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Uncatalyzed and Amine Catalyzed Decarboxylation of Acetoacetic Acid: An Examination in Terms of No Barrier Theory[1]

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Rate constants for decarboxylation of acetoacetic acid, its anion, and its imine with aminoacetonitrile have been calculated from equilibrium constants and distortion energies using No Barrier Theory. The mechanisms of decarboxylation of both acetoacetic acid and its imine involve preequilibrium formation of the zwitterion.

Key Words: decarboxylation; amine catalysis; imine; No Barrier Theory; calculation of rate constants.

INTRODUCTION

Decarboxylation of carboxylic acids is generally thermodynamically favorable but kinetically unfavorable. For example, the decarboxylation of acetic acid in aqueous solution is favored by a free energy change of −6 kcal/mol yet is a very slow reaction under ordinary conditions; this value is calculated from values of the free energies of formation in aqueous solution for acetic acid (*1*), methane (*1*), and carbon dioxide (*2*). β-Ketoacids are famous exceptions to this generalization because they have a low energy path for decarboxylation by way of the enol of the product ketone. This decarboxylation can be made even easier by temporary conversion of the ketone to an imine, which can give an iminium carboxylate zwitterion with a very good electron sink to facilitate loss of CO_2. Conversion of the keto acid to its anion makes decarboxylation more difficult because the immediate product must be the enolate and not the enol. The difference is not large in absolute terms but noticeable on a human time scale: the difference at 30°C is between a 7-h and a 430-h half-life.

[1] This work is dedicated to F. H. Westheimer, on the occasion of his 90th birthday.

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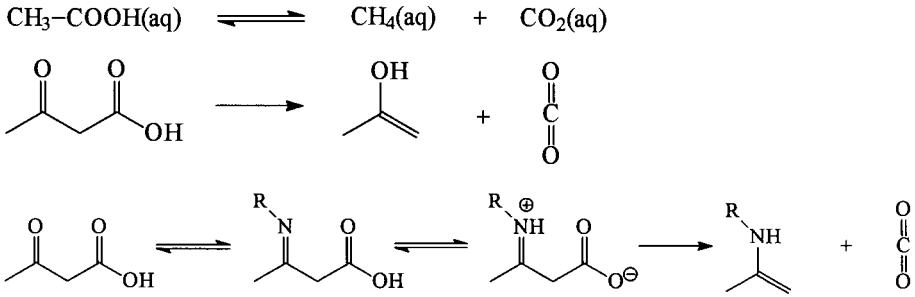

Decarboxylation of β-ketoacids has been extensively studied (*3–11*). There remains some uncertainty about details of the mechanism, and in particular about whether the proton transfer is concerted with the C-C bond breaking (*3,10,12,13*). Amine catalysis has been known for a long time (*5,14,15,11,10,16*), but is less understood in detail because of the multistep nature of the catalysis. In the case of aminoacetonitrile, which was an efficient catalyst for the decarboxylation of acetoacetic acid, a detailed kinetic analysis was carried out, leading to a rate constant for the actual decarboxylation of the imine (*17*). Amine catalysis is one of the mechanism used by enzymes which catalyze decarboxylation (*18,19,20,21,3*) and has been incorporated into abzymes (catalytic antibodies) (*22*).

This work will examine the decarboxylation of acetoacetic acid and its anion, and the corresponding imine with aminoacetonitrile, which was found to be an efficient catalyst for the decarboxylation. The catalysis will be shown to be explicable in terms of No Barrier Theory, which offers a satisfactory explanation of the origins of the intrinsic barrier for these reactions.

RESULTS

No Barrier Theory depends on the following postulates:

(1) Reactants are in equilibrium with starting material or product at each point along each reaction coordinate.

(2) For any process where only one elementary reaction coordinate changes, the energy will be a quadratic function of the corresponding reaction coordinate.

(3) Heterolytic bond cleavage constitutes an elementary reaction coordinate.

(4) Proton transfer between electronegative atoms can be treated as an elementary reaction coordinate.

Reaction coordinates are defined to run from 0 to 1.

From these we can calculate the free energy hypersurface, and thus find the lowest energy path over this surface from starting material to products. Transition state energies so calculated are in good agreement with experiment for a variety of reactions: proton transfer to form enolates (*23*), cyanohydrin formation (*24*), carbonyl hydration (*25*), addition of amines to carbonyls (*26*), reaction of nucleophiles with carbocations (*27*).

