* orbital at C-2 with the *p* orbital of the carbonyl carbon is maintained by a perpendicular orientation of the C—C bond that is being broken with the plane of that ring This model predicts transition state structures **21** and **22** for the decarboxylation of **17** and **19**, respectively In both cases, the incipient cyclohexane ring will be in a half-chair conformation with the *t*-Bu group equatorial and the 2-methyl group in the plane defined by the C=C double bond Since steric interactions appear to be similar in the two transition states, their energies should be comparable In that case, the relative rates of reaction will depend only on the relative energies of the reactants Since methyl groups show slightly greater preference for the equatorial position in cyclohexanes than carboxyl groups do,[27] the slightly greater reactivity of the isomer with the equatorial carboxyl can be reasonably explained by its instability relative to its epimer



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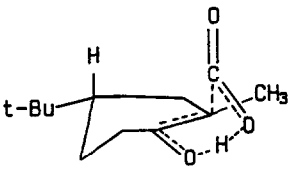

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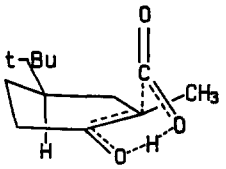
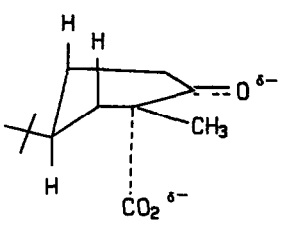


22

The relative reactivity of the anions can also be rationalized on the basis of differing energies of the two isomeric reactants, although in this case the cause of the instability of the anion of **19** is probably due to electrostatic rather than steric factors The transition state for the decarboxylation of the anions of *β*-keto acids is generally accepted[26b] as being a simple C—C bond cleavage to give the anion, analogous to base-catalyzed enolization However, the response to stereoelectronic control is quite different for the two reactions The transition state for decarboxylation is thought to resemble the enolate ion, as depicted in structures **23** and **24**, for loss of an axial and equatorial carboxyl, respectively Again, it is not unreasonable to expect that steric interactions in the two transition states are similar, so that the overall energies of the two isomeric transition states are comparable



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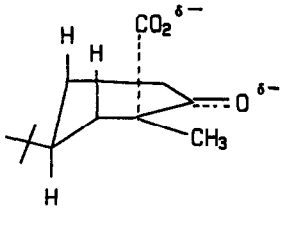
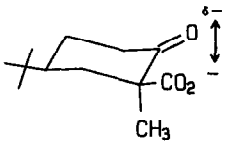


24

The energies of the anions of the reactants, however, should be quite different The anion of **17** is more stable than that of **19**, due to dipole–dipole repulsion in the anion of **19**, shown in **25** In support of this rationale, **17** is substantially more acidic than **19** (pK_as of 5 21 and 5 79 in 70% methanol),[26a] even though *cis*-4-*t*-butylcyclohexane carboxylic acid is less acidic than the *trans* isomer by almost 0.5 pK units Thus, in the case of **25**, the decarboxylation is enhanced by relief of electrostatic repulsion in the transition state



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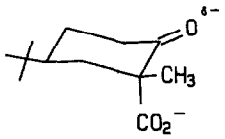
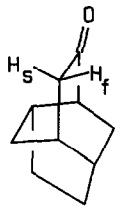


26

Although the vast majority of reactions involving discrimination between axial and equatorial positions in cyclohexanone enol formation show quite small effects, stereoelectronic control in the base-catalyzed hydrogen exchange of twistan-4-one (**27**) is quite large [28] In this compound the methylene group α to the carbonyl is oriented such that one of the C—H bonds is aligned in the correct orientation for overlap with the π-orbital of the carbonyl (**28**), whereas the other is about 60° out of alignment (**29**) Fraser and Champagne[28] found that the relative rates of exchange of these protons in sodium methoxide/methanol-O-*d* is 290 1 They assigned the rapidly exchanging proton to the one labeled H_f in **30** on the basis of NMR coupling constants



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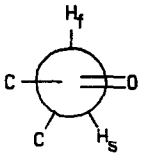
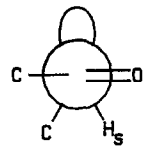


30



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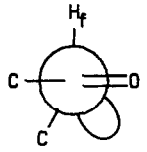
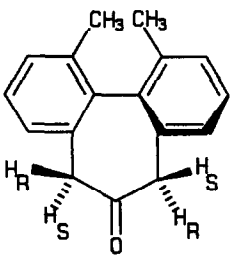


29

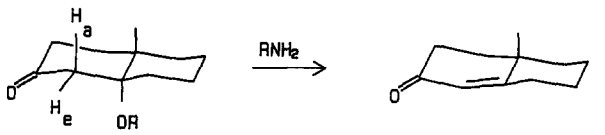
Three possible causes for the more rapid exchange of H_f than H_s were considered stereoelectronic, steric, and internal return A steric effect was ruled out on the basis of a lack of change in selectivity when the bulkier phenoxide is used as the base instead of methoxide, and internal return was eliminated by a determination of isotope effects in the reverse direction The authors concluded that "the only reasonable explanation for the observed 290 1 rate ratio in the exchange of **27** is the effect of stereoelectronic control "

In similar work, Fraser and Champagne[29] examined the stereoselective exchange of the diastereotopic protons of **31** The lack of rotation about the aryl—aryl bond causes the C—H bonds of the two protons (H_R and H_S) to be oriented differently with respect to the π-orbital of the CO group Fraser and Champagne found that H_R exchanges 73 times faster than H_S in methoxide-methanol-O-*d* and 30-fold faster with phenoxide in methanol-O-*d* This observation was rationalized on the basis of a more highly strained transition state being required for the exchange of H_S than H_R The conformation required to maintain overlap of the partial C—H bond for H_S with the carbonyl π-orbital involves considerable angle strain



