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"Kinetic" vs. Thermodynamic Acidities of Enones in the Gas Phase

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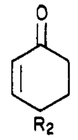
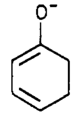
With ICR spectrometry, the gas-phase acidities of the α'- and γ-positions of 2-cyclohexen-1-one, as well as the acyclic analogues 2-butenal and butenone, have been determined. The vinylogous site is favored by 6.5 ± 0.4 kcal/mol in the cyclic enone and 8.2 ± 0.4 kcal/mol in the open chain forms. MNDO calculations parallel this. In 2-cyclohexen-1-one-*4,4-d*$_2$ there is a slightly greater rate for deprotonation by *tert*-butoxide than for dedeuteration, but this may be attributed to either an isotope effect or a scrambling of the label in the γ-dedeuterated anion.

In an α,β-unsaturated enone such as **1** there are two sites for deprotonation by bases of reasonable strength: the γ-site leading to the vinylogous enolate **2** and the α'-site giving the cross-conjugated enolate **3**. The α-site, for stereoelectronic reasons, will be of considerably lower acid strength in cyclic enones, since it cannot be involved in π-delocalization to the carbonyl group. Selection of the reactive site in solution is dependent on the nature of the attacking base, the solvent, counterion, and reactant concentration.[1] In general, exothermic proton transfer to heteroatom bases gives the cross-conjugated anion, while endothermic deprotonation with a weak base can give a close mixture of the two forms.[1f] It has been shown that the α'-site is slower by about an order of magnitude in endothermic deuterium exchange, compared to the γ-position.[1c] There are cases involving anomalous mechanisms, however.[1e] As part of a general program of investigation of the gas-phase counterparts of "well-known" solution-phase reactions, in order to separate the roles of the intrinsic structure and the external effects of solvent and counterions, we have examined the gas-phase equilibrium and kinetic acidities of both sites in **1**, by ion cyclotron resonance spectrometry. The deuterium-labeled form **1b** was also employed in an attempt to differentiate between the kinetic acidities of the two sites. The open chain forms **4** and **5** have been examined, as well as the γ-blocked 4,4-dimethyl substituted compound **6**.



1a, R=H
b, R=D



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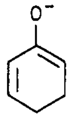

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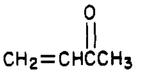
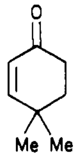


$CH_2{=}CH\overset{\overset{O}{\|}}{C}CH_3$

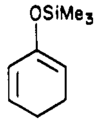
4

$CH_3CH{=}CHCH{=}O$

5



6



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Experimental Section

The ICR instrumentation[2] and techniques used to determine kinetics, equilibria,[3] and double resonance information[4] have been previously described. All reactions cited were confirmed by double resonance. The ionization gauge was turned off after stable pressures had been achieved, in order to reduce pyrolysis of the compounds. The pyrolysis of **1**, for example, leads to formation of cyclohexadienone by loss of H_2, which upon deprotonation gives phenoxide. Most chemicals were obtained commercially, and all were purified by distillation or preparative gas chromatography before use. Compound **1b**, synthesized by Dr. Richard Clikeman and obtained from Prof. J. B. Lambert, was ca. 95% *4,4-d*$_2$ by proton NMR. The alkyl nitrites used as sources of alkoxide ions on thermal electron impact were generated in situ.[5] Nitrogen trifluoride was the source of fluoride ion. Thiolate ions were formed by thermal electron impact on the appropriate disulfide.[6] The *O*-trimethylsilyl cyclohexadiene **7** was prepared by the literature methods.[7] All synthesized compounds displayed appropriate NMR spectra.

