INGOLD LECTURE.
Reactive Intermediates: Carboxylic Acid Enols and Other Unstable Species

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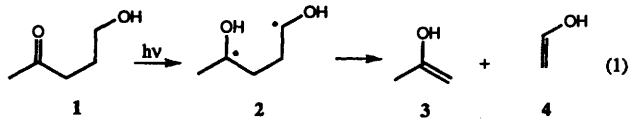
1 Introduction

Enols are the tautomeric isomers of carbonyl compounds through which many important chemical and biological reactions occur, and, if we wish to understand these reactions, and through understanding to control them, we must understand the chemistry of enols. Most enols, however, are also quite unstable, both thermodynamically and kinetically, and their lifetimes in solution are usually very short. This has impeded their study. Enols have been known for more than a century,[1] but very little hard quantitative information about the rates and equilibrium constants of their reactions was available for very nearly all of that time. The situation changed dramatically about 15 years ago when we and others developed methods for generating enols in greater than equilibrium amount under conditions where they could be observed directly and their reactions studied in detail. This has produced a wealth of reliable new information about enol isomers of simple aldheydes and ketones.[2] That work is now being extended to the more difficult task of examining the much more labile enols of carboxylic acids, esters, and amides.

This review will begin with a short description of some of our work on enols of aldehydes and ketones in order to illustrate the methods that we have used and the kinds of information that can be obtained. That will then be followed by an application of these methods to enols of carboxylic acids and their derivatives.

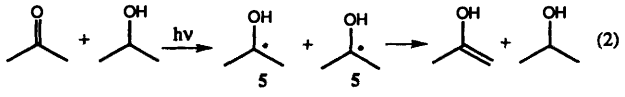
2 Methods

We have found flash photolysis to be an especially useful technique for studying the chemistry of short-lived enols. An example of this method is provided by the Norrish type II photoelimination of 5-hydroxypentan-2-one **1**, eqn. (1).[3] Irradiation of this substance leads to hydrogen abstraction from the γ-position by the oxygen atom of the photoexcited carbonyl group to give the diradical **2**, which then



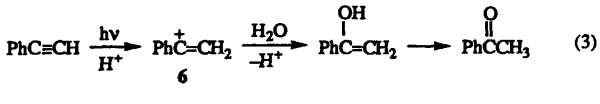
fragments to the enol of acetone **3** and the enol of acetaldehyde **4**. These reactions occur very rapidly, and, if the process is initiated by a sufficiently short and intense burst of light in a flash photolysis apparatus, the enols can be generated much faster than they ketonize to their carbonyl isomers. The ketonization reactions can then be monitored by following changes in UV absorbance of the enols. Ketonization of acetone enol is about two orders of magnitude faster than ketonization of acetaldehyde enol, and accurate rate constants for both enols can easily be obtained.

We have also made enols by the flash photolytic oxidation of alcohols and reduction of carbonyl compounds,[4] as is illustrated in eqn. (2) for acetone. Irradiation of acetone in the presence of iso-



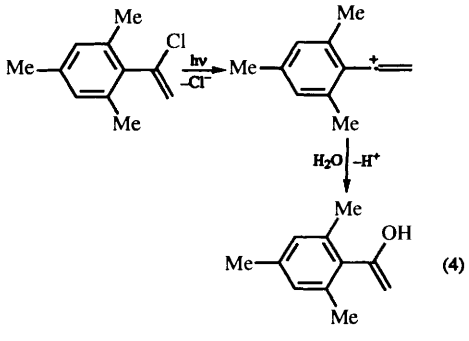
propyl alcohol leads to an intermolecular analogue of the Norrish type II reaction, giving a pair of ketyl radicals **5**; these then disproportionate, producing the enol of acetone and regenerating the alcohol.

Photohydration of acetylenes, eqn. (3), is another useful method



of generating enols.[5] The thermal hydration of acetylenes is known to occur through enol intermediates, but, in the strongly acidic solutions needed to effect this process, the enol ketonizes as fast as it is formed and consequently cannot be observed. Photoexcitation, however, greatly enhances the reactivity of acetylenes towards electrophilic addition, and now the enol is generated much more rapidly than it is consumed; its reactions may therefore be monitored.

The photohydration of acetylenes occurs through vinyl cation intermediates such as **6**, and vinyl cations can also be produced by photoionization of vinyl halides. We have consequently found that we can generate enols by the flash photolytic solvolysis of vinyl chlorides as well,[6] as is illustrated in eqn. (4).