31

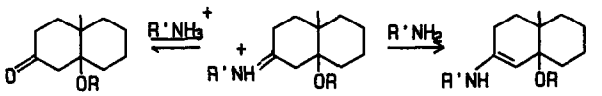
A significant degree of stereoelectronic control has also been observed in proton transfers from iminium ions. Ferran *et al* [30a] examined the discrimination between axial and equatorial protons in the primary amine-catalyzed elimination of **32** to **33** (eqn 18). This reaction proceeds by rate-determining abstraction of a proton at C-1 from the iminium ion, followed by elimination of O*R* (eqn 19) With both trifluoroethylamine ($R' = CF_3CH_2$) and cyanomethylamine ($R' = NCCH_2$) as catalysts, the axial proton is abstracted 16–18-fold more rapidly than the equatorial proton in the conversion of alcohol **34a** to **35a** ($R = H$) In contrast, a much larger effect is exhibited in the analogous reactions with acetate as the leaving group. Amine-catalyzed deprotonation of **34b** shows a preference of 110-fold for abstraction of H_a over H_e Since the rate-limiting step in the formation of the α,β-unsaturated ketone is the formation of the enamine, the stereoelectronic effect observed here represents the discrimination on the proton-abstracting step A similar large stereoelectronic factor (130-fold) was observed for the hydroxide-catalyzed elimination of **32b**, which also proceeds through rate-determining proton abstraction One explanation of the relatively large discriminations observed in the case of acetate as the leaving group involves steric hindrance to proton abstraction of the equatorial hydrogen by the leaving group In this regard, the high axial/equatorial selectivity for proton abstraction is not seen in the absence of the beta acetoxy group [30b]



(18)

32 a R = H
b R = Ac

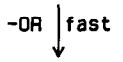
33



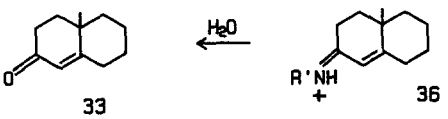
32 a R = H
b R = Ac

34

35



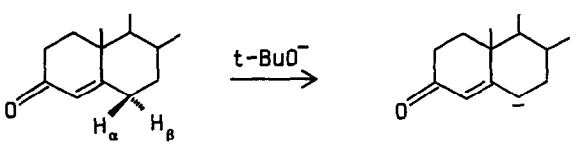
(19)



33

36

An analogous stereoelectronic effect has been observed in the deprotonation of 4-androstene-3,17-dione (**37**) at C-6 (eqn 20) [31] The 6β-proton (axial) is lost 53-fold faster than the 6α-proton (equatorial) with *t*-butoxide as the base Stereoelectronic control of this reaction is due to better overlap of the axial C—H bond with the π-orbital of the C=C double bond



(20)

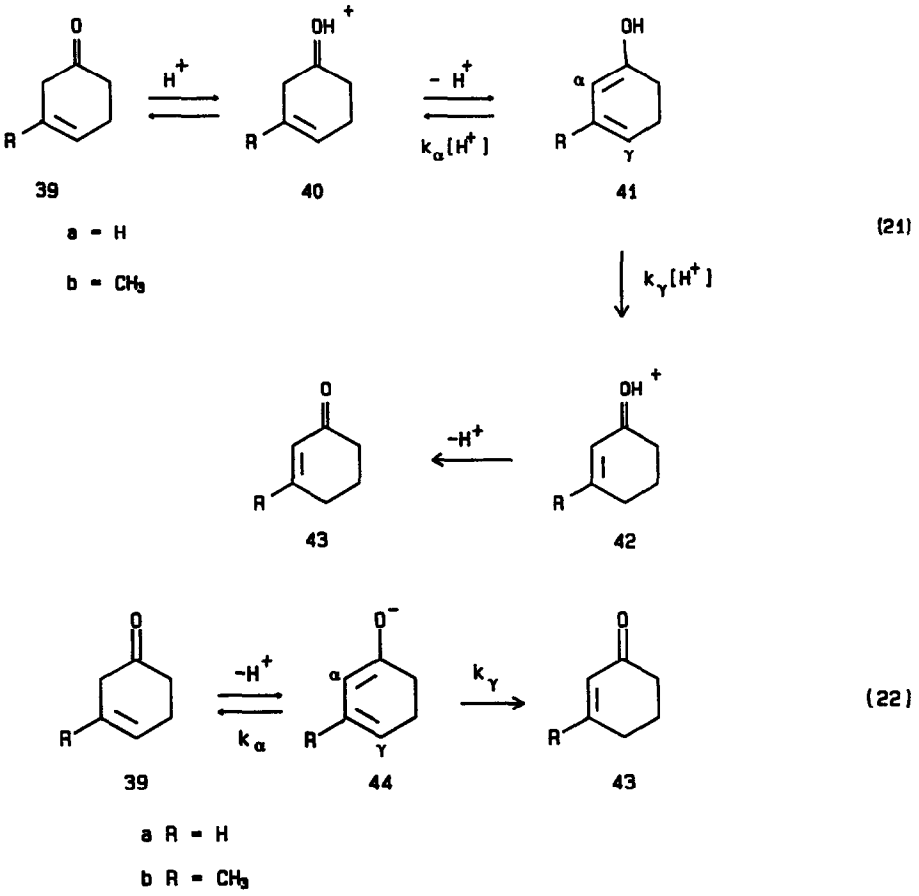
37

38

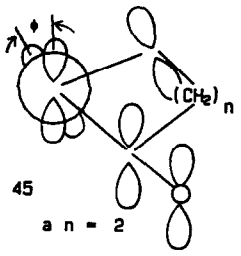
In summary, the observed discrimination between loss of axial and equatorial substituents in cyclohexanones is quite variable There is little doubt that the preferred orientation of the partial bond to the entering or leaving group at the transition state is parallel to the π-orbital of the carbonyl Although the bond to an α-axial substituent is correctly oriented for reaction, this orientation can also be realized for equatorial substituents (in the normal chair form) by a ring flip to produce a twist-boat conformation Since the twist-boat cyclohexanone is only *ca* 3 kcal mol^{-1} less stable than the chair form, a rate difference of *ca* 100-fold is the maximum to be expected In most cases, smaller values are observed, probably due to an attenuation of the effect from an enol(ate)-like transition state If the transition state is enol-like, loss of either the axial or equatorial substituent gives a similar transition state and only a modest stereoelectronic effect is seen