Results

Establishment of a proton-transfer equilibrium between **1a** and ethanethiol reveals that it is 0.9 kcal/mol less acidic than the thiol,[3] giving it a ΔG°_{acid} of 352.0 ± 2.0 kcal/mol and ΔH°_{acid} of 360.3 ± 2.5 kcal/mol. The ΔS°_{acid} for both acidic sites of cyclohexenone is taken as 26.0 eu, since no loss of rotational entropy is associated with deprotonation of the ring.[3] While the site of deprotonation is not known from this experiment alone, the results below indicate that this acidity reflects the formation of anion **2**. Compound **6**, with the γ-site blocked, is 1.3 kcal/mol more acidic than acetoxime, for a ΔG°_{acid} of 358.5 ± 2.0 kcal/mol and ΔH°_{acid} of 366.8 ± 2.3 kcal/mol. The *gem*-dimethyl groups should not increase the acidity by more than a few tenths of a kcal/mol, relative to **1**, since they are distant from the charge-bearing atoms. The difference in acidity between the α'- and γ-sites in cyclohexenone is thus 6.5 ± 0.4 kcal/mol; the smaller uncertainty here compared to that of the absolute acidities reflects the fact that this is a relative measurement.

Butenone **4** is 0.7 kcal/mol less acidic than *t*-BuCH=NOH (ΔG°_{acid} = 357.7 ± 2.5 kcal/mol).[3] Taking ΔS°_{acid}

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as the same as for acetophenone[3] gives a ΔH°_{acid} (**4**) of 365.2 ± 2.5 kcal/mol, or 1.6 kcal/mol more acidic than **6**. While the 2-butenal (**5**) is capable of isomerization to the β,γ-unsaturated form (7.6 kcal/mol less stable than **5** by group additivity)[8] on reprotonation of the anion, we nevertheless observe good proton transfer equilibria with a number of thiols to give ΔG°_{acid} = 350.3 ± 2.5 kcal/mol and ΔH°_{acid} 357.0 ± 3.0 kcal/mol, 8.2 kcal/mol more acidic than **4** and 3.3 kcal/mol more acidic than the cyclic form **1**.

Deuterated enone **1b** was used to verify the sites of reactivity and to provide information on relative rates. Reaction of **1b** at 5×10^{-7} torr with the simple alkoxide bases MeO^-, t-BuO^-, and t-$BuCH_2O^-$ results in both $(M - H)^-$ and $(M - D)^-$ signals from the enone, at reaction times of less than 100 ms. This corresponds to a 10% reaction efficiency.[9] For t-BuO^- as the base, the rate of production of $(M - D)^-$ is 75% of that for $(M - H)^-$. When the weaker bases MeS^- and EtS^- are used, only the $(M - D)^-$ ion is present at short times. In the unquenched mode, which represents an integration of ion signals over all times, so that products of very slow reactions are observed, the $(M - H)^-$ also appears when **1b** is reacted with CH_3S^-, as well as M^- and $(M - 3)^-$. We attribute this multiple deuterium exchange to reaction of the $(M - D)^-$ with **1b** to effect a general scrambling of deuterium. Multiple exchanges of this type are well documented in ion/molecule chemistry.[10] Although such thermoneutral proton transfer between carbon acids is slow on the ICR time scale,[11] when the spectrometer is operated in the unquenched mode, sufficient time is available for it to occur. Weaker bases such as HS^- give neither the $(M - H)^-$ nor $(M - D)^-$ ion. This bracketing of the two acidities is consistent with the equilibrium values obtained for **1** and **6**.

The enolate produced by deprotonation of **1** by methoxide does not undergo deuterium exchange with CH_3OD. If this anion is **2**, the acidity difference between the γ-site and methanol is 19 kcal/mol, too large a difference for deuterium exchange to proceed readily.[10] Deuterium exchange into the anion of **1** was seen by Hunt and coworkers.[10c] The conditions were different than in the present work, however; a stronger acid, EtOD, was used, and the source temperature was 175 °C, mucher hotter than the 40 °C here. Enolate **3** should exchange deuterium with CH_3OD since its basicity is much closer to that of MeO^-; acetone enolate, of comparable basicity, exchanges all five hydrogens under such conditions.[10] When **3** is specifically produced by fluorodesilylation[12] of O-(trimethylsilyl)-1,3-cyclohexadien-1-ol (**7**) in the ICR spectrometer, using F^- from NF_3, the results enolate exchanges one hydrogen for deuterium with CH_3OD. When **3**, produced in this fashion, is treated with a variety of standard acids, to determine the threshold for proton transfer, acids as strong as methanethiol (ΔH°_{acid} = 352.7 kcal/mol) are required to protonate it. The lack of deuterium exchange into the enolate(s) produced by deprotonation of **1** by methoxide thus implies that **3** may not be produced by this reaction. If this is the case, then the observed rates represent the branching ratio out of the activated complex and not necessarily a clean kinetic isotope effect. Scheme I shows a possible pathway for proton loss from **1b** not involving **3**.