No Barrier Theory is in the spirit of Marcus Theory (*28–31*) and allows both an explanation of, and a method for calculating the value of, the intrinsic barrier for a reaction. The intrinsic barrier of Marcus Theory arises from the distortion energies of No Barrier Theory. If the distortion energies for the simple processes are high then

the intrinsic barrier will be high. The fact that different families of reactions can be treated with no empirical intrinsic barriers speaks to the power of this new approach.

In order to apply No Barrier Theory we require equilibrium constants for the decarboxylation reactions. These cannot be measured directly but must be calculated using thermodynamic quantities. The relevant values are collected in Table 1. For amine catalyzed decarboxylation, equilibrium constants for formation of imine from starting material and of enamine from product are needed. The former is available from kinetic analysis (*17*), but the latter has not been reported. The experimental rate and equilibrium constants which are available are collected in Table 2. The calculations involved in the application of No Barrier Theory require various p*K*a values not all of which can be measured directly; various estimations were necessary. p*K*a values, both measured and estimated are found in Table 3.

Thermodynamics of ethyl acetoacetate. The enthalpy of formation of ethyl acetoacetate in the gas phase has been determined by combustion calorimetry and is -140.1 ± 0.36 kcal/mol (*32*). In the gas phase ethyl acetoacetate is an equilibrium mixture containing 47% keto and 53% enol at 298.15 K (*33*). The thermodynamic quantities at 298.15K for

$$CH_3COCH_2COOC_2H_5 \rightleftharpoons CH_3C(OH)=CHCOOC_2H_5$$

TABLE 1

Thermodynamic Quantities for Compound Discussed in This Paper[a]

A. Compounds for which ΔG_f(aq) has not previously been reported.

Compound	ΔH_f(g)	$S°$(g)	ΔG_f(g)	ΔG_t[b]	ΔG_f(aq)
$CH_3COCH_2COOCH_2CH_3$	-140.1 ± 0.36[c]	106.21[d]	−100.89	−4.20[d]	−105.09
CH_3COCH_2COOH					−120.04
$CH_3C(=NCH_2CN)CH_3$	33.08[d]	91.95[d]	62.81		
$CH_3C(NHCH_2CN)=CH_2$	37.99[d]	90.55[d]	68.13		

B. Compounds for which ΔG_f(aq) has been reported

Compound	ΔG_f(aq)	Compound	ΔG_f(aq)
CO_2	-92.25 ± 0.06[e]	$CH_3C(OH)=CH_2$	-27.02 ± 0.21[f]
CH_3COCH_3	-38.48 ± 0.21[f]		

[a] All at 25°C; enthalpies and free energies are in kcal/mole, entropies are in cal/deg/mole, standard states are ideal gas at 1 atm and 1M aqueous solution with an infinitely dilute reference state. Unless otherwise noted, enthalpies of formation are from reference (*92*), entropies are from reference (*93*), free energies of formation in the gas phase are calculated from the corresponding enthalpies of formation and the standard entropies, and free energies of formation in aqueous solution are calculated from the corresponding free energies of formation in the gas and free energies of transfer.

[b] Free energy of transfer from the gas at 1 atm to 1M aqueous solution.

[c] Reference (*32*).

[d] Calculated as described in the text.

[e] Reference (*2*).

[f] Reference (*1*).

TABLE 2

Rate and Equilibrium Constants Used in This Work[a]

Reaction	log K	log k
$CH_3C(OH)=CH_2 \rightleftharpoons CH_3COCH_3$	+8.33[b]	
$CH_3C(NHCH_2CN)=CH_2 \rightleftharpoons CH_3C(=NCH_2CN)CH_3$	+4.02	
$CH_3COCH_2COOH \rightleftharpoons CH_3C(OH)=CH_2 + CO_2$	+7.82	
$CH_3COCH_2COOH \rightarrow CH_3COCH_3 + CO_2$	−0.50	−4.54[c]
$CH_3COCH_2COO^- \rightarrow CH_3COCH_2^- + CO_2$	−7.86	−6.35[c]
$CH_3C(=NCH_2CN)CH_2COOH \rightarrow CH_3C(=NCH_2CN)CH_3 + CO_2$	+2.86	1.0[c]

[a] In aqueous solution; calculated as described in the text unless otherwise noted.
[b] Reference (*59*).
[c] Reference (*17*).

are: $\Delta H = -3.17$ kcal/mol, $\Delta S = -10.38$ cal/K/mol, $\Delta G = -0.08$ kcal/mol (*33*,*34*). From this we may deduce that the heat of formation of the keto tautomer is −138.42 kcal/mol, and that the heat of formation of the enol tautomer is −141.59 kcal/mol.

