selenirene (**24**) reappear and those belonging to ethynyl selenol (**23**) are enhanced.

Further efforts using the above approach to prepare other members in this series and to determine how the "antiaromatic quartet" influences their chemical and physical properties are underway.

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A. Krantz,* J. Laureni
Department of Chemistry, State University of New York Stony Brook, New York 11794
Received December 27, 1976

A Ketene Intermediate in *S*-Acetoacetyl Coenzyme A Hydrolysis. Direct Comparison of Relative Leaving Abilities of Anionic Oxygen and Sulfur(II) Groups from an Acyl Center

Sir:

It has long been accepted that thiol esters have pronounced acidic properties with respect to the hydrogen atoms on the α-carbon site and many of the coenzymic functions of *S*-acetyl coenzyme A have been rationalized on this basis.[1-3]

Aryl acetoacetates with powerful leaving groups and acidic α-hydrogen atoms undergo hydrolysis and acyl transfer by means of an elimination-addition (E1cB) mechanism (eq 1a)

$$\begin{array}{l} CH_3COCH_2COXR \rightleftharpoons CH_3C\bar{O}CHCOXR + H^+ \\ \qquad\qquad\qquad\qquad \downarrow \\ CH_3COCH_2CON \xleftarrow{NH} CH_3COCH{=}C{=}O + \bar{X}R \end{array} \qquad (1)$$

(a) X = O, (b) X = S

involving a ketenoid transition state.[4] More recently, general reviews of the area of elimination-addition acyl transfer have appeared[5,6] and established its centrality in the transfers of many biologically important compounds.[6] However, little attention has been paid to the possibility, either in enzymic or nonenzymic reaction, of such a route for thiolacetoacetates (eq 1b), of which *S*-acetoacetyl coenzyme A is an important example. Accordingly, we have studied the basic hydrolysis of a series of leaving-group-substituted thiolacetoacetates bearing directly on this question[5] of a ketenoid transition state for *S*-acetoacetyl coenzyme A reactions.

The most useful criterion[4-6] for distinction of such E1cB reactions from associative, bimolecular mechanisms, involving tetracoordinate intermediates,[7] is the value of β_{LG}, the Brønsted exponent for correlation of the logarithms of the rate constants with the pK_a of the conjugate acid of the leaving group. The magnitudes of β_{LG} found for E1cB reactions are commonly very much higher than in corresponding bimolecular solvolyses.[4-6]

Thiolacetoacetates were synthesized either by literature procedures[8] (alkyl) or by amine-catalyzed reaction of diketene with the thiol (aryl); details will be reported subsequently. In degassed, 0.01 to 0.10 M sodium hydroxide solutions (ionic strength = 0.1, 25 °C) in the presence of 10^{-5} M ethylenediaminetetraacetic acid, the observed pseudo-first-order rate constants for thiolacetoacetate hydrolyses were found to be independent of hydroxide ion concentration. Kinetics were followed spectrophotometrically using the UV absorption band (~300 nm) of the ester enolate ions; in some cases a pH-stat method was used, yielding consistent results. Under these conditions (high pH) we are able to measure directly the reaction of the conjugate base form of the substrate. Values of $k^S_{plateau}$ (the pH independent value of k_{obsd} (s^{-1}) for thiolacetoacetates in strongly basic media) for seven esters yielded a Brønsted relationship (eq 2) with β_{LG} (−1.13) close to that observed by Pratt and Bruice[4] (−1.28) for the E1 collapse of aryl acetoacetate anions (eq 3, calculated by least-squares analysis of some of their data[4]). This large, negative value of β_{LG} provides strong evidence [3,5,6] of an E1cB route for thiolacetoacetates.

$$\log k^S_{plateau} = 7.60 - 1.13\ pK_{LG} \quad (r = 0.997) \qquad (2)$$

$$\log k^O_{plateau} = 11.50 - 1.28\ pK_{LG} \quad (r = 0.999) \qquad (3)$$

The pK_{LG} range studied was 6–10.6, the faster, aryl thiolacetoacetates being studied by means of stopped-flow spectrophotometry. Other parameters (e.g., deuterium kinetic solvent isotope effects, activation parameters) have been used to differentiate between uni- and bimolecular hydrolytic mechanisms for esters but are often equivocal.[5,6] We have found that, at 40.0 °C, k_H/k_D = 1.5 for the plateau term for *S*-acetoacetyl-*N*-acetylcysteamine, comparable with previous values for E1 collapse of ester anions.[4,6] For this ester, $\Delta S^{\ddagger}_{25°C}$ for the $k_{plateau}$ term is +11.3 eu, again consistent with a markedly unimolecular transition state. The apparent second-order rate constant ($k_{HO^-} = k_{plateau} \times K_a/K_w$) for *S*-acetoacetyl-*N*-acetylcysteamine, hydrolyzing by the E1cB route, is some 600-fold greater than the observed[9] value of the k_{HO^-} for *N*,*S*-diacetylcysteamine. The magnitude of the "rate enhancement" is markedly leaving group dependent (because of the difference in β_{LG} values) and we estimate a rate difference of 10^5–10^6-fold for the 4-chlorothiophenyl esters,[10] taking the pK_a of 4-chlorophenyl thioacetoacetate as 8. At the thioethyl ester level, little difference is seen.