Scheme I

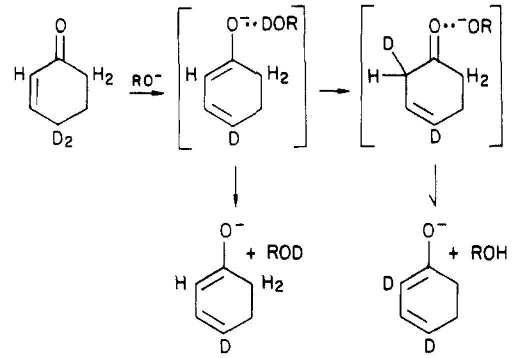

Table I. Experimental and MNDO Acidities of Some Ketones and Aldehydes

compound	ΔH°_{acid}(exptl),[a] kcal/mol	ΔH°_{acid}(MNDO),[b] kcal/mol
cyclohexenone (1)		
α'	365 ± 5[c]	359.8
γ	360.3	348.9
4,4-dimethylcyclohexenone (6)	366.8	
butenone (4)	365.2	369.9
butenal (5)	357.0	355.7
acetone	368.8[d]	372.0
acetaldehyde	366.4[d]	372.1
acetophenone	363.2[d]	

[a] Equilibrium experiment, ±2.3 kcal/mol unless otherwise stated. [b] Reference 18. [c] Bracketing experiment for deprotonation by t-$BuCH_2O^-$ and not by CH_3S^-, see text. [d] Reference 3.

Discussion

The acidities of the two sites in 2-cyclohexen-1-one are in the order expected based on a simple delocalization of charge argument. The only other data available for the effect of vinylogation on gaseous anion stability involves the relative acidities of propene and 1,3-pentadiene. The latter acidity is derived from the electron affinity of the pentadienyl radical[13] and the C–H bond strength of 1,3-pentadiene,[14] by using the thermochemical cycle $\Delta H^\circ_{acid}(AH) = DH^\circ(A - H) + IP(H^\bullet) - EA(A^\bullet)$.[15] Insertion of the ethenyl group between the acidic carbon and the vinyl π-delocalizing functionality results in an increase in ΔH°_{acid} of 11.6 kcal/mol, larger than for the enone. This increase in the effect of vinylogation can be attributed to a saturation effect:[16] propene is less acidic than the ketone, so more negative charge remains on the carbanionic site, and the effect of the additional stabilizing group is greater.

From Table I, butenone **4** is seen to be 3.6 kcal/mol more acidic than acetone and 2.0 kcal/mol less acidic than acetophenone. This ordering of substituent effects as CH_3