3 2 *Protonation of dienols*

Stereoelectronic considerations may be important in the selectivity observed in protonation of dienols and dienolate ions These species are intermediates, respectively, in the acid-catalyzed and base-catalyzed isomerizations of β,γ-unsaturated ketones to the corresponding α,β-unsaturated isomers (eqns 21 and 22) In the acid-catalyzed isomerization of 3-cyclohexenone (**39a**), the intermediate dienol (**41a**) protonates more rapidly at C_α than C_γ ($k_\alpha/k_\gamma = 50$).[32a] In contrast, the rate-determining step in the isomerization of 3-methyl-3-cyclohexenone (**39b**) is deprotonation at C_α, that is $k_\alpha/k_\gamma \ll 1$ Noyce and Evett[32] generalized from these and other results that in cases where the β-carbon is tertiary, protonation of dienols occurs predominantly at C_γ, whereas for dienols that have a secondary β-carbon, protonation is preferentially at C_α



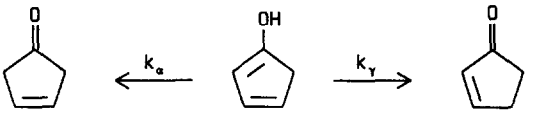
Naively it might be expected, however, that protonation in all cases should lead to the more stable product, since the transition state must have some product-like character to it. A possible explanation for the preferential protonation at C_α in secondary compounds is a lack of the correct stereoelectronic orientation for protonation at C_γ due to the existence of some twisting between the two double bonds of the dienol (**45**) Whalen *et al* [33] have suggested that in the case of cyclohexadienol the dihedral angle ϕ is about 18° (**45b**) As a result, the positive charge produced at the β-carbon by protonation at C_γ will not be stabilized as effectively by the oxygen as it is for protonation at C_α In agreement with this hypothesis, the observed ratio of k_α/k_γ is less than unity for the isomerization of 3-cyclopentenone, in which all the C atoms of the intermediate dienol (**47**) should lie in the same plane (**45a**, $\phi = 0$) [33] Here, the C—H bond that is being formed at C_γ is parallel to all of the *p*-orbitals of the π-system and the positive charge should be effectively stabilized by the OH group The ratio of protonation at the two carbons then should depend on the dihedral angle between the two double bonds. For a dihedral angle of 0° (cyclopentadienol), protonation is favored at C_γ, as the angle increases, protonation becomes progressively less favorable at C_γ, and the ratio of k_α/k_γ should increase



45

a n = 2

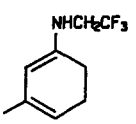
b n = 3

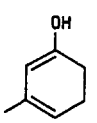


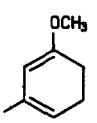
46 47 48

An analogous explanation was used to rationalize the results observed by Whalen *et al* [33] for the general base-catalyzed isomerization of 3-cyclohexanone and 3-cyclopentenone For the cyclohexadienolate ion, the ratio k_α/k_γ is large with phosphate as the acid, whereas for the cyclopentadienolate ion the ratio is only 3. It is of interest that the k_α/k_γ ratio is higher for the dienolate anion than for the dienol itself in both series Since O^- is a better electron-donating group than OH, this result suggests that the substituent sensitivity is greater for protonation at C_α than at C_γ, consistent with better stereoelectronic orientation for protonation at C_α

A comparison of the k_α/k_γ ratios for three derivatives 3-methyl-3-cyclohexenone, the trifluoroethylamine enamine (**49**), the enol (**43b**) and the enol ether (**50**) shows a similar pattern In the case of both **43b** and **50**, protonation is predominantly at C_γ,[32a,34] yet **49** protonates slightly faster at C_α than C_γ [35] Because of the somewhat nonplanar diene system,[33] the additional electron donating ability of nitrogen in **49**, compared to the oxygens of **43b** and **50**, is transmitted more effectively to C_α than C_γ Thus, the k_α/k_γ ratio is larger for **49** than **43b** or **50**

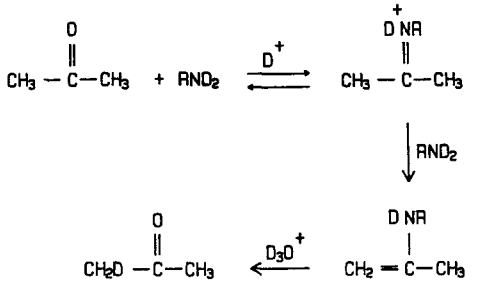






49 43b 50

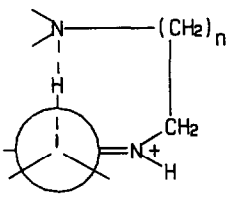
k_α/k_γ 1 4[35] v small[32a] 0 1[34]



(23)

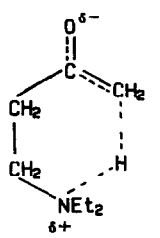
3 3 *Intramolecular reactions*

Hine *et al* [36] have examined the catalysis of proton exchange of aldehydes and ketones by a variety of primary and secondary amines This reaction occurs through the intermediacy of a protonated Schiff base that is deprotonated in one pathway by a second molecule of amine (eqn 23) These workers have found that, with suitable bifunctional amines, intramolecular catalysis of the deprotonation of acetone is a major pathway [36] The most effective catalysts are those that form an 8-membered cyclic transition state (**51**) This preference was explained on the basis of stereoelectronic factors In order for effective catalysis to occur, it is necessary for the C—H bond to be oriented parallel to the π-orbital of the Schiff base. For this geometry to be possible, at least eight atoms must be in the ring at the transition state Larger ring sizes likely cause a greater loss of entropy, and thus are not optimal for bifunctional catalysis. Smaller ones are too strained