Paramount among the things one would like to know about enols is the magnitude of the equilibrium constants for their formation

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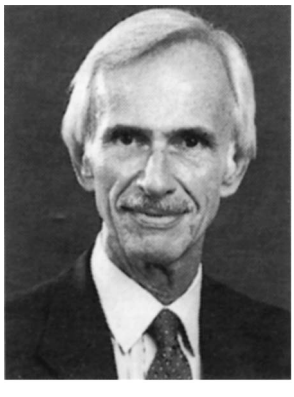


from keto isomers. Such keto–enol equilibrium constants, K_E, have traditionally been determined by the Kurt Meyer halogen titration method, which uses the fact that enols react with halogens whereas their keto isomers do not. This method works well when enol contents are not too low, as is the case, for example, with β-dicarbonyl compounds. With most monofunctional aldehydes and ketones, however, the method fails badly because enol contents here are in the parts-per-million or even parts-per-billion range, and impurities that react with halogen must be excluded at better than these levels.

This difficulty may be avoided by determining keto–enol equilibrium constants as ratios of rate constants: those for enolization, k_E, divided by those for ketonization k_K: $K_E = k_E/k_K$. Values of k_E are easily obtained by long-established methods such as halogen scavenging of the enol as it forms, and values of k_K may be supplied by the flash photolytic methods we have developed. This technique produces keto–enol equilibrium constants whose accuracy is limited only by that with which the component rate constants can be determined, and it can give good results no matter how small the value of K_E actually is.

Another important property of enols is the acid strength of their hydroxy groups. Standard methods for determining acidity constants of stable acids cannot, of course, be applied to short-lived enols, but accurate estimates of enol pK_a values may nevertheless be obtained from the way their rates of reaction change with pH. Fig. 1 shows a typical enol ketonization rate profile. At high acidity

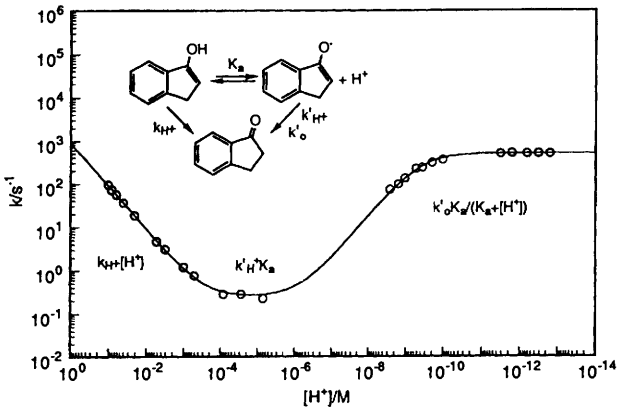
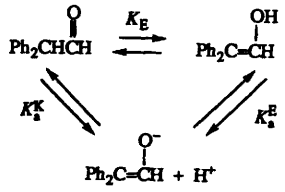


Figure 1 Rate profile for the ketonization of the enol of indan-1-one in aqueous solution at 25 °C

there is an acid-catalysed process that involves rate-determining protonation of the enol on its β-carbon by hydronium ion; this is represented by the diagonal segment with slope = −1 on the left side of Fig. 1. As the acidity drops, this reaction gives way to ketonization by β-carbon protonation of the very much more reactive enolate ion; since this process produces a hydronium ion in an initial pre-equilibrium step and then uses it up in the rate-determining step, the overall reaction is independent of acidity and it consequently appears as the 'uncatalysed' segment of slope = 0 near the centre of Fig. 1. At still lower acidities, the concentration of hydronium ions is too low to sustain this process and β-carbon protonation of enolate ion by solvent water takes over; since the hydronium ion produced in the pre-equilibrium is now not used up in the rate-determining step, the rate of reaction becomes inversely proportional to hydronium ion concentration and directly proportional to hydroxide ion concentration, giving the region of apparent hydroxide ion catalysis represented by the segment of slope = +1 on the right side of Fig. 1. Eventually, however, the position of the pre-equilibrium shifts from enol to enolate, and the advantage of converting a less reactive to a more reactive substrate is lost; hydroxide ion catalysis then becomes saturated and the rate levels off to a constant value giving the second 'uncatalysed' segment of slope = 0 at the far right of Fig. 1. Straightforward analysis of rate data in the region of transition from hydroxide ion catalysis to catalysis saturation gives both the rate constant for the carbon protonation step and the equilibrium constant for the prior equilibrium step. The latter, of course, is the acid dissociation constant of the enol. We have used this method to determine pK_a values of very short-lived enols, some with lifetimes of only a microsecond.