The entropy of both tautomers of gaseous ethyl acetoacetate was calculated using DFT (*35*) and corrected for the number of low energy conformations. Exploration of conformations for the keto tautomer by PCModel (*36*) showed that there are three low energy conformations corresponding to rotation about the C-O bond of the ester, three corresponding to rotation about the CH_2-COO bond, and two corresponding to

TABLE 3

p*K*a Values for Compounds Discussed in This Work[a]

Compound	p*K*a
CH_3COCH_2COOH anti OH	3.58[b]
CH_3COCH_2COOH syn OH	1.19
$CH_3C(O\underline{H}^+)CH_2COOH$	−7.65
$CH_3C(O\underline{H}^+)CH_2COO\underline{H}$	1.95
$CH_3C(=N(\underline{H}^+)CH_2CN)CH_2COOH$	0.53
$CH_3C(=N(\underline{H}^+)CH_2CN)CH_2COO\underline{H}$	2.62
$CH_3C(=N(\underline{H}^+)CH_2CN)CH_2COO^-$	2.17
$CH_3C(=NCH_2CN)CH_2COO\underline{H}$	4.26
$CH_3C(OH)=CH_2$	10.94[c]
$CH_3C(-NHCH_2CN)=CH_2$	31
CO_2H^+ linear	−39
CO_2H^+ bent	−31
$CH_3C(O\underline{H}^+)CH_2COOH$ (O^+H perpendicular)	−21.34
$CH_3C(O\underline{H}^+)CH_2COO\underline{H}$ (O^+H perpendicular)	1.95
$CH_3C(OH)=CH_2$ ($O\underline{H}$ perpendicular)	7.41

[a] In aqueous solution; estimated as described in the text unless otherwise noted.
[b] Reference (*44*).
[c] Reference (*59*).

rotation about the CH_3CO-CH_2 bond, for a total of 18 conformations. For the enol tautomer there are three low energy conformations corresponding to rotation about the C-O bond of the ester. The entropy values so calculated are: 110.15 cal/K/mol for the keto tautomer, and 100.13 cal/K/mol for the enol tautomer. Combining these values and the entropy of mixing, we obtain the free energy of formation of the equilibrium mixture in the gas phase as −100.89 kcal/mol.

The solubility of ethyl acetoacetate in water is 14.3 g/100 ml at 16.5°C (*37*); this corresponds to 1.1 M. In water ethyl acetoacetate is 0.5% enol (*34*,*38*). The vapor pressure at 16.5°C can be calculated from the Antoine parameters (*39*), as 0.39 Torr. The total free energy of transfer is thus −4.55 kcal/mol at 16.5°C. To correct this to 25°C one must estimate the enthalpy of transfer. This may be done using experimental values for related compounds reported by Cabani *et al. (40*), starting with the value for methyl butyrate (−11.50 kcal/mol). This is corrected using the difference between methyl acetate (−10.16 kcal/mol) and ethyl acetate (−10.90 kcal/mol) to give the heat of solvation of ethyl butyrate as −12.24 kcal/mol. This is corrected for the introduction of a keto group using the difference between acetone (−9.77 kcal/mol) and propane (−4.38 kcal/mol) to give the heat of solvation of ethyl acetoacetate as −16.63. From this value and the free energy of transfer calculated above we obtain the entropy of transfer as 41.65 cal/K/mol. The desired free energy of transfer at 25°C can now be calculated as −4.21 kcal/mol. The estimation of the heat of transfer for ethyl acetoacetate is necessarily approximate, but even if the error were 5 kcal/mol (larger than the effect of introducing a keto group in place of a methylene) the resulting change in ΔG_t at 25°C would be only 0.14 kcal/mol, because the temperature change is small. The free energy of formation of the equilibrium mixture in aqueous solution can now be calculated as −105.09 kcal/mol.

