reward is freedom from the bell-shaped curve assumptions of the traditional approach. More importantly, the new methods free the scientist to choose statistical methodology appropriate to the problem at hand, rather than choosing on the basis of mathematical tractability.

None of this means that mathematics has disappeared from statistical theory, only that it is disappearing from routine statistical applications. The question of which computer-based method to use, and when to use it, is becoming a central concern of mathematical statistics.

REFERENCES AND NOTES

1. The data in Box 1, from the Stanford arm of the LRC-CPPT experiment, is courtesy of D. Feldman and J. Farquhar, Stanford University; see (7).
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15. We thank R. Olshen for allowing us to use his CART example.

Enols and Other Reactive Species

YVONNE CHIANG AND A. JERRY KRESGE

Rapid advances in the chemistry of enols and other reactive species have been made possible recently by the development of methods for generating these short-lived substances in solution under conditions where they can be observed directly and their reactions can be monitored accurately. New laboratory techniques are described and a sample of the new chemistry they have made available is provided; special attention is given to ynols and ynamines and the remarkable effects that the carbon-carbon triple bonds of these substances have on their acid-base properties.

THE CHEMISTRY OF ENOLS IS CURRENTLY EXPERIENCING A renaissance (*1*) primarily because of the development of methods for generating these usually very reactive substances in solution under conditions where their reactions can be studied in detail. Such studies are worthwhile because enols and enolate ions are essential intermediates in many important reactions of carbonyl compounds, and a number of biological reactions also involve enol formation; if we wish to understand these processes, and through understanding to control them, we must understand the chemistry of enols.

We began work in this area by examining enol isomers of simple aldehydes and ketones. That work, however, soon led to the investigation of other reactive species, such as enols of carboxylic acids and their derivatives, ketenes, carbenes, ynols, and ynamines. The latter are especially fascinating substances: they are believed to exist in interstellar space and are postulated as prebiotic molecules. We have discovered that the carbon-carbon triple bond in ynols and ynamines exerts a remarkable influence on the acid-base properties of their hydroxyl and amino groups; theoretical calculations at the ab initio level have helped us understand the origins of this effect.

This article begins with an account of our work on enols and continues with a description of what we have learned about ynols and ynamines. Although the discussion is limited largely to research done in our own laboratory, we owe much to stimulation provided by the pioneering work of Guthrie *et al.* (*2*), Capon *et al.* (*3*), Dubois, Toullec, and co-workers (*4*), and Rappoport and co-workers (*5*), and we are indebted as well to an early review by Hart (*6*).

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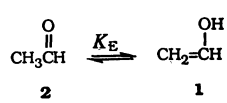
Generation of Enols

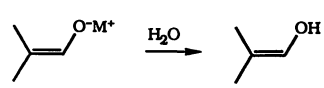
Simple enols such as vinyl alcohol, **1**, can be formed readily from their keto isomers, **2**, Eq. 1.



(1)

The reaction, however, is reversible, and the position of equilibrium generally lies strongly on the keto side; the amount of enol present at equilibrium is consequently seldom sufficient to permit direct observation, even by the most sensitive spectroscopic methods. Investigation of enol chemistry therefore requires generation of the enol in greater than the equilibrium amount in the medium of interest. We have developed a number of ways of accomplishing this in aqueous solution.

We first made enols by hydrolysis of their alkali metal salts, Eq. 2,



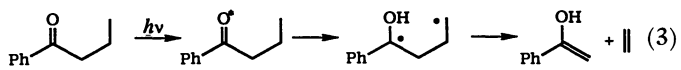
(2)

using solutions of these salts in aprotic solvents prepared by standard synthetic methodology (7). Addition of a small quantity of such a solution to a large amount of water resulted in a very fast oxygen-to-oxygen proton transfer and produced the enol in an essentially wholly aqueous medium. Conversion of the enol to its keto isomer then proceeded at a slower rate, which we could monitor accurately by following the marked change in the ultraviolet spectrum that accompanies the ketonization reaction.