As shown in eqn. (5), keto–enol isomerization and acid ionization of the enol form two legs of a thermodynamic cycle whose third member is ionization of the keto form as a carbon acid. Once the equilibrium constants K_E and K_a^E for the first two legs have been determined, therefore, that for the third member, K_a^K, can be calculated as the product $K_E K_a^E$. In some cases the keto isomer is sufficiently acidic to allow K_a^K to be determined directly, and then the cycle serves as a test of the internal consistency of the data, for the pK values should sum to zero around the cycle. The diphenylacetaldehyde system, shown in eqn. (5), provides an especially good example of such a situation, for here we were able to measure each of the three constants by two independent methods.[7] The results obtained, $pK_E = 0.98 \pm 0.04$, $pK_a^E = 9.40 \pm 0.01$ and $pK_a^K = 10.42 \pm 0.02$, do sum up to a value that is less than the rather small combined experimental uncertainty of the individual measurements: $\Sigma pK = 0.04 \pm 0.05$.



(5)

A sample of results we have obtained for representative simple aldehydes and ketones is presented in Table 1. It may be seen that

Table 1 Equilibrium constants for some simple aldehyde and ketone systems in aqueous solution at 25 °C[a]

Substrate	pK_E	pK_a^E	pK_a^K
	6.23	10.50	16.73
	8.33	10.94	19.27
	7.96	10.34	18.31
	3.86	11.63	15.49
	0.98	9.40	10.42
	6.39	11.70	18.09

[a]Ionic strength = 0.10 mol l^{-1}; acidity constants are concentration quotients at this ionic strength.

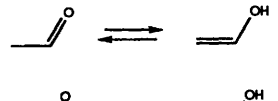
K_E for acetaldehdyde is very small: less than 1 ppm of enol is in equilibrium with the keto form. The enol content of acetone is even lower, by some two orders of magnitude. This difference between acetone and acetaldehyde may be attributed to stabilization of the keto isomer of acetone by its additional methyl group, and the next entry in Table 1 shows that phenyl is just about as good as methyl in this respect. Methyl substitution in the β-position, as in isobutyraldehyde, on the other hand, raises K_E, which may be understood in terms of alkyl group stabilization of the enol double bond. Phenyl groups in this position are even better than methyls, as shown by the relatively large enol content of diphenylacetaldehyde. A conformational effect appears to operate in the case of cyclohexanone, for its enol content is considerably greater than that of corresponding acyclic ketones and also greater than that of cyclopentanone and cycloheptanone.[4]

The acid strength of these enols is similar to that of phenols, as might be expected from the vinyl alcohol structures they have in

common There is not much variation in pK_a^E with structure for the group of substances shown in Table 1, much less than that in pK_E or pK_a^K Structural effects on pK_a^K, moreover, appear to parallel those on pK_E, and there is in fact a fairly good linear relationship between these two quantities for a substantial number of aldehydes and ketones [8]

3 Mandelic Acid and Derivatives

As is illustrated by the examples provided above, the enol isomers of simple aldehydes and ketones are usually highly labile and thermodynamically unstable substances Carboxylic acid enols are even more labile and unstable This is apparent, for example, from a comparison of the keto–enol transformation of acetaldehyde, eqn (6), with that of acetic acid, eqn (7) For acetaldehyde, pK_E = 6 23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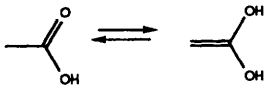
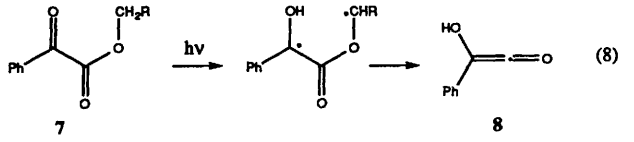