The free energy of hydrolysis of the ester may be estimated as −1.7 (the value for methyl acetate (*41*) or methyl trifluoroacetate (*42*); the value is very insensitive to the acyl substituent, and is the same, within the uncertainty of the data, as the free energy of hydrolysis of ethyl acetate, calculated using tabulated free energy of formation data (*1*); equilibrium constants for methyl and ethyl acetate formation in 50% acetic acid 50% water were within a factor of 1.6 (*43*)), and thus the free energy of formation for the acid in aqueous solution may be calculated as −120.04 kcal/mol. The p*K*a is 3.58 (*44*) and thus the free energy of formation of acetoacetate ion is −115.15. The values in the literature are −118 kcal/mol (*45*) and −114 kcal/mol (*46*).

Thermodynamics of imine formation. The equilibrium constant for formation of the imine from acetoacetate and aminoacetonitrile has been evaluated (*17*). The value for the reaction of neutral acetoacetic acid and neutral aminoacetonitrile to give the total (neutral plus zwitterionic) imine is $K = 0.25$ (*17*). No value for the equilibrium constant for formation of the imine from acetone and aminoacetonitrile has been reported so it is necessary to estimate it. The equilibrium constants for imine formation used in this estimation are: acetone plus methylamine (at 25°C) 0.23 M^{-1} (*47*); isobutyraldehyde plus methylamine (at 35°C) 118 M^{-1} (*48*); and isobutyraldehyde plus aminoacetonitrile (at 35°C) 11.28 M^{-1} (calculated from a value for $K'_{im} = ([CA] + [Im])[H_2O]/(([Hy] + [Al])[Am])$ (*49*) by dividing by the concentration of water, multiplying by $1 + K_h$ ($K_h = 0.429$ (*48*)) and dividing by $1 + K_{ca}$ (using the value, 0.24 (*48*) for $CF_3CH_2NH_2$, which has a similar p*K*a, since K_{ca} is relatively

insensitive to amine p*K*a (*48*))). Assuming that the substituent effect of the nitrile is the same for isobutyraldehyde and acetone, and is the same at 25 as at 35°C, we estimate that the equilibrium constant for imine formation from acetone and aminoacetonitrile is 0.23 * 11.28/118 = 0.022 M^{-1}.

Thermodynamics of imine-enamine tautomerization. By an indirect calculation based on an extended kinetic analysis Hine determined that the equilibrium constant relating the imine from acetone and *trans*-2-dimethylaminomethylcyclopentylamine and its enamine tautomer was 10^{-5} (*50*). It was necessary to estimate the corresponding equilibrium constant for *N*-isopropylidenecyanomethylamine. This was done by calculating the free energies of formation in the gas phase and estimating the free energies of transfer. Enthalpies of formation were calculated from B3LYP/6-31G**//RHF/6-31G** energies as described (*51*) and entropies were calculated using results from frequencies calculated at the B3LYP/6-31G**//B3LYP/6-31G** level (*35*), with care to see that the correct rotational symmetry numbers were used and correcting for the entropy of mixing due to low energy conformations.

Free energies of transfer were estimated using group additivity (*1,52*). It was necessary to estimate some of the contributions since there are no free energy of transfer data for either imines or enamines. For imines it was assumed that the imine nitrogen was equivalent to a pyridine nitrogen, and that

$$\Delta G_t(\text{pyridine}) - \Delta G_t(\text{benzene}) = \Delta G_t(\text{imine}) - \Delta G_t(\text{alkene}),$$

where alkene corresponds to imine with N replaced by CH. This allows estimation when the free energy of transfer for the analogous alkene is available or can be calculated from well established parameters. The models for E-*N*-isobutylidenemethylamine and *N*-isopropylidenemethylamine are E-3-methyl-2-pentene (ΔG_t estimated by group additivity (1) as 3.52 kcal/mol) and 2-methyl-2-butene (ΔG_t = 3.21 kcal/mol (1)). ΔG_t is available for pyridine (ΔG_t = −2.80 kcal/mol (*53*)) and benzene (ΔG_t = 1.03 kcal/mol (*53*)). Thus we estimate ΔG_t for *N*-isopropylidenemethylamine to be −0.62 kcal/mol, and for *E*-*N*-isobutylidenemethylamine to be −0.31 kcal/mol. As an alternative approach we can calculate a value for $[N_I(C)]$ (where N_I is an imine nitrogen understood to be bonded to a double bonded carbon). The assumed equality above is equivalent to:

$$\Delta G_t(\text{pyridine}) - \Delta G_t(\text{benzene}) = [N_I(C)] - [C_dH(C)]$$