This method of generating enols requires mixing two solutions and consequently cannot be applied to substances with lifetimes shorter than the mixing time. This limitation unfortunately excludes

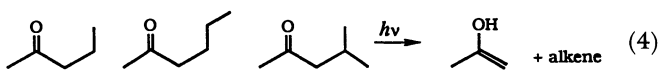
a number of the more interesting enols, and in order to study these we have developed other methods that avoid mixing. All of these other methods use very fast photochemical processes to produce the enol directly in the reaction medium. The photochemistry is initiated by a short, intense burst of light supplied by a flash photolysis apparatus, and the decay of the enol is monitored by fast absorption spectroscopy.

Flash photolysis was first used to study enol chemistry by Wirz and co-workers at the University of Basel, who generated the enol of acetophenone by Norrish type II photoelimination of butyrophenone (*8*), Eq. 3 (Ph = phenyl).



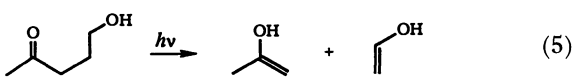
(3)

Working in collaboration with Wirz, we used this reaction to make the enol of acetone from each of the three ketones shown in Eq. 4 (*9*)



(4)

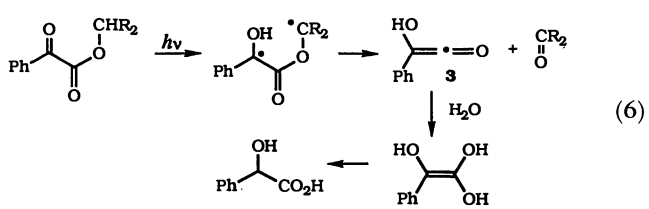
and also from the hydroxy ketone given in Eq. 5 (*10*).



(5)

The latter process provides the enol of acetaldehyde as well, but that enol ketonizes some 100 times more slowly than does the enol of acetone, and we were consequently able to determine rates of both reactions accurately.

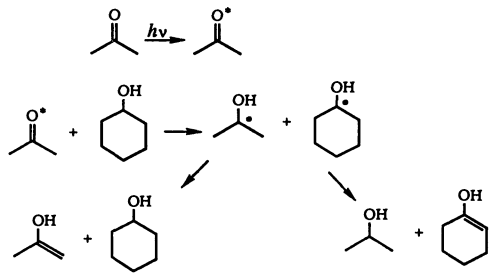
We have also used the Norrish type II reaction to generate a carboxylic acid enol, that of mandelic acid, via the hydration of hydroxyphenylketene, **3**, Eq. 6 (R = alkyl group) (*11*).



(6)

This enol is believed to be an intermediate in a much-studied enzymatic reaction that catalyzes the racemization of mandelic acid (*12*), and through our work we were able to show that the mechanism of this reaction cannot be one in which the enzyme makes the enol and then discharges it to ketonize spontaneously in solution. If the enol is an intermediate, it must be bound to the enzyme throughout the racemization process in a way that stabilizes the enol by some 15 kcal mol^{-1}.

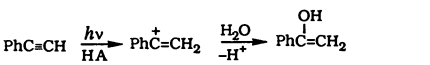
Flash photolysis of seemingly appropriate precursors, however, sometimes fails to produce enols by Norrish type II reaction, and we have therefore developed other methods. An especially useful one is the photooxidation of alcohols (*13*) illustrated in Eq. 7 for the case of cyclohexanone enol. This process is the intermolecular counterpart of the Norrish reaction in which photoexcited acetone, having no γ-hydrogen atom to undergo intramolecular transfer, abstracts an α-hydrogen from cyclohexanol. This process produces two ketyl radicals that disproportionate in two ways, giving two different enols. Here again the reaction partners can be chosen so as to give sufficiently different rates to allow accurate determination of



(7)

both rate constants.

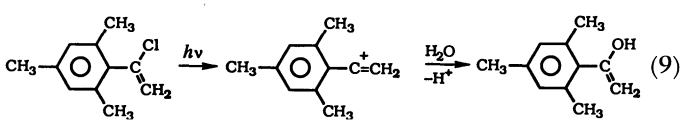
We have also generated enols by the photohydration of acetylenes (*14, 15*), Eq. 8.



(8)

This reaction occurs thermally as well, but high acidities are required, and that speeds up ketonization to the point where it becomes a fast and unobservable reaction after the rate-determining step (*16*). Photoexcitation, however, increases the reactivity of acetylenes enormously (*17*), and in a flash photolysis experiment formation of the enol is more rapid than its ketonization; the enol may consequently be observed and studied.