(7)

and the hydronium ion catalytic coefficient for ketonization of the enol is k_H^+ = 33 mol $^{-1}$ l s $^{-1}$ Neither of these quantities has as yet been measured directly for acetic acid, but reliable estimates can be made Guthrie has presented several different arguments that lead to the consistent result pK_E = *ca* 20,[9] and $k_H^+ = 10^8 - 10^9$ mol $^{-1}$ l s^{-1}, may be estimated on the basis of the experimentally determined value $k_H^+ = 7 \times 10^5$ mol $^{-1}$ l s $^{-1}$ for the dimethyl ether of acetic acid enol, CH_2=C(OMe)$_2$,[10] and the fact that methyl vinyl ethers are one to two orders of magnitude less reactive than the corresponding enols [8] This comparison shows that the enol content of simple carboxylic acids with no enol-stabilizing substituents can be expected to be many orders of magnitude smaller than that of simple aldehydes and ketones and that the rates of ketonization of these carboxylic acid enols will be so fast as to approach the diffusion controlled limit

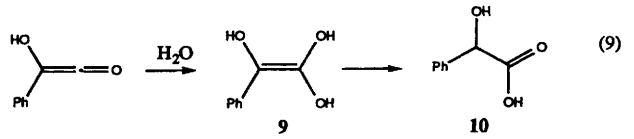
Daunting realizations such as these have directed studies of carboxylic acid enols to systems in which special structural features stabilize the enol One such approach uses bulky aromatic substituents to block access to the enol double bond, through whose protonation ketonization must take place This is a technique that has produced remarkably stable enols of aldehydes and ketones, as shown in work pioneered by Fuson some 50 years ago and lately elaborated by Rappoport [11] Its application to carboxylic acid systems has produced enols with lifetimes as long as several hours, [12,13] but these long lifetimes have also produced complications in the form of radical-producing oxidation reactions of the very electron-rich enols

Our own approach has been to increase the lifetime of the enol somewhat less by introducing substituents that we know, from our studies of aldehyde and ketone systems, stabilize enols through their electronic effects When we began our work, there were reports in the literature that irradiation of esters of benzoylformic acid **7** leads to a Norrish type II reaction, eqn (8), which produces


(8)

7 **8**

hydroxy(phenyl)ketene **8** [14] We reasoned that in aqueous solution this ketene would be hydrated to an enol **9**, eqn (9), and that the β-OH and β-Ph groups of this enol might slow its ketonization to


(9)

9 **10**

mandelic acid **10** sufficiently so that the enol would decay more slowly than it was formed and thus be observable We found that flash photolysis of benzoylformic acid esters in aqueous solution did indeed produce transient species which, through solvent isotope effects and the form of acid–base catalysis, we could identify as a rapidly reacting ketene and a somewhat more stable but still rapidly reacting enol [15]

The rate profile for ketonization of mandelic acid enol is shown in Fig 2 It is similar to rate profiles for the ketonization of simple

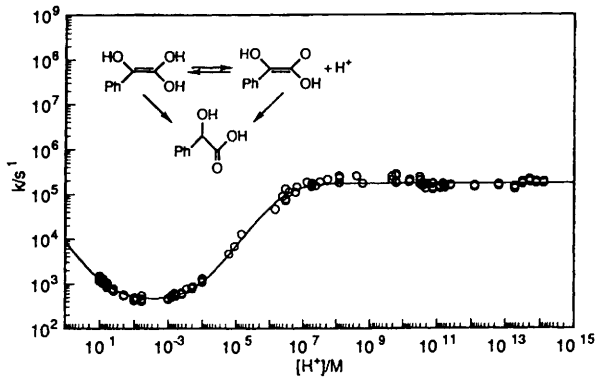


Figure 2 Rate profile for the ketonization of mandelic acid enol in aqueous solution at 25 °C

aldehyde and ketone enols (*cf* Fig 1), with the exception that the bend representing acid ionization of the enol comes at a lower acidity because this enol is a stronger acid (pK_a^E = 6 62) This is typical of carboxylic acid enols and may be attributed to the presence of the second, geminal hydroxy group, a similar acid-strengthening effect may be seen in going from ethanol **11**, with pK_a = 15 9, to acetaldehyde hydrate **12**, with pK_a = 13 6


11 **12**

In order to obtain a keto–enol equilibrium constant for the mandelic acid system by the rate constant ratio method ($K_E = k_E/k_K$), we measured rates of acid-catalysed enolization of the acid This reaction proved to be very slow, and we had to resort to high temperatures (140—155 °C) in order to get conveniently measurable rates Extrapolation of these data to 25 °C then gave a rate constant, which, when combined with the acid-catalysed rate of ketonization, provided the result pK_E = 15 4 Combination of that value with pK_a^E = 6 6 then produced pK_a^K = 22 0 for mandelic acid ionizing as a carbon acid