Using the known value of $[C_dH(C)]$ (*1*) one obtains

$$[N_I(C)] = \Delta G_t(\text{pyridine}) - \Delta G_t(\text{benzene}) + [C_dH(C)] = -4.13 \text{ kcal/mol}$$

For enamines it was assumed that

$$\Delta G_t(CH_2{=}C(CH_3)\text{-}OR) - \Delta G_t(C_6H_5\text{-}OR) \sim \Delta G_t(CH_2{=}C(CH_3)\text{-}NHR) - \Delta G_t(C_6H_5\text{-}NHR)$$

and that

$$\Delta G_t(CH_2{=}CH\text{-}OR) - \Delta G_t(C_6H_5\text{-}OR) \sim \Delta G_t(CH_2{=}CH\text{-}NHR) - \Delta G_t(C_6H_5\text{-}NHR),$$

i.e., that the effect of changing from a benzene ring to an alkene is the same for enol ethers and enamines

These assumptions are equivalent to:

$$\{[C_d(C)(O)] + [O(C)(C_d)]\} - \{[C_B(O)] + [O(C)(C_B)]\} \sim \{[C_d(C)(N)] + [NH(C)(C_d)]\} - \{[C_B(N)] + [NH(C)(C_B)]\}$$

and

$$\{[C_dH(O)] + [O(C)(C_d)]\} - \{[C_B(O)] + [O(C)(C_B)]\} \sim \{[C_dH(N)] + [NH(C)(C_d)]\} - \{[C_B(N)] + [NH(C)(C_B)]\}$$

Although individual group contributions for enol ethers are not available, the sums are ($\{[C_d(C)(O)] + [O(C)(C_d)]\} = -3.03$ kcal/mol and $\{[C_dH(O)] + [O(C)(C_d)]\} = -2.28$ kcal/mol (*54*)). The contributions for substituted benzenes are available (*1*) or can be calculated from literature data.

Values for $[NH_2(X)]$ (needed to calculate $[C_B(N)]$ from ΔG_t for aniline), $[C_B(N)]$, and $[NH(C)(C_B)]$ were calculated from the free energies of transfer of methylamine (-2.70 kcal/mol (*53*)) aniline (-4.30 kcal/mol (*55*)) and *N*-methylaniline (-2.61 kcal/mol (*56*)) respectively.

The values so obtained were: $[NH_2(X)] = -5.45$ kcal/mol; $[C_B(N)] = 0.60$ kcal/mol; and $[NH(C)(C_B)] = -5.21$ kcal/mol:

How good are the above assumptions likely to be? We can examine the first by comparing

$$\{[C_d(C)(O)] + [O(C)(C_d)]\} - \{[C_B(O)] + [O(C)(C_B)]\} = -3.03 - (-2.54) = -0.49 \text{ kcal/mol}$$

with $\{[C_d(C)2] + [CH_2(C)(C_d)]\} - \{[C_B(C)] + [CH_2(C)(C_B)]\} = -0.60 - (-0.70) = 0.10$ kcal/mol.

The differences are clearly small, even for a more drastic change that is being assumed here.

Similarly for the second assumption, comparing

$$\{[C_dH(O)] + [O(C)(C_d)]\} - \{[C_B(O)] + [O(C)(C_B)]\} = -2.28 - (-2.54) = 0.26 \text{ kcal/mol}$$

with

$$\{[C_dH(C)] + [CH_2(C)(C_d)]\} - \{[C_B(C)] + [CH_2(C)(C_B)]\} = 0.02 - (0.70)$$
$$= 0.72 \text{ kcal/mol}$$

Again the difference is small.

Thus we end with the following estimated values:

$$\{[C_d(C)(N)] + [NH(C)(C_d)]\} = -5.10$$
$$\{[C_dH(N)] + [NH(C)(C_d)]\} = -4.35$$

Using these values we may now estimate free energies of transfer for the simple enamines:

$$(CH_3)_2C{=}CH\text{-}NHCH_3 \quad \Delta G_t = -0.33 \text{ kcal/mol}$$
$$CH_3C(NHCH_3){=}CH_3 \quad \Delta G_t = -0.45 \text{ kcal/mol}$$

For the next step what we want is the difference, ΔG_t (enamine) − ΔG_t(imine), which is −0.70 kcal/mol for *E*-*N*-isobutylidenemethylamine and −0.33 kcal/mol for *N*-isopropylidenemethylamine.