As Eq. 8 shows, enols are formed in the photohydration of acetylenes by hydration of vinyl cations. Vinyl cations can also be generated by photosolvolysis of vinyl halides (*18*), and we have used this process to generate enols as well. In particular, we have studied the enol of 2,4,6-trimethylacetophenone in this way (*15*), Eq. 9;



(9)

this substance is of interest in connection with the very stable, sterically hindered enols containing several such 2,4,6-trimethylphenyl groups that were first prepared by Fuson and co-workers several decades ago (*19*) and are currently being reinvestigated by Rappoport and co-workers (*5*).

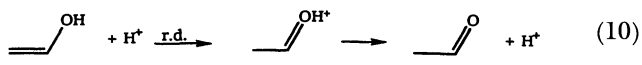
Enol Chemistry

Paramount among the things that a chemist would like to know about enols is the magnitude of equilibrium constants for their formation from carbonyl compound isomers, that is, the values of K_E (defined as [enol]/[keto]) for reactions such as that of Eq. 1. Such "enol contents" have traditionally been determined by halogen titration, a method invented by Meyer nearly a century ago (*20*). The technique is based on the fact that enols react with halogens, whereas their keto isomers do not. This works well when enol contents are high, but it fails when they are low. For example, the most recent determinations of K_E for cyclohexanone, made by three successive refinements of the Meyer technique, differ by more than three orders of magnitude (*21*), and the lowest of these is ten times greater than the enol content we determined for this substance using a method that is free of the difficulties associated with halogen titration of substances at very low concentrations.

Our method is based on the simple fact that an equilibrium constant for a chemical reaction is equal to the ratio of its forward to reverse rate constants; thus, for the reaction of Eq. 1, $K_E = k_E/k_K$,

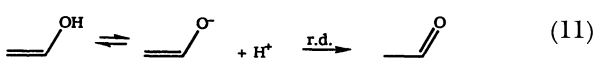
where k_E is the specific rate of enolization and k_K is that for ketonization. Rates of enolization are easily measured, for example, by halogen scavenging of the enol as it forms in the rate-determining step of the halogenation reaction, and the literature contains many values of k_E. Determination of k_K is more difficult, but this may now be accomplished by generating the enol with one of the methods we have developed and then monitoring its conversion to the keto isomer. Such determinations of K_E, moreover, may be made under a variety of experimental conditions, for, as the typical rate profile shown in Fig. 1 indicates, ketonization, and therefore enolization as well, is catalyzed by both acids and bases. The equilibrium constant, of course, must remain invariant under changing catalyst conditions, and comparison of results obtained with different catalysts can be used to verify the reliability of the experimental methods.

We have found that the low pC_{H^+} portion of rate profiles such as that given in Fig. 1 represents ketonization through rate-determining (r.d.) protonation of the enol on the β carbon, followed by a rapid loss of hydrogen from the hydroxyl group, Eq. 10.



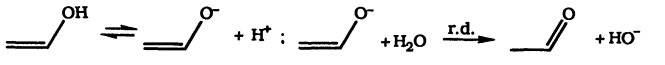
(10)

The "uncatalyzed" reaction in the center of the profile also occurs by rate-determining protonation on β carbon, but in this case the substrate is the enolate ion formed by prior ionization of the enol, Eq. 11;



(11)

the first step of this sequence produces a proton while the second consumes one, and the rate of the overall process is therefore independent of proton concentration. At higher pC_{H^+} an apparent hydroxide ion catalysis takes over, but this too occurs through rate-determining proton transfer to β carbon of the enolate ion, this time from a solvent water molecule acting as the proton donor, Eq. 12;

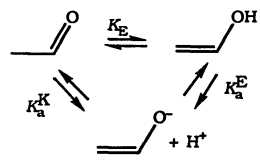


(12)

the rate of this process is thus inversely proportional to $[H^+]$ and consequently directly proportional to $[HO^-]$. Enolate ions are much more reactive to electrophilic addition of protons at β carbon than are enols—we have found rate ratios as great as 10^9—and reaction occurs preferentially through the enolate ion even when this is the minor species. At sufficiently high pC_{H^+}, however, enolate becomes the predominant species, and the advantage of converting a less reactive to a more reactive species is lost; hydroxide ion catalysis then becomes saturated and the rate levels off into the final uncatalyzed region of the rate profile.