51

Although Hine found preferential formation of an 8-membered transition state for proton abstraction, previous workers had found intramolecular catalysis of enolization with 6- and 7-membered cyclic transition states [37] Surprisingly, Bell and Timimi[37a] found that intramolecular catalysis through a 6-membered ring is 4-fold more effective than through a 7-membered ring in the enolization of diethylamino-2-alkanones (**52** vs **53**) An examination of molecular models suggests that stereoelectronic considerations should favor the larger ring (**53**) Perhaps, there is a bridging water molecule that is involved in the proton transfer with **52**, relieving the strain associated with the stereoelectronic requirements for proton transfer In a similar vein, the transition state (**54**) for intramolecular enolization of *o*-carboxyacetophenone[37b] cannot easily accommodate loss of the α-hydrogen in the same plane as the π-orbital of the carbonyl without intervention of a water molecule or rotation about the phenyl—$COCH_3$ bond, causing loss of conjugation



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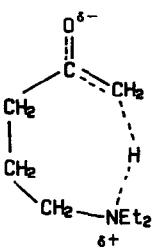

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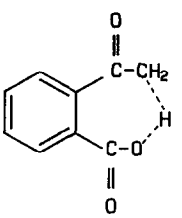
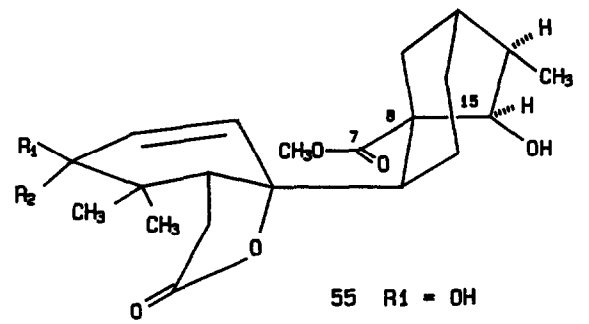
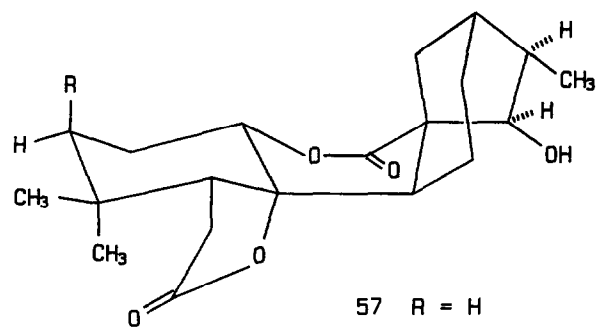


54

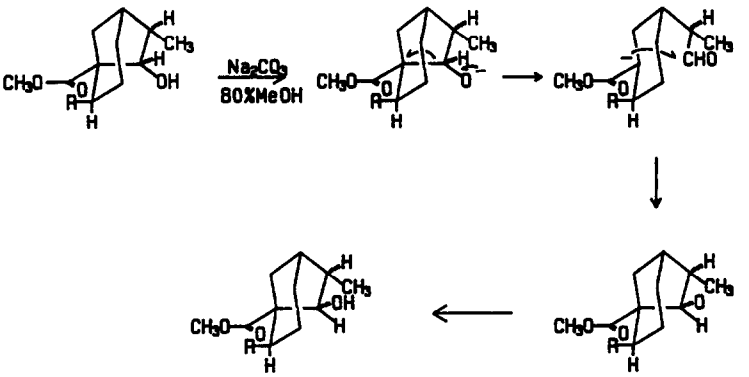
Stereoelectronic considerations have also been invoked to rationalize several observations concerning intramolecular alkylation, acylation, and condensation reactions Fujita and Nagao[38] have shown that several diterpene alcohols (e g **55, 56**) epimerize at C-15 by retro-aldol cleavage, followed by reformation of the C—C bond (eqn 24) The structurally similar compounds **57** and **58**, however, do not undergo epimerization The authors explained this difference by noting that free rotation of the bond between C-7 and C-8 in **55** and **56** allows overlap of the bond between C-8 and C-15 with the carbonyl π-orbital during cleavage of that bond and, consequently, delocalization of the incipient negative charge during the bond breaking process is favorable In **57** and **58**, on the other hand, two conformations are possible, a boat and a chair. Although the boat is relatively strain-free it does not give overlap of the bond between C-8 and C-15 with the π-orbital of the ester group The chair conformation, which does give reasonable overlap, is unfavorable because of ring strain and steric congestion generated in the other rings. In addition, the C—O single bond in the chair is twisted such that the ester resonance is partially lost Thus, cleavage of the C-8—C-15 bond is stereoelectronically disfavored A similar explanation can be applied to the observation[38] that cleavage of **59** is complete after three days at room temperature with 0 05 N K_2CO_3 in 80% MeOH (eqn 25), whereas the same treatment of **61** gives no reaction



55 R1 = OH
R2 = H
56 R1 = H
R2 = OH



57 R = H
58 R = OAc



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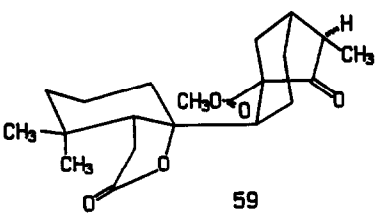