As the $k_{plateau}$ term refers to the unimolecular fragmentation of the ester conjugate base, it reflects largely the bond-breaking process (–CO–XR cleavage in eq 1) and the first, direct comparison of the relative leaving tendencies of oxygen and sulfur anionic leaving groups becomes possible for an acyl center. Such an approach to leaving group comparison was first suggested by Pratt and Bruice for malonate esters.[4] In the case

of the acetoacetyl derivatives, for a leaving group of pK_{LG} = 10, the oxy anion departs some 250-fold faster than the thiolate species; for pK_{LG} = 6.0, the advantage of oxygen over sulfur is some 1000-fold. Use has been made in the literature[7] of the *greater* leaving ability of RS^- than RO^- from sp^3 carbon, but we know of no case in which a direct comparison has been possible for a reaction of well-established mechanism.

As *S*-acetoacetyl coenzyme A was one of the thiol esters used to construct eq 2, its hydrolysis in aqueous solution must occur by the E1cB route and a ketene pathway. In E1cB-transfer reactions, the nucleophile attacks *after* the rate-determining step and exerts but little influence on the transition state.[5,6] We have found that the presence of up to 1.67×10^{-2} M aniline *decreases* rather than increases $k^{S}_{plateau}$ for *S*-acetoacetyl-*N*-acetylcysteamine, but at this alkalinity no acetoacetanilide is formed. Carbinolamine formation with the β-keto group may explain the inhibiting effect of aniline. For *S*-acetoacetyl-*N*-acetylcysteamine, $k^{S}_{plateau}$ is invariant down to about pH 9, where protonation of the conjugate base (ester, pK_a = 8.65 (spectrophotometric titration), 8.50 (kinetic pH profile)) begins to be detectable as a rate decrease.

In view of these observations, we are investigating a series of thiolacetates (including *S*-acetyl coenzyme A), to determine the participation, or otherwise, of a ketene route for their hydrolyses. Carbanions from thioacetates, if formed, would be expected to be very efficient in leaving group expulsion[11a] by analogy with a series of sulfonyl esters which exhibit E1cB hydrolysis (viz., $XSO_2OC_6H_4p\text{-}NO_2$; $k_{plateau}$ for X = $PhCH^- \gg MeN^- \gg O^-$, which is the order of ester pK_a values viz., ~21, 9, and 2, respectively).[11] In this light we might mention the elegant experiments performed to show that (*S*)-malate is formed by enzyme-catalyzed reaction of glyoxalate and *S*-acetyl coenzyme A, with inversion of configuration at the acetyl methyl group.[12] This has been held to implicate the planar (enzyme bound) enolate ion of *S*-acetyl coenzyme A, but is also consistent with collapse of this species to (enzyme bound) ketene, followed by reaction with glyoxalate in the active site. It is also appropriate to mention *S*-malonyl coenzyme A and other biological malonic thiol esters at this stage as malonyl thiol esters have been shown to form enolate ions in base.[4]

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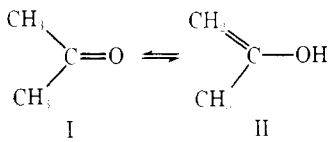
N. F. Yaggi, K. T. Douglas*
Department of Chemistry, Duquesne University
Pittsburgh, Pennsylvania 15219
Received March 14, 1977

The Enol of Acetone

Sir:

In the condensed phase, acetone is known to exist almost entirely in its keto form (I).[1] The enol tautomer (II), although yet to be directly observed experimentally, has been estimated by bromine titration methods to lie at least 8.2 kcal/mol higher in free energy.[1a] Because prototopic tautomerism is, from all evidence, an extremely facile process, it has not been possible to prepare the enol forms of molecules such as acetone independently of their thermodynamically more stable keto tautomers. Therefore, all that is, in fact, known about the stabilities of such species derives from experiments on two-component equilibria in which the enol is by far the minor component.



I II

We describe in this communication a simple experiment which enables the determination of the thermodynamic stability of the enol form of acetone independent of that of its keto tautomer.[2] The predominant ion–molecule reactions which occur when a mixture of isopropylthiol, perdeuterioacetone, and a base, B, of known proton affinity are added to a pulsed ion cyclotron resonance (ICR) spectrometer[3] (in approximate proportions 100:10:1 and total pressure 3×10^{-6} Torr) are shown in Scheme I. Electron impact on *i*-PrSH leads to a buildup of the protonated compound by way of reaction of initially formed fragment ions with isopropylthiol itself. This in turn reacts exothermically with deuterated acetone to yield the oxygen-protonated compound and with B to produce BH^+. If B is a sufficiently strong base it will be able to abstract acetone's oxygen-bound proton, thus providing an additional source of BH^+. If stronger still, it will be capable of deuteron

Scheme I