Standard treatment of ketonization rate data obtained in the region of partial saturation of hydroxide ion catalysis yields both the rate constant for the rate-determining carbon protonation step and the equilibrium constant for the prior rapid ionization. This equilibrium constant is of course the acidity constant of the enol; enol acidity constants may therefore be determined in this way despite the fact that some enols are very short-lived: we have been able to accomplish this for enols with lifetimes as short as a microsecond.

The acid ionization of enols and their formation from keto isomers constitute two legs of a thermodynamic cycle whose third member is ionization of the keto form directly as a carbon acid, Eq. 13.



(13)

Knowledge of keto-enol equilibrium constants, K_E, and enol acidity constants, K_a^E, then leads directly to evaluation of keto acidity constants, K_a^K: $K_a^K = K_E K_a^E$. Some representative results we have obtained in this way are listed in Table 1, together with corresponding values of K_E and K_a^E. It may be seen that values of pK_a^K are usually sufficiently large to preclude direct measurement in dilute aqueous solution. This, however, is not always so and in such cases the cycle of Eq. 13 provides a check on the internal consistency of the data, for the sum of the pK values around the cycle must be zero. An especially favorable example is provided by diphenylacetaldehyde: we were able to determine each of the three equilibrium constants for this system in two independent ways and found the sum of the pKs to be 0.043 ± 0.046, which corresponds to a combined experimental uncertainty of ±10% (*22*).

The sample of our results in Table 1 shows that aldehydes have greater enol contents than ketones. This difference may be understood in terms of stabilization of the keto isomer by electron donation to the positively charged carbonyl carbon atom: ketones have two alkyl or aryl groups to provide such stabilization, whereas aldehydes have only one. An extreme example of stabilization of the keto isomer and consequent reduction of the enol content is provided by carboxylic acids: $pK_E = 15.4$ for mandelic acid. The opposite effect, destabilization of the keto group, is apparent in the raised enol contents of the trimethylsilyl, carboxyl, and carboxylate systems of Table 1. Alkyl or aryl substitution one carbon atom away from the carbonyl group also increases enol contents, but in this case by lowering the energy of the enol isomer through the well-known double bond stabilizing effect of these groups (*23*). There is also an interesting ring size effect that increases the enol content of cyclohexanone over that of analogous acyclic ketones.

The data of Table 1 show further that the acid strength of enols is similar to that of phenols. An exception is the enol of mandelic acid, but its increased acid strength is consistent with the expected acidifying effect of a second hydroxyl group situated on the same carbon atom, as seen, for example, in the increased acidity of gem-diols over monobasic alcohols. There is on the whole not much variation in pK_a^E, certainly less than in pK_E or pK_a^K, and changes in pK_a^K appear to mirror changes in pK_E; there is, in fact, a good linear correlation between pK_a^K and pK_E that might be used to estimate values of pK_a^K for systems where this quantity cannot be measured.

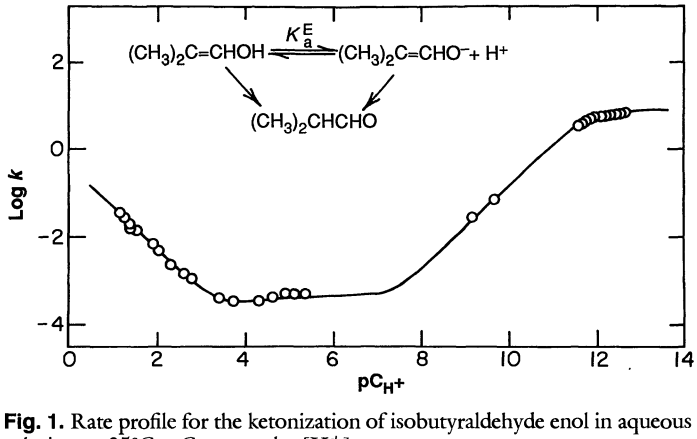
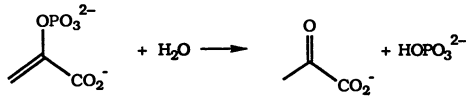


Fig. 1. Rate profile for the ketonization of isobutyraldehyde enol in aqueous solution at 25°C; $pC_{H^+} = -\log[H^+]$.