Using the free energies of transfer estimated above and the free energies in the gas phase calculated as described, the free energy change for conversion of *N*-isopropylidenemethylamine to *N*-isopropenylmethylamine can be calculated as 6.1 kcal/mol, in satisfactory agreement with the value estimated by Hine from a kinetic analysis for the imine of acetone and *trans*-2-dimethylaminomethylcyclopentylamine, i.e., 6.8 kcal/mol (*50*).

For the case of interest in this paper, the imine and enamine derived from acetone and aminoacetonitrile, there will be additional terms required for the nitrile group and for the interaction between the nitrile and the amino or imino nitrogen. For lack of information permitting a more detailed examination we must make the (not unreasonable) assumption that the distant polar interactions between nitrile and enamine nitrogen or imine nitrogen will be the same. This means that the difference between the free energy of transfer of enamine and imine pairs will be the same for all cases. This clearly is only an approximation, yet should be close because absent steric bulk which causes shielding from solvent the only difference is in the distant polar interactions which are not expected to be very different; the p*K*a value of the two nitrogens should be similar since a simple imine has a p*K*a of about 7 (7.6 for *N*-isopropylidenemethylamine (*57*), 6.88 for *E*-*N*-isobutylidenemethylamine (*58*)) and an enamine is expected to have p*K*a similar to aniline, i.e., 4.58 (*44*) (just as an enol (e.g., vinyl alcohol, p*K*a 10.50 (*59*)) has a p*K*a similar to a phenol (phenol itself, p*K*a 9.95 (*44*))). This means that the equilibrium constant for imine–enamine conversion in solution can be calculated from the equilibrium constant in the gas using only this roughly constant difference in free energies of transfer.

We must, however, consider the uncertainties in the estimated values. Conversion of DFT energies into heats of formation (*51*) requires an extrapolation because there are very few calorimetric values (and none for simple imines (*60*)), which can be used for calibration. For a set of five heats of formation for imines, three of which were calculated at the G2 (*62*) level of theory (*63,64*), and two of which (1-azacyclopentene (*65*) and *N*-methylbenzaldimine (*66*)) are experimental, the atomic level parameter set (*51*) (supplemented by one new parameter for doubly bonded nitrogen) gave an rms error of 3.67 kcal/mol; the modified atomic level parameter set (*51*) (which needed no new parameters) gave an rms error of 1.81 kcal/mol. The method for estimating entropies gives an rms error of 1.28 cal/K/mol for a set of 128 compounds (*35*). The calculation of free energies of transfer requires a number of estimated contributions so we will take the uncertainty as 1.0 kcal/mol. These uncertainties lead to an uncertainty in each free energy of formation of 2.10 kcal/mol, and in the free energy for the imine–enamine equilibrium of 2.97 kcal/mol.

Alternatively the quality of the estimation process can be assessed by comparing the estimated free energies of formation for *N*-isopropylidenemethylamine and *E*-*N*-isobutylidenemethylamine with values calculated from free energies of formation of methylamine (*2*), the carbonyl compounds (*1*), and water (*2*), and the equilibrium constants. The values are: *N*-isopropylidenemethylamine, estimated 24.11 kcal/mol, experimental 24.12 kcal/mol; and *E*-*N*-isobutylidenemethylamine, estimated 27.99 kcal/mol, experimental 28.82 kcal/mol. The estimated values are within 1 kcal/mol of the experimental values, which is in excellent agreement considering the expected uncertainties in the method.

pKa values. In the application of No Barrier Theory, the energies of various "corner intermediates" must be calculated. These often involve proton transfer processes, and thus various p*K*a values are required some of which had to be estimated.

The p*K*a of acetoacetic acid in water (where it is almost entirely the keto tautomer (*34*)) is 3.58 (*44*). For carbonyl protonated acetoacetic acid, the p*K*a for dissociation of the protonated carbonyl may be estimated starting with acetone, for which Yates and Cox reported a value of -5.37 using an X-function to extrapolate from sulfuric acid solutions (*67*). The effect of substituents will be assumed to be similar to that in amidines R-C(NH_2)=NH_2^+, for which $\rho = -11.98$, with σ_{meta} (*68*). From values for CH_3 and CH_2COOCH_3 (assumed to be the same as for CH_2COOH) taken from Perrin *et al.* (*68*) we calculate the p*K*a difference as -2.28, leading to a p*K*a of -7.65. The effect of carbonyl protonation on the p*K*a of the carboxylic acid is assumed to be the same as the effect of N-protonation on 2-pyridylacetic acid, for which Button and Taylor (*69*) report microscopic p*K*a values for the neutral and cationic species of 4.26 and 2.63, respectively, for an effect of the plus charge equal to -1.63. This leads to a p*K*a for the carboxylic acid in carbonyl protonated acetoacetic acid of 1.95.