These results show the enol content of mandelic acid to be very low but still significantly greater than the estimate pK_E = 20 for acetic acid [9] The difference may be attributed to the β-OH and β-Ph groups of mandelic acid enol, for such substituents are known to stabilize enol isomers in simple aldeheyde and ketone systems [2]

Our characterization of the mandelic acid keto–enol system, in addition to being of general chemical interest, has proved to be of specific value to biological chemists in connection with the enzymatic racemization of mandelic acid by mandelate racemase, and the current controversy over whether the enzyme achieves its efficiency by an electrostatic effect or by formation of a strong hydrogen bond [16]

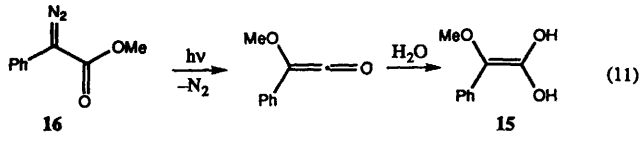
We have written the acid ionization of mandelic acid enol, eqn (10), as involving one of the geminal hydroxy groups, specifically


(10)

that *trans* to phenyl, because we found the *trans*-enol of phenylacetaldehyde, **13**, to be a stronger acid than the *cis*-isomer **14** [17] In principle, however, the ionization of mandelic acid enol might also

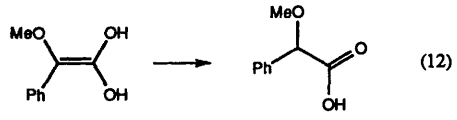
13 14

involve the hydroxy group α to phenyl. In order to investigate this matter, we wished to examine an enol for which such ionization is blocked by conversion of this hydroxy to methoxy, and we hoped to be able to make that substance, **15**, by hydration of the ketene generated through the photo-Wolff reaction shown in eqn. (11).



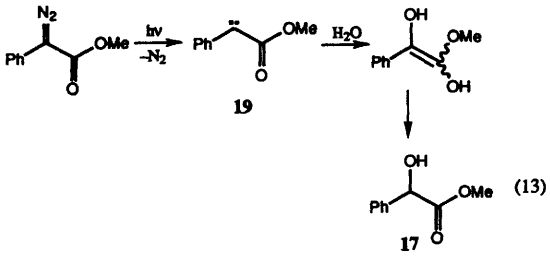
16 15 (11)

Flash photolysis of methyl phenyldiazoacetate **16** did produce a transient species which we identified as an enol, but the product of the reaction was methyl mandelate **17** rather than the expected methyl ether of mandelic acid **18**, eqn. (12).[18] We postulate that this



18 (12)

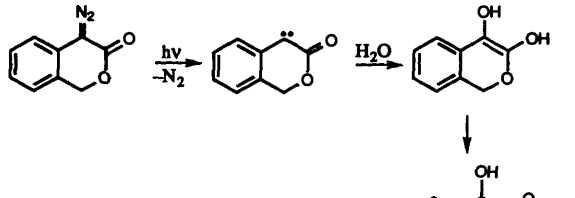
substance was formed by insertion of the methyoxycarbonylcarbene **19**, formed by loss of nitrogen from methyl phenyldiazoacetate, into an O–H bond of solvent water. Such carbene insertion reactions are well known, and a number of different mechanisms have been proposed for them, all of which involve only the carbenic carbon. Our detection of an enol intermediate in the process indicates that the carbonyl group is involved as well and that the reaction occurs as shown in eqn. (13); the process might therefore be



19 17 (13)

more accurately described as conjugate addition of water across the entire carbonylcarbene functional group.

We have since found other examples of such conjugate additions, in the cyclic system shown in eqn. (14) and also in the amide system



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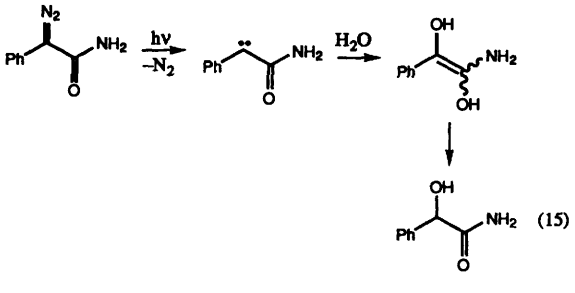
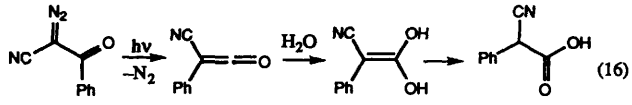


(15)

shown in eqn. (15). This has taken us into the chemistry of enols of carboxylic acid esters and enols of carboxylic acid amides.