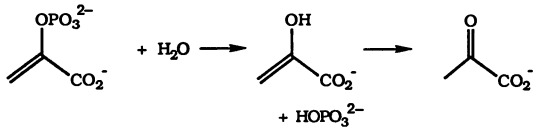
The carboxylate-substituted system listed in Table 1 has an interesting biological significance, because its enol, in the form of the phosphate ester phosphoenolpyruvate, **4**, plays an important role in many metabolic pathways. It is a so-called "energy rich" molecule whose reactions are used to drive unfavorable biological processes. Phosphoenolpyruvate is, in fact, the most energy rich of these substances: its hydrolysis, Eq. 14,



(14)

4

is exoergic by $\Delta G° = -14.6$ kcal mol^{-1} (*24*) ($\Delta G°$ represents the Gibbs free energy), which makes this reaction nearly twice as exoergic as the conversion of adenosine triphosphate to adenosine diphosphate, the principal energy-producing process in living systems. The hydrolysis of phosphoenolpyruvate may be viewed as occurring in two stages, hydrolysis of the ester to give enol, followed by ketonization of the enol, Eq. 15.



(15)

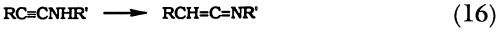
Our determination of $pK_E = 5.11$ then gives $\Delta G° = -7.0$ kcal mol^{-1} for the second stage, which shows that the masked enol function in phosphoenolpyruvate accounts for nearly one-half of its high energy content.

Ynols and Ynamines

Ynols, **5**, are triple bond analogs of enols, and ynamines, **6**, are their

5 **6**

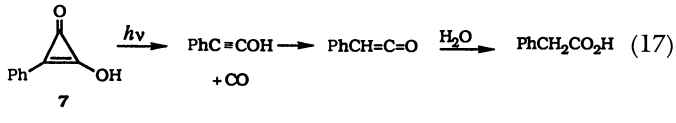
amine counterparts. Although ynols are believed to exist in interstellar space (*25*), they were observed on Earth only in the gas phase (*26*) and in low-temperature matrices (*27*) before our investigation of them in aqueous solution (*28*). Primary and secondary ynamines had also been observed only under unusual conditions (*29*) before our generation of them in aqueous solution (*30*), probably because they undergo facile rearrangement to ketenimines, Eq. 16;



(16)

tertiary ynamines cannot rearrange in this way and are consequently well-known, stable substances (*31*).

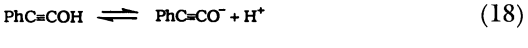
Our research on ynols began with photodecarbonylation of phenylhydroxycyclopropenone, **7**. Flash photolysis of this substance in aqueous solution produced phenylacetic acid via two successively formed short-lived intermediates, which we identified as phenylynol and phenylketene, Eq. 17.



(17)

7

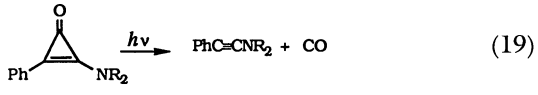
We found further that conversion of the ynol to the ketene was an acid-catalyzed reaction that occurred by rate-determining proton transfer to carbon and that this substrate existed predominantly as the phenylynolate ion, even at the highest acidity we could use, $pC_{H^+} = 2.8$, limited by the fastest rate we could measure, $k = 3 \times 10^7$ s^{-1}. This allowed us to set the upper limit $pK_a \leq 2.8$ for the ionization of phenylynol as an oxygen acid, Eq. 18.



(18)

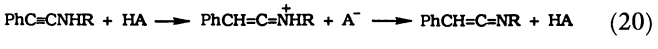
This remarkable result makes phenylynol more acidic than most carboxylic acids and a much stronger acid than its double bond analog, the enol of phenylaldehyde, PhCH=CHOH, for which $pK_a = 9.6$ (*32*). This difference is reminiscent of the well-known greater acidity of acetylene, CH≡CH, in comparison to ethylene, $CH_2=CH_2$.