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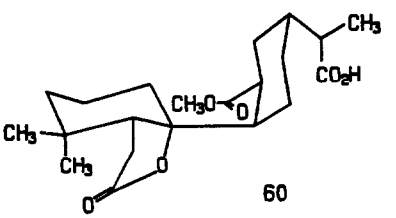

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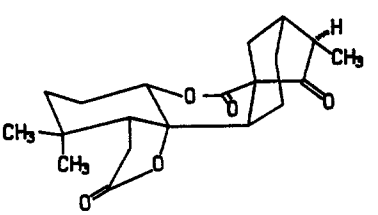

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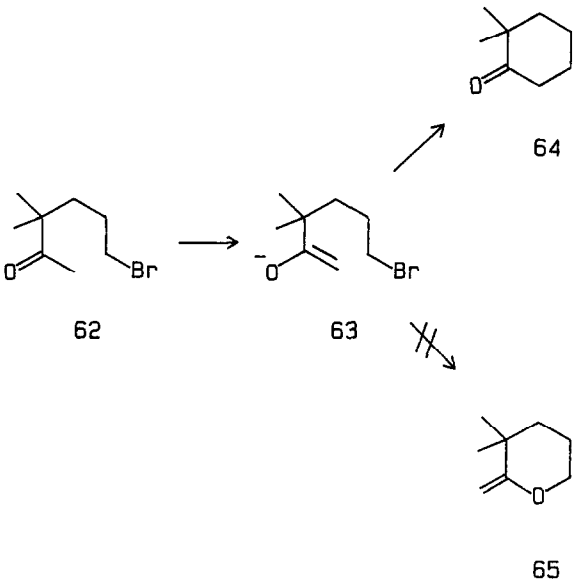
(26)

Baldwin[39] has used stereoelectronic considerations to explain the fact that 6-membered ring ketones can be formed by intramolecular endocyclic alkylation of enolates, but 5-membered ring ketones can not be synthesized in this manner. Intramolecular alkylation from either the potassium or lithium enolate generated from the bromoketone **62** gives only ketone **64** (>95%), with no detectable formation of the enol ether **65** (eqn 27) In contrast, the bromoketone **66**, under the same conditions, yields exclusively the enol ether **69** (>97%), rather than the ketone **68**



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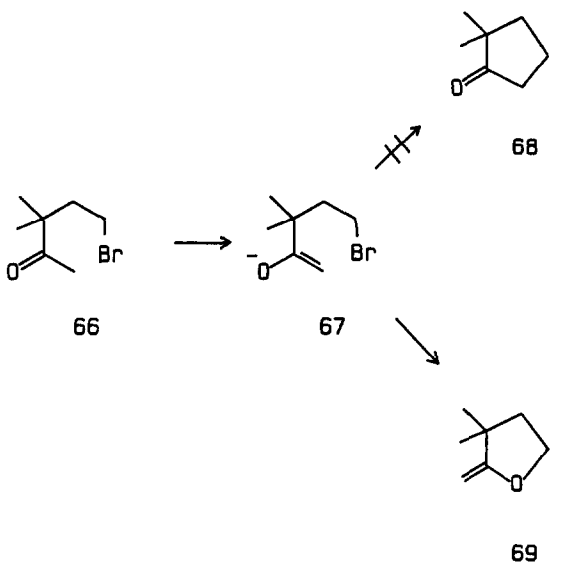
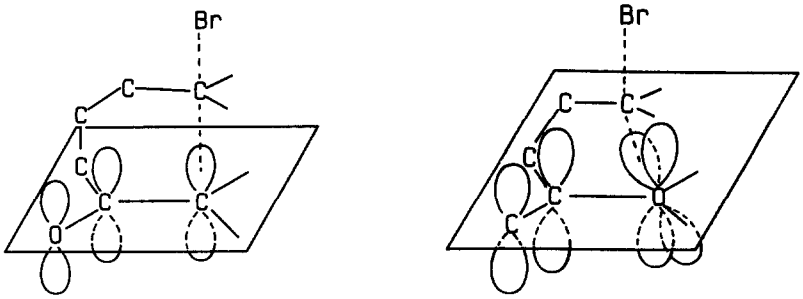


(28)

The difference in behavior can be rationalized by a consideration of the geometries of the transition states for C- and O-alkylation Stereoelectronic theory predicts that carbon alkylation will occur through attack on the enolate carbon perpendicular to the C–C–O plane for maximum overlap with the π-system (**70**). In contrast, oxygen alkylation can take place by electrophilic attack at an oxygen lone pair in the plane of the π-system (**71**) The lack of carbon alkylation to form the 5-membered cyclic ketone **68** is due to the difficulty of the electrophile in approaching the carbon perpendicular to the plane of the C–C–O system In order for the electrophile to attack from this direction, there must be substantial ring strain in the 5-membered ring. However, attack at the oxygen to form the enol ether by approach of the electrophile in the plane of the ring causes no



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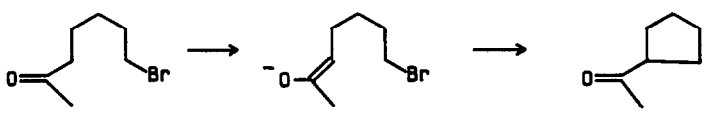
undue ring strain Recent theoretical calculations of the transition state structures for reaction of acetaldehyde enolate with methyl fluoride confirm the difference in the geometries of transition states for carbon and oxygen alkylation of enolates.[40] Although the same stereoelectronic requirements hold for formation of 6-membered rings, the extra carbon enlarges the ring sufficiently such that the approach of the electrophile can be perpendicular to the C–C–O plane, and carbon alkylation predominates In the case of exocyclic alkylations, reaction at carbon to form 5-membered rings is observed due to a reduced ring strain in the transition state relative to the corresponding endocyclic reaction (eqn 29 vs eqn 28)



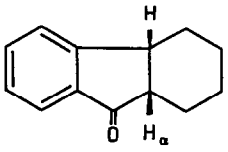
72 73 74 (29)

3 4 *Free* vs *restricted rotation*

The lack of a large stereoelectronic effect in the enolization of simple cyclohexanones is most likely due to the possibility of enolization through a boat-like transition state that allows orbital overlap requirements to be met. Since the boat form of cyclohexanone is only about 3 kcal mol^{-1} less stable than the chair form,[24] the maximum rate discrimination to be expected in this system is about a factor of 100-fold Because of the obvious implications for the mechanisms of enzymatic reactions, it is of interest to determine if substantially larger rate accelerations can be obtained by 'locking' a hydrogen in the correct orientation for enolization. How much faster would this hydrogen be lost than a hydrogen on a carbon that is free to rotate so that the C—H bond can take up all possible orientations?