4 Phenylcyanoacetic Acid

We have found that the enol **20** of phenylcyanoacetic acid **21** can be generated from a diazo compound precursor, **22**, eqn. (16).[19] In this



22 20 21 (16)

case flash photolysis gives the Wolff rearrangement rather than conjugate addition of water to a carbonylcarbene, and the ketene so produced is hydrated to the enol.

The rate profile for ketonization of this enol, shown in Fig. 3, is

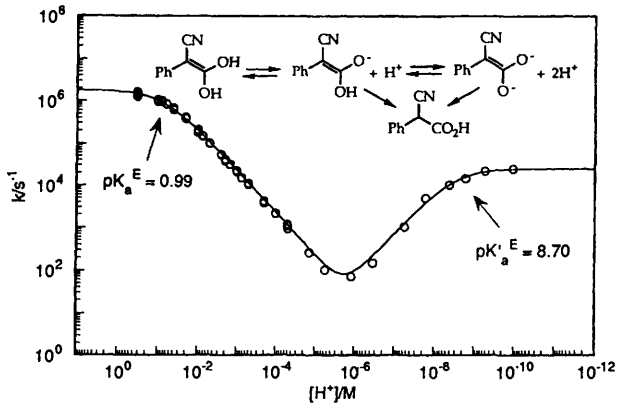
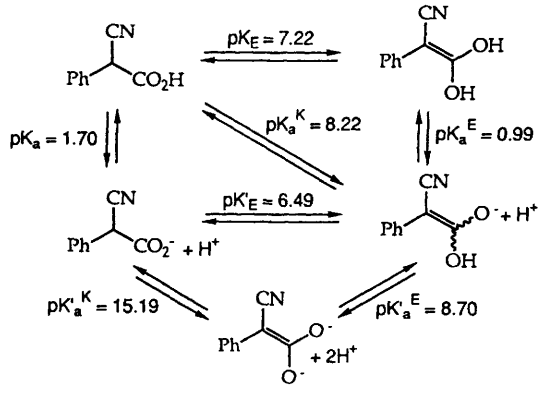


Figure 3 Rate profile for the ketonization of phenylcyanoacetic acid enol in aqueous solution at 25 °C

somewhat different from those of Figs. 1 and 2 in that there is an additional bend at the high acidity end. Through solvent isotope effects and the form of acid–base catalysis, we have been able to assign this bend to ionization of the first O–H group of the enol, and the bend at $[H^+] = ca.\ 10^{-9}$ mol l^{-1} to ionization of the second O–H group. The plateau before the first bend then represents reaction through pre-equilibrium ionization of the enol followed by rate-determining carbon protonation of the enolate ion, and the diagonal segment of slope = −1 represents the same reaction with enolate ion as the initial state. Near $[H^+] = 10^{-6}$ mol l^{-1}, carbon protonation of the more reactive dianion by water takes over, with reaction first starting from the monoanion as the initial state, giving a region of apparent hydroxide-ion catalysis, and then reaction starting from the dianion as the initial state, leading to catalysis saturation.

With the aid of rates of enolization measured by bromine scavenging, we were able to characterize the phenylcyanoacetic acid keto–enol system completely. The results are presented in Scheme 1. It may be seen that the enol is quite strongly acidic with $pK_a^E = 0.99$



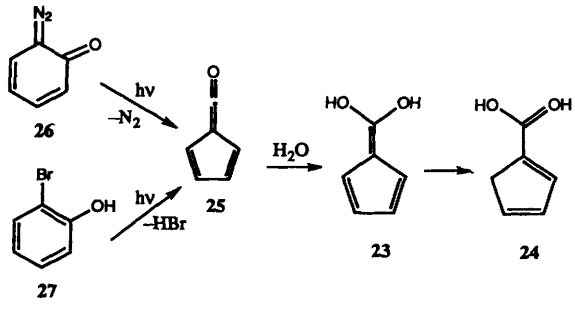
Scheme 1

for its first ionization, this makes the enol more acidic than the carboxylic acid group of its keto form[1] Even in its second ionization, with pK'^{E}_{a} = 8 70, this enol is more strongly acidic than the enols of simple aldehydes and ketones (*cf* Table 1), which attests to the strong acidifying effect of the cyano group The difference between the first and second pK_a, ΔpK_a = 7 7, is not unlike that for the first and second ionization of carbonic acid, ΔpK_a = 6 4