This striking effect of the triple bond on acid strength also appears in the acid-base properties of ynamines. We generated ynamines in aqueous solution by a reaction similar to that which we used to obtain ynols: photodecarbonylation of phenylaminocyclopropenones (*30*), Eq. 19.



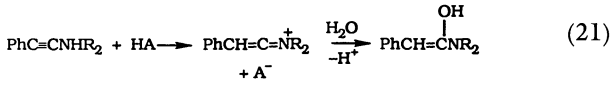
(19)

This is a general process that can be used to prepare primary, secondary, or tertiary ynamines. We found that all three classes of ynamines undergo ready protonation at β carbon to give a cationic intermediate in which the positive charge is stabilized by delocalization into the amino group. This cation then either loses a proton from nitrogen, forming a ketenimine if the ynamine is primary or secondary, Eq. 20,



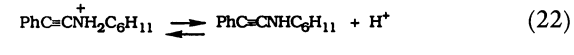
(20)

or combines with water, giving an amide enol if the ynamine is tertiary, Eq. 21.



(21)

In sufficiently strongly acidic solutions protonation of the ynamine on the amino nitrogen can also be expected to take place, converting the ynamine into an unreactive form and inhibiting the reactions of Eqs. 20 and 21. We found no such inhibition in the most acidic solutions we could use, which again were limited by the fastest rate constants we could measure. This restriction set an upper limit of, for example, $pK_a \leq 0.3$ for ionization of the conjugate acid of *N*-cyclohexylphenylynamine, Eq. 22.



(22)

That result makes this ion at least 10 p*K* units more acidic than the conjugate acid of cyclohexylamine itself ($pK_a = 10.6$).

The conversion of primary and secondary ynamines to ketenimines is also catalyzed by bases, and the form of the catalysis indicates that this reaction occurs by rapid and reversible removal of a proton from nitrogen followed by rate-determining reprotonation on carbon by a solvent water molecule, Eq. 23.

$$PhC{\equiv}CNH_2 + HO^- \rightleftharpoons PhC{\equiv}CNH^- + H_2O \longrightarrow PhCH{=}C{=}NH \quad (23)$$

The rate of this second step is not known, but an upper, diffusion-controlled limit can be set. That then provides a limit for the equilibrium constant of the first step of this reaction, which in turn leads to a limit for the acidity constant of the ynamine ionizing as a nitrogen acid, Eq. 24.

$$\underset{\mathbf{8}}{PhC{\equiv}CNH_2} \rightleftharpoons PhC{\equiv}CNH^- + H^+ \quad (24)$$

In the case of the parent substance phenylynamine, **8**, this limit is $pK_a \leq 18$. That makes this amine at least 17 pK units more acidic than ammonia itself, for which $pK_a = 35$ (*33*).

Some insight into the origin of this remarkable acidifying effect of the carbon-carbon triple bond may be gained from the results of ab initio molecular orbital calculations (*34*). These calculations give energies of reaction for the gas phase ionizations listed in Table 2. It may be seen that agreement with experimental values is good where these are available. It may also be seen that these calculations predict substantial acidifying effects for the acetylenic group in the gas phase, just as is observed in solution.

The results of these calculations may be formulated into isodesmic reactions, such as those of Table 3, and these may then be used to examine the effect of the acetylenic group in the initial and final states of these ionizations separately. The first entry of Table 3 deals with the initial states of the ynol and enol reactions. It shows that transfer of an –OH group from acetylenic to vinylic carbon is an exoergic or downhill process, and that puts the energy of the ynol relative to unsubstituted acetylene above that of the enol relative to unsubstituted ethylene; this difference is in a direction that will make the energy gap between initial and final states smaller for the ynol than for the enol and consequently makes the ynol the stronger acid. The second entry of Table 3 deals with the final states of these reactions. Transfer of $-O^-$ from acetylenic to vinylic carbon has the opposite energetic effect: it is a downhill or endoergic process. The energy of the ynolate relative to unsubstituted acetylene is thus below that of the enolate relative to unsubstituted ethylene and that too is in a direction that will reduce the energy gap between initial and final states for the ynol system compared to the enol system, again making the ynol the stronger acid. This analysis thus indicates that the greater acidity of ynols over that of enols is a combination of initial state and final state effects. The last two entries of Table 3 show that the same is true of ynamines compared to their double bond analogs, enamines.