This question has been approached in our laboratory[41] using *cis*- and *trans*-hexahydrofluorenone (**75** and **76**, respectively) Molecular models show that the cyclopentanone ring in **76** (and to a lesser extent in **75**) is rigid and that the C—H_α bond is aligned parallel to the π-orbital of the carbonyl If stereoelectronic considerations are important, then **76** should enolize substantially faster than similar compounds in which the C—H_α bond is not restricted to one orientation Both **75** and **76** enolize over 10^3-fold more rapidly than cyclohexyl phenyl ketone (**77**) both in acid and in base It should be noted, however, that a substantial fraction of the rate difference between these compounds is due to unfavorable steric interactions in the enol(ate) of cyclohexyl phenyl ketone (**78**) The formation of the enol(ate) requires the juxtaposition of two cyclohexyl hydrogens and an *ortho* hydrogen of the phenyl ring Since the reactant can rotate about the bond between the carbonyl and the cyclohexyl group, this interaction is not present Thus, enolization in **77** is retarded by an unfavorable steric interaction that can only be relieved by rotation about the bond between the enol carbon and the phenyl ring, reducing conjugation It was estimated[41] that the rate acceleration of **75** and **76** vs **77**

is due about equally (10- to 100-fold) to these steric interactions and stereoelectronic control The magnitude of the stereoelectronic control in this system is consistent with several theoretical discussions concerning the effect of freezing out of one bond rotation [42]



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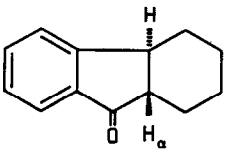

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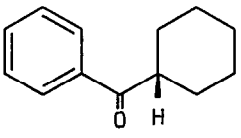

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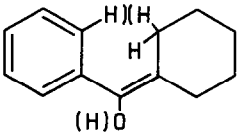

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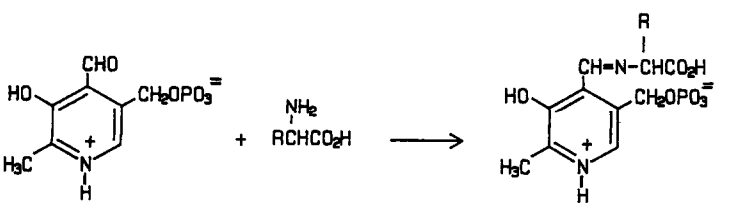
Although this stereoelectronic effect is relatively modest, it does point the way towards an understanding of how enzymes might function to increase the rate of particular reaction In a case such as the enolization of cyclohexyl phenyl ketone, the transition state, of necessity, has severe steric interactions due to the stereoelectronic requirement of bond overlap Thus, the conformation of the transition state is not that of the ground state If an enzyme were to bind the ketone in the stereoelectronically correct conformation in the ground state, then the rate acceleration would be due to both stereoelectronic control and the binding of a higher energy (reactive) conformation If steric interactions in the transition state of a reaction are particularly severe, then quite large rate accelerations could be realized

4. STEREOELECTRONIC CONTROL IN ENZYMATIC REACTIONS

4 1 *Specificity*

It was recognized many years ago by Dunathan[43] that conformational and stereoelectronic considerations are important in determining the specificity of pyridoxal phosphate enzymes This group of enzymes catalyzes a variety of reactions of amino acids, including racemizations, decarboxylations and retro aldol cleavages These reactions occur through the intermediate formation of a Schiff base (**81**, eqn 30) that can decompose by labilization of one of the three substituents on the α-carbon of the amino acid [44] Cleavage of the bond to the α-hydrogen can result in racemization or transamination (**82**), whereas bond breaking of the carboxylate group gives decarboxylation (**83**), and loss of the *R* group of a serine-derived Schiff base yields retro aldol products (**84**) In accordance with stereoelectronic principles, the lowest energy transition state for the cleavage of one of these bonds will have that bond perpendicular to the plane of the imine system Dunathan[43] proposed that the specificity of pyridoxal phosphate enzymes is due to conformational control of the Schiff base intermediate by the enzyme. Each pyridoxal phosphate enzyme presumably binds its substrate such that the bond to be cleaved is correctly oriented for maximum overlap with the π-system



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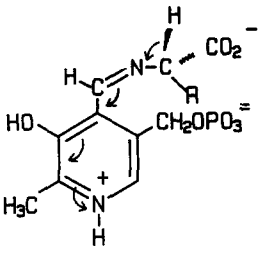

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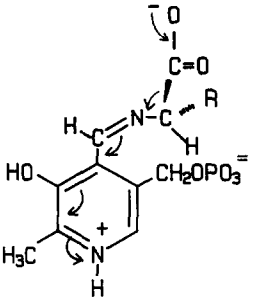

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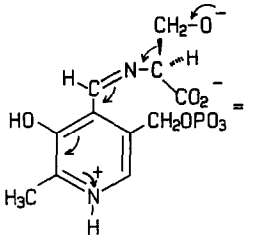