If direct proton transfer is to be part of the concerted transition state, the initial carboxylic acid must be in the less stable conformation with the OH syn to the C-COOH bond. This conformation is less stable but more acidic. DFT calculations (B3LYP/3-21+*G**) lead to an energy difference of 3.26 kcal/mol. Thus the p*K*a of the syn conformation of acetoacetic acid would be 1.19 if it were not hydrogen bonded; an intramolecular hydrogen bond would lower the acidity by stabilizing the acid form.

The p*K*a for protonated carbon dioxide was estimated using the same procedure as was used for protonated ketene (*70*). The proton affinity of carbon dioxide has been measured (*71*). The free energy of transfer is known (*2*). Then from the equation in Ref. (*70*) we obtain −39 as the pK_{BH^+} for carbon dioxide. The p*K*a would shift if the carbon dioxide were bent to the angle of a carboxylic acid; the extent of this shift was estimated by calculating the energies of the four species by DFT/COSMO methods, assuming that the differences would be more meaningful than the absolute values.

$$CO_2(\text{linear}) + CO_2H^+(\text{bent}) \rightleftharpoons CO_2H^+(\text{linear}) + CO_2(\text{bent}).$$

The products of the equation as written are 11.10 kcal/mol less stable than the starting materials meaning that protonated bent CO_2 is 8.12 p*K*a units less acidic than protonated linear CO_2. The calculations were carried out with planar protonated bent CO_2, with the H anti to the remote oxygen; this corresponds to the product of decarboxylation without proton transfer of the syn conformation of the carboxylic acid.

The acidity of the OH in acetoacetic acid protonated on the ketone oxygen using the *p*-orbital rather than a lone pair orbital was estimated using the energy difference between normally and orthogonally protonated acetone (*72*), i.e., 18.8 kcal/mol. The p*K*a so estimated was −21.34. To a first approximation it was assumed that the p*K*a of the carboxylic acid in ketone protonated acetoacetic acid was independent of the mode of protonation.

The conformation of the enol of acetone with the OH in the plane orthogonal to the plane of the double bond was calculated (B3LYP/3=21+*G**) to be 3.53 kcal/mol higher energy than the planar form. The p*K*a was accordingly reduced to 7.41.

The p*K*a of the iminium ion in the N-protonated cyanomethylimine of acetoacetic acid is estimated starting from the accepted value for the *N*-methyliminium ion of acetone, 7.6 (*57*). The effect of the carboxylic acid is assumed to be the same as for 2-carbomethoxymethylpyridinium (4.15) vs 2-methylpyridinium (5.94 (*69*), i.e., −1.79, and the effect of the cyanomethyl group is assumed to be the same as the effect on an ammonium, i.e., −5.28 [5.34 (cyanomethylamine) (*44*) − 10.62 (methylamine) (*44*)= −5.28]. The result is an estimated p*K*a of 0.53. The p*K*a of the carboxylic acid in the N-protonated cyanomethylimine of acetoacetic acid is estimated to be the same as for 2-carboxymethylpyridinium, i.e., 2.62 (*69*).

The p*K*a of the carboxylic acid in the neutral form of the cyanomethylimine of acetoacetic acid was estimated to be 4.26, the value in neutral 2-pyridylacetic acid. The p*K*a of the iminium ion in the zwitterion of this imine was calculated from the other three p*K*a values as 2.17.

The p*K*a of the cyanomethylenamine of acetone was estimated starting from an estimate of the p*K*a of the methylenamine of acetone, 35 (*73*). The effect of a cyanomethyl group in RCH_2NHR' acting as an acid should be similar to the effect in RCH_2OH as an acid. The latter is described by a ρ^* of −1.32 (*74*), and CN has $\sigma^* = 3.30$ (*68*); thus the effect of CN is $\Delta pKa = 4.35$, and the p*K*a of the cyanomethylenamine of acetone is estimated to be 31.

Estimated p*K*a values should be reliable to within ±1 or 1.5 p*K* unit except for protonated carbon dioxide (probably no better than ±5 p*K*), orthogonally protonated