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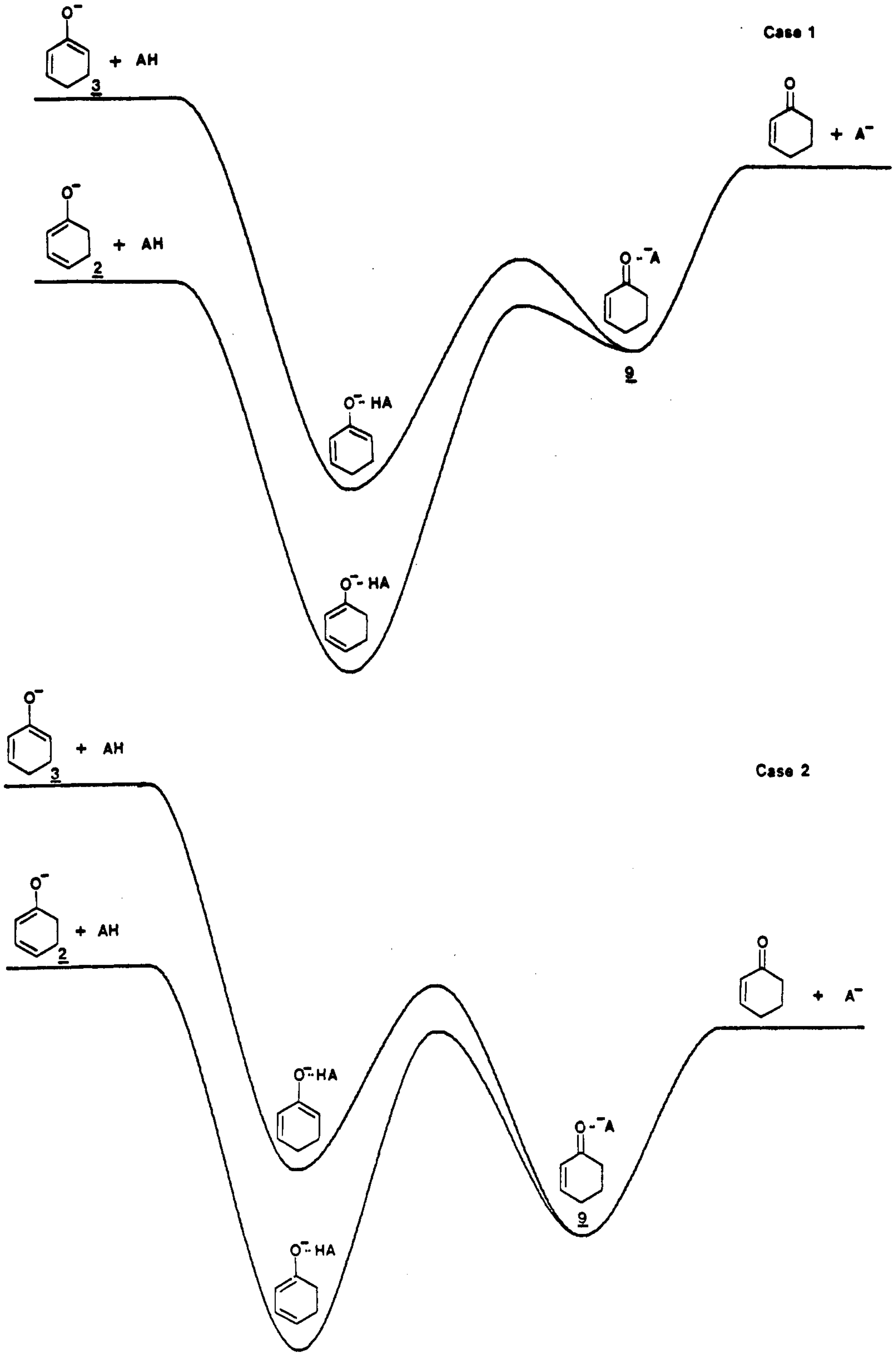

Figure 1. Gas-phase reaction coordinates for protonation and isomerization of enolates 2 and 3 by an acid AH.

$< CH{=}CH_2 <$ Ph is the inductive order,[17] consistent with the substituents' being on an atom with a zero MO coefficient in the allyl anion type HOMO involved. Butenal 5 is 9.4 kcal/mol more acidic than acetaldehyde, a slightly smaller change upon vinylogation than for propene.

In order to further examine the effects of structure on energy in these molecules, we have performed MNDO semiempirical molecular orbital calculations[18] on the various species studied here, with complete geometry optimization. This technique has been shown to yield gas-phase acidities for compounds with delocalized anions accurate to ca. 3–5 kcal/mol, though for localized anions the calculated acidities are too weak by 5–25 kcal/mol.[18] Both calculated acidities for 1, given in Table I, are more acidic than the respective experimental values. In the open

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chain cases, for ketone **4** the calculated number is 5 kcal/mol less acidic than the experimental value, while the calculated value for butenal is within the experimental uncertainty. The general overestimation of the cyclic acidities may be due to the tendency of the MNDO method to give optimized rings that are more planar than found experimentally; this should affect the difference in ring strain upon rehybridization at the acidic carbon. The calculations give appropriate changes in bond lengths and angles upon proton removal for all the acids examined. The calculated increase in stability of 10.9 kcal/mol for **2** relative to **3** is reflected in the charge densities on the various atoms as given by MNDO: in **3** the increase in anionic charge upon proton removal is largely situated on the oxygen and C-6 atoms, with little increase at C-4 or C-2, while for **2** the negative charge is spread more equally over oxygen, C-2, and C-4.