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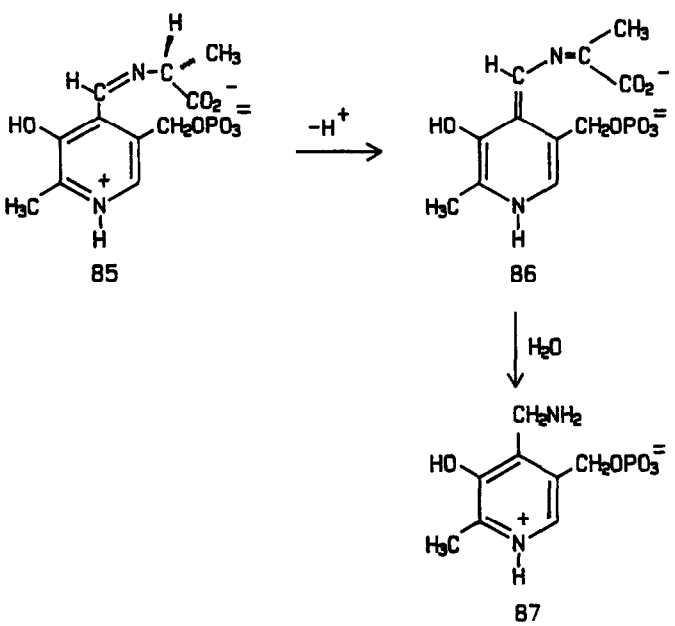
The specificities of a variety of enzymatic reactions were analyzed in terms of this model Bacterial amino acid decarboxylases show incorporation of only one atom of deuterium when the reaction is run in deuterium oxide[45] due to the requirement that protonation of the intermediate anion occur at the same position as the original carboxylate moiety Furthermore, the monodeuterated product of decarboxylation of glutamate, monodeutero-γ-aminobutyrate, does not exchange the other hydrogen for deuterium in the presence of the enzyme These results are consistent with the enzyme binding both reactant and product in a single conformation with only one bond perpendicular to the plane of the imine system

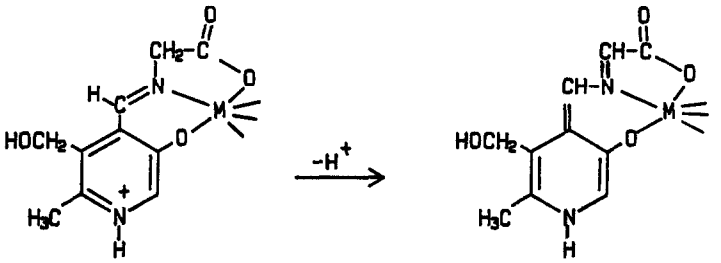
Serine hydroxymethyl transferase[46] catalyzes the reversible aldol condensation of glycine and several different aldehydes In the cleavage direction with serine, the reaction occurs by loss of formaldehyde (**84**) Although this enzyme is specific for L-amino acids, D-amino acids are bound and D-alanine undergoes a transamination with the pyridoxal group, irreversibly inactivating the enzyme (eqn 31) The transamination can be rationalized by assuming that the binding of the substrate is controlled by interactions involving the carboxyl group of the amino acid Using this model, it can be seen that the proton of D-alanine is conformationally equivalent to the hydroxymethyl group of L-serine (**85** vs **84**) Thus, the enzyme cleaves the bond with the same orientation in both cases Similarly, only one of the hydrogens of glycine should be (and is) labilized by this enzyme [43,46]



85 86 87

(31)

Model systems with pyridoxal derivatives are also consistent with stereoelectronic control as a major factor in the specificity of these enzymes Fischer and Abbott[47] have shown that the two hydrogens of the glycine moiety of bis(pyridoxylidene glycinato)cobalt(III) (**88**) are exchanged at significantly different rates (10- to 1000-fold, depending on temperature) in dilute basic solution (eqn 32). In the ion, these two hydrogens are held such that only one is correctly oriented for continuous overlap with the π-orbitals of the azomethine group during cleavage



(32)

88 89

Tsai *et al.*[48] also examined the role of stereoelectronic control in nonenzymatic reactions involving pyridoxal phosphate They correlated the rates of racemization and H_α exchange of a series of amino acid Schiff base derivatives of pyridoxal phosphate with the proportion of the conformer for each derivative having the C_α—H bond parallel to the Schiff base π-system. Relative amounts of the conformers for each system were estimated using CPK models and conformational calculations. Steric interactions in the conformers favorable to reaction were invoked to explain the low reactivity of amino acids with bulky substituents.

4 2 *Speed*

Although stereoelectronic constraints on transition states for enzymatic enolization of ketones and related reactions are clearly operable, the majority of work in this area has only shown that reaction specificity can be controlled by the requirement for continuous overlap In order to evaluate whether absolute rates of reactions can be affected by stereoelectronic considerations, it is necessary to show that enzymatic binding of a substrate in the correct conformation can result in substantial rate acceleration

To simplify matters, we will assume that there are only two conformations for a particular substrate and that only one of these is reactive, although the argument is valid for any number of conformations If the two conformations rapidly interconvert, then the rate of the reaction is controlled by the free energy difference between the one of lowest energy and the transition state. A rate acceleration will thus be observed for differential binding of the transition state relative to the ground state

Let us assume first that the reactive conformation is of lower energy than the unreactive one If this conformation is recognized preferentially by the enzyme, both the ground state and the transition state will be bound Although the energy of the transition state is lowered by this binding, the ground state energy is also lowered (Fig 1a) Since the rate of reaction depends on the difference in energy between the reactants and transition state, and both are stabilized, the net rate acceleration will be minimal If, on the other hand, the reactive conformation is of higher energy than the unreactive one, then preferential binding of this conformation will substantially reduce the energy of both this conformation and the transition state Since the overall energy of the reactant is not greatly affected, while the transition state is stabilized, the energy of activation is decreased and catalysis occurs (Fig 1b)