Table 1. Keto-enol equilibrium and acidity constants for some carbonyl compounds in aqueous solution at 25°C.

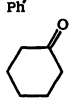
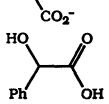
Substrate	pK_E	pK_a^E	pK_a^K	Reference
	6.23	10.50	16.73	(*10*)
	8.33	10.94	19.27	(*37*)
	7.96	10.34	18.31	(*38*)
	3.86	11.63	15.49	(*7*)
	0.98	9.40	10.42	(*22*)
	6.39	11.70	18.09	(*13,39*)
	4.88	11.54	16.42	(*40*)
	3.16			(*41*)
	5.11	11.55	16.66	(*41*)
	15.4	6.62	22.0	(*11*)

Table 2. Calculated energies of reaction. Geometry optimizations were done at the HF/6-31+G* level and improved energies were obtained from MP4/6-311/+G** calculations at these optimized geometries; zero-point energy contributions were added using HF/6-31+G* frequencies scaled by 0.9. Results for the first three reactions are from (*34*) and those for the second three are from (*35*).

Reaction	ΔE^* (kcal mol^{-1})
$CH{\equiv}COH \rightleftharpoons CH{\equiv}CO^- + H^+$	333
$CH_2{=}CHOH \rightleftharpoons CH_2{=}CHO^- + H^+$	357 (357)
$CH_3OH \rightleftharpoons CH_3O^- + H^+$	384 (382)
$CH{\equiv}CNH_2 \rightleftharpoons CH{\equiv}CNH^- + H^+$	361
$CH_2{=}CHNH_2 \rightleftharpoons CH_2{=}CNH^- + H^+$	376
$CH_3NH_2 \rightleftharpoons CH_3NH^- + H^+$	405 (402)

*Values in parentheses are experimental quantities obtained from (*42*).

These initial state and final state differences may be rationalized in terms of inductive and conjugative effects of the groups involved. The –OH group has an electron-withdrawing inductive effect, as have also the CH≡C– and $CH_2{=}CH$– groups. Juxtaposition of these groups in the initial state ynols and enols will therefore be destabilizing, but it will be more so in the case of the ynol because its inductive effect is stronger; this is apparent, for example, from the substituent constants $\sigma_I = 0.29$ for CH≡C– and $\sigma_I = 0.11$ for $CH_2{=}CH$– (*36*). This differential effect raises the relative energy of the ynol compared to that of the enol, just as predicted by the isodesmic reactions for the initial states of these reactions.

Conjugative effects are likely to be more important than inductive effects in the final states of these reactions because of the ionic species involved and also because of the very strong electron-supplying conjugative effect of $-O^-$. The CH≡C– and $CH_2{=}CH$– groups can either supply or accept electrons by conjugation; in this case they will act as electron acceptors in order to stabilize the negative charge on $-O^-$. The CH≡C– group, however, will be the better electron acceptor because it has two π-systems to the

Table 3. Energy changes for isodesmic reactions.

Reaction	ΔE^* (kcal mol^{-1})
$CH{\equiv}COH + CH_2{=}CH_2 \rightarrow CH_2{=}CHOH + CH{\equiv}CH$	−10
$CH{\equiv}CO^- + CH_2{=}CH_2 \rightarrow CH_2{=}CHO^- + CH{\equiv}CH$	+15
$CH{\equiv}CNH_2 + CH_2{=}CH_2 \rightarrow CH_2{=}CHNH_2 + CH{\equiv}CH$	−4
$CH{\equiv}CNH^- + CH_2{=}CH_2 \rightarrow CH_2{=}CHNH^- + CH{\equiv}CH$	+10

*Based on energies calculated as described in Table 2.

CH_2=CH– group's one, and also because the C–O bond in CH≡CO^- is shorter (distance r = 1.219 Å) than that in CH_2=CHO^- (r = 1.251 Å) (*34*) and will consequently allow better overlap of the orbitals that interact in this conjugation. This differential effect lowers the relative energy of the ynolate compared that of the enolate, again just as predicted by the isodesmic reactions based on our calculations. Similar arguments may be made for the ynamine and enamine systems (*35*).

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