Anion reactivities can often be related to the vertical detachment energy of the electron in the HOMO (paralleling the radical's electron affinity).[18] For **2** and **3**, the calculated HOMO energies are nearly the same, 2.26 and 2.17 eV, respectively. The experimental systems closest in structure to **2** and **3** where electron affinities have been measured are phenylacetaldehyde enolate (EA = 2.10 ± 0.08 eV) and acetophenone enolate (EA = 2.06 ± 0.08 eV).[19] The comparable experimental values for the linear and cross-conjugated enolates indicates that the similar HOMO energies in the MNDO calculations are reasonable and that the anion stabilities here must be rationalized in terms of other structural factors than the HOMO energies alone.

The apparent production of **2** rather than **3** upon fluorodesilylation of **7**, when there is ample literature precedent for regiospecificity by this reaction,[12] can be interpreted as an induced rearrangement of the anion by the probe reaction, protonation by a Brønsted acid. Proton transfer reactions in the gas phase are generally represented by a double-minima surface, where the wells correspond to species held together by hydrogen bonds or loose ion–dipole interactions.[20] The reaction coordinates of Figure 1 are constructed by using the literature thermochemistry for acidities[3] and estimates of the hydrogen bond strengths of the enolate–alcohol cluster ion obtained from a correlation of known $RO^-{\cdot\cdot}HOR$ bond strengths with alcohol acidities.[21] The surfaces thus derived reveal that **2** and **3** will form different cluster ions on hydrogen bonding to the probe acid HA, but both must go through the common intermediate **9** on the route to cyclohexenone and A^-. If the acid HA is less acidic than the α'-site, or intermediate in acidity between the two sites (case 1), the most favorable exit pathway from **9** is not to cyclohexenone but to **2**, resulting in no net mass change for the ion. Only when HA is more acidic than the γ-site (case 2) will production of A^- be the favored channel. Intermediate **9** will be created in different excited states for protonation of **2** compared to **3**, which may result in different rates of decomposition, but the threshold behavior for exiting in the two channels should not be changed by this.

In solution, differentiation of the two isomeric anions is achieved kinetically.[1] The gas-phase data indicate that for the base *tert*-butoxide, the rate constants for proton and deuteron loss from **1b** are comparable, and consistent with a small positive isotope effect. In the gas phase, these tend to be small when highly excited transition states are involved,[22] with some exceptions.[23] While this appears to support the solution-phase results, that the type of base and its solvation are important in the kinetic differentiation, at the same time these results must be interpreted with care. As noted above, it is not clear that the $(M - H)^-$ ion from **1b** is **3**. Even if it were, both reaction channels are exothermic (−13 and −6.5 kcal/mol for production of **2** and **3**, respectively). Such reactions in the ICR spectrometer are of the chemically activated type shown in Figure 1, where the intermediates are formed adiabatically, in vibrationally excited states above the surface, since there is no solvent to carry away the excess energy. Activation barriers are thus at the bottom of the wells, due to the ion–dipole and ion-polarizability interactions of the ion and neutral. If the well is sufficiently deep, the barrier top will not extend above the energy level of the reactants. Under these conditions, it is not simply the potential energy surface that controls the rate of the reactions but also the number of vibrational and rotational states above it at the adiabatic energy level of the reactants. The potential surface affects this, in that a high barrier will result in fewer states at the reactants' energy, but a simple function like the Arrhenius equation is not adequate to interpret these data. At the present time, a simple statement concerning the relative kinetic acidities of the two sites cannot be made.

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Registry No. **1**, 930-68-7; **4**, 78-94-4; **5**, 4170-30-3; **6**, 1073-13-8.

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