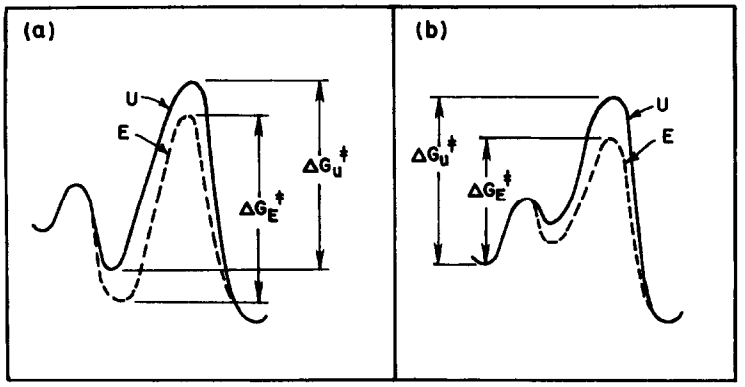
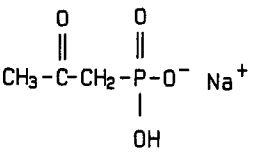


Fig 1 Free energy profile for substrate with two conformations for an uncatalyzed reaction (U), and an enzyme-catalyzed reaction (E) In (a), the energy of the unreactive conformation is higher than that of the reactive one In (b) the reactive conformation is higher in energy In both cases, the enzyme is assumed to bind the transition state and the reactive conformation with the same interaction energy



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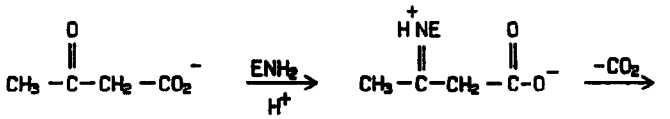
The rate acceleration due to the enzyme acetoacetate decarboxylase can be analyzed by this model This enzyme catalyzes the decarboxylation of acetoacetate through the intermediate formation of an enzyme Schiff base (eqn 33),[49] and there is substantial evidence that stereoelectronic considerations are important By analogy with decarboxylations of keto acids[26] loss of CO_2 should occur parallel to the π-orbital of the imine Kluger and Nakaoka[50] have used sodium acetonylphosphonate (**90**) as a probe for the binding of the substrate at the active site of the enzyme Since the C—P bond is not cleaved by acetoacetate decarboxylase, the phosphonate moiety may be used as a model for the carboxylate of the substrate Kluger and Nakaoka found that, although acetoacetate decarboxylase catalyzes the deuteration of acetone in deuterium oxide and the exchange of the 3 position protons of 2-butanone, there is no enzyme-catalyzed labilization of the protons of the monoanion of acetonylphosphonate In contrast, one of the two diasteroeotopic protons of both methyl and ethyl acetonylphosphonate are exchanged in deuterium oxide in the presence of the decarboxylase



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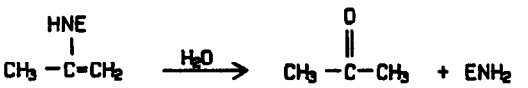

These authors interpreted their results in terms of binding of the phosphonate group in the normal carboxylate binding pocket Since the carboxylate of the substrate, and thus the phosphonate of the inhibitor, bind in the stereoelectronically correct position for decarboxylation, there cannot be overlap of the sigma orbital of the C—H bonds of the phosphonate with the π-system. In the case of the phosphonate esters, binding is not as restricted because of the lack of a charged group, and the correct orientation for enolization can be achieved The lack of exchange in acetonyl phosphonate suggests that the normal binding mode of the enzyme is one in which the carboxyl group of the substrate is oriented parallel to the π-orbital of the enzymatic Schiff base, as expected for optimal decarboxylation

It has been known for some time that simple primary amines also catalyze the decomposition of β-keto acids through a Schiff base intermediate [51] This reaction has been studied in simple systems using cyanomethylamine as a model for acetoacetate decarboxylase [52] This amine has a pK_a (5 34)[52] similar to that for the active site lysine in acetoacetate decarboxylase (pK_a 6 0) [53] Guthrie and Jordan[52b] found that the rate constant for decarboxylation of the neutral cyanomethylimine of acetoacetate is about 3×10^5 larger than the rate constant for the spontaneous decarboxylation of neutral acetoacetic acid However, the rate constant for acetoacetate decarboxylase-catalyzed decarboxylation (k_{cat}) is about 100-fold larger than decomposition of the model system Guthrie and Jordan suggested that the enzyme may bind the imine zwitterion in a reactive conformation, with the bond to be cleaved parallel to the π-orbital of the imine If the predominant conformation of the model Schiff base is one in which there is hydrogen bonding between the negatively charged carboxylate and the protonated imine, then the reactive conformation may be substantially higher in energy It is just this situation that lends itself to acceleration by specific binding of the reactive conformation If the hydrogen bond is equivalent to only 3 kcal mol^{-1}, binding that involves loss of this bond would give a rate acceleration of *ca* 10^2-fold, explaining the discrepancy between the enzyme and the model system

5. SUMMARY

Stereoelectronic considerations are clearly important in the interpretation of processes that involve either the formation or reaction of enols and enolate ions Although it has been postulated that these reactions do not require orbital overlap between the incipient *p*-orbital and the π-system of the reactant,[17] overwhelming evidence indicates that this overlap is in fact required It is risky, however, to predict product ratios and relative rates of reaction from just this consideration Alternative transition states that satisfy the stereoelectronic requirements may exist and the possibilities must be evaluated on the basis of other (particularly steric) factors

Acknowledgements—Work from the author's laboratory was supported by grants from the National Institute of Health and the Petroleum Research Fund administered by the American Chemical Society The author wishes to thank Professors A J Kresge and T A Spencer for providing copies of manuscripts in advance of publication, and Professors Kresge and R L Schowen for helpful comments

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