The cyano group also stabilizes the neutral enol strongly, raising the enol content of phenylcyanoacetic acid over that of mandelic acid by eight orders of magnitude

5 Cyclopentadienecarboxylic Acid and Derivatives

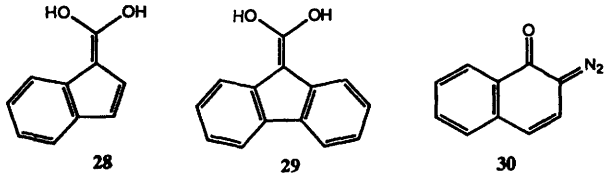
The cyclopentadiene moiety also stabilizes enols strongly, and this effect has been used in studies of aldehyde and ketone[20] as well as carboxylic[21–23] acid systems The enol **23** of cyclopentadienecarboxylic acid itself **24**, was made by hydration of the ketene **25**, which was generated in two ways by photo-Wolf reaction of the corresponding diazo compound, **26**, and also by photo-induced elimination of HBr from 2-bromophenol, **27**, as shown in eqn 17



(17)

This enol and that of mandelic acid[15] were the first carboxylic acid enols to be characterized in aqueous solution, unfortunately, however, there are problems with some of the originally published data on the cyclopentadienecarboxylic acid system,[21b] and revised values have not yet been made public

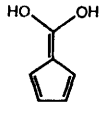
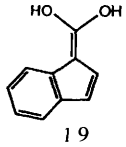
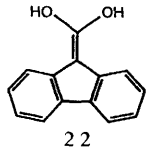
The monobenzo **28**[21b,22] and dibenzo **29**[23] analogue of cyclopentadienecarboxylic acid enol have also been investigated The



former is of some commercial importance to the photolithographic industry, for the diazonaphthoquinone **30** precursors of its derivatives are constituents of photoresists[24] and the enols are intermediates in the photolithographic process [22]

It may be seen from the results obtained, summarized in Table 2, that these enols are quite strongly acidic, this is because their conjugate bases are stabilized by delocalization of negative charge into the five-membered ring, which produces an aromatic cyclopentadienyl anion The enol contents are high as well because the enols are stabilized by fulvenoid aromatic delocalization It is significant that the acids become somewhat weaker and the enol contents somewhat smaller with increasing benzo substitution, for the resonance energy of the cyclopentadienyl ring can be expected to decrease with benzo substitution

Table 2 Summary of results for cyclopentadienecarboxylic acid keto–enol systems[a]

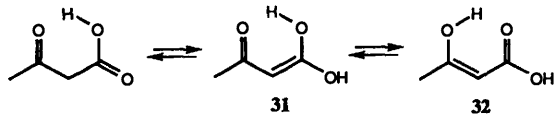
			
pK^{E}_{a}	1 3	1 9	2 2
pK'^{E}_{a}	8 7[b]	8 3	9 6
pK_{E}	8 4[b]	9 3	9 5
pK'_{E}	5 0[b]	6 6	8 3
pK'^{K}_{a}	13 7	15 2	17 9

[a]Ionic strength = 0 10 mol l^{-1}, acidity constants are concentration quotients at this ionic strength Equilibrium constants are as defined in Scheme 1 [b]Revised value provided by Professor Wirz

6 Acetoacetic Acid

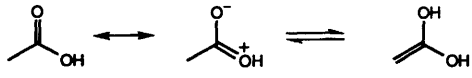
Keto–enol tautomerism in β-keto esters has been investigated almost since the beginning of enol chemistry, and these systems provide some of the most extensively documented examples of such isomerism available today In striking contrast, very few studies of tautomerism in β-keto acids have been carried out, and only one of these has dealt with the prototype substance, acetoacetic acid [25]

The acetoacetic acid system is especially interesting because two different enols may be formed, the carboxylic acid enol **31**, and the ketone enol **32**, eqn (18) The ketone enol might be expected to be



(18)

the much more stable of the two and the overwhelmingly predominant enol form in solution, for keto–enol equilibrium constants for simple ketones are very much greater than those for simple acids *cf* pK_E = 8 for acetone *vs* pK_E = 20 for acetic acid Much of this difference between acetone and acetic acid, however, must be an initial-state effect, inasmuch as the keto form of acetic acid is stabilized by conjugation of its carbonyl group with the adjacent hydroxy substituent, eqn (19), whereas such conjugative initial

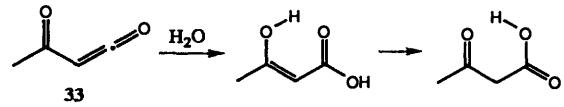


(19)

state stabilization is not possible in the case of acetone Initial state effects, of course, have no bearing on the relative abundance of the two enols of acetoacetic acid, for both are in equilibrium with the same initial state keto form [eqn (18)] The relative amounts of the two enols will be determined, rather, by the intrinsic stabilities of the enols themselves, and this may well be not as disparate as suggested by the acetone–acetic acid comparison

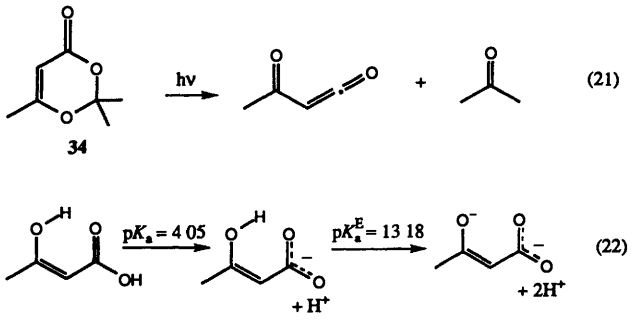
It is difficult to address this matter experimentally because the enol content of acetoacetic acid is small (pK_E = 2 25, *vide infra*) and the enol(s) are short-lived We have therefore performed *ab initio* calculations on the system at the MP2/6—311+G** level The results show an energy difference of ΔE = 11 kcal mol^{-1} (1 cal = 4 184 J) between the two enols, with the ketone enol as the more stable isomer [26] This result is thus qualitatively consistent with the prediction made from the acetone–acetic acid comparison It is significant, however, that the calculated energy difference is less than the 16 kcal mol^{-1} that corresponds to the pK_E difference for acetone–acetic acid

We obtained the enol of acetoacetic acid by hydration of acetylketene **33**, eqn (20), which was generated by flash photolysis

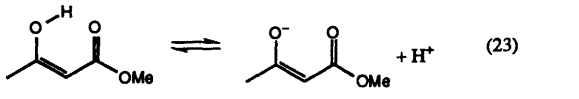


(20)

of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **34**, eqn (21) [27] The rate profile for ketonization of the enol showed bends that could be attributed to ionization of its two acidic groups and from which the pK_a values shown in eqn (22) were obtained The first of these, pK_a = 4 05, shows the carboxylic acid group of the enol to be considerably more acidic than the value, pK_a = 5 67, that can be predicted from a correlation of acidity constants of substituted acrylic acids [28]

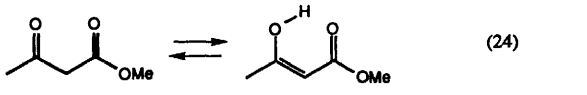


The difference may be attributed to the hydrogen bond formed between the hydroxy group of the enol and the carbonyl group of the acid, which is not taken into account by the correlation, this hydrogen bond will become stronger as the acid ionizes, thus stabi lizing the ionized state This hydrogen bond also stabilizes the unionized state of the second ionization, making the enol a weaker acid than it would otherwise be This enol, with $pK_a^E = 13\ 18$, is in fact unusually weakly acidic *cf* $pK_a^E = 9\ 48$ for ionization of the enol of the corresponding methyl ester, eqn (23) [29] Another factor



contributing to the weak acidity of the enol of acetoacetic acid is electrostatic repulsion between the two negative charges in the dianionic product

In the only other investigation of the acetoacetic acid keto–enol system,[25] rates of enolization were determined by bromine scavenging, and combination of those with our results for ketonization leads to $pK_E = 2\ 25$ This is a rather low value for a β-dicarbonyl system, for example, $pK_E = 1\ 10$ for tautomerism of the corresponding methyl ester, eqn (24) [29] The difference may again be



attributed to hydrogen bonding, this time in the initial state of the acetoacetic acid reaction, eqn (18), an effect that is absent from the methyl ester system

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