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THE TRANSACETOACETYLATION REACTION: MECHANISTIC IMPLICATIONS.

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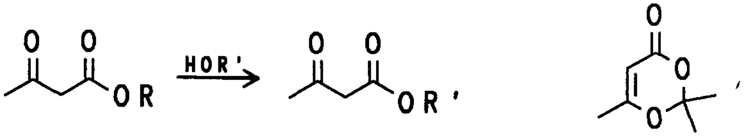
Acetoacetylated (1) materials are of interest as intermediates in the pharmaceutical, agrichemical, chemical and polymer industries.[1,2] The lachrymatory properties of diketene along with concerns regarding its toxicity and shipping have predicated a need for alternative acetoacetylation technologies. One such alternative is the transesterification of the corresponding nucleophile with an appropriate acetoacetate (transacetoacetylation). While this method has found limited synthetic application,[3a,c,d] we are unaware of any work on the mechanism of this reaction since the pioneering work of Bader and Carroll.[3a,b,e] The potential utility of this process led us to expand on this work and examine the mechanism of this reaction in more detail.



1a-g 1' 2

Figure 1

The rates for the thermal reaction of a variety of acetoacetates with n-butanol in xylene are summarized in Tables 1 and 2.[4] Examination of the data from these studies indicates that the transacetoacetylation reaction is mechanistically distinct from typical transesterification reactions. Most notably the experimental rate constants are independent of alcohol concentration (entries 1-6 of Table 1) and the more sterically encumbered t-butyl acetoacetate (t-BAA, 1a) and t-amyl acetoacetate (t-AmAA, 1g) react 15-20 fold faster than other acetoacetates. Further evidence that the transacetoacetylation reaction proceeds by a mechanism different from that of typical transesterification reactions is apparent from the absence of any pronounced effect of either catalyst or solvent on the rate of reaction.[5] It is also interesting to note that the observed rate constants at 91.7°C for 1a are also ca. 50% faster than those for the analogous reaction of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (2, TKD, the diketene-acetone adduct); which has been shown to undergo an analogous first-order reaction with alcohols, phenol and amines.[6c]

The lack of a dependence of the observed rate constants on the nucleophile concentration, the absence of any pronounced effect of common transesterification catalysts and the surprisingly rapid rate of the more sterically encumbered tertiary esters demonstrate that a mechanism involving a tetrahedral intermediate such as that proposed by

Bader[3a,b] cannot be of great importance. The reaction must proceed via a unimolecular, rate-determining decomposition to a reactive intermediate, such as acetylketene (3).

Table 1
Rate Constants for Reaction of ROAcAc With n-BuOH at 91.85°C

Entry	Compound #	R	kx10^{4a}	(S)^b	[nBuOH]^c	[ROAcAc]^c
1	1a	tBu	1.716	(0.07)	0.492	0.474
2	1a	tBu	1.662	(0.03)	2.623	0.475
3	1a	tBu	1.859	(0.03)	1.027	0.472
4	1a	tBu	1.559	(0.05)	0.174	0.068
5	1b	Et	0.102	(0.002)	0.526	0.473
6	1b	Et	0.136	(0.001)	4.987	0.477
7	1c	Me	0.097	(0.001)	0.611	0.551
8	1d	iBu	0.138	(0.004)	1.068	0.474
9	1e	iPr	0.140	(0.007)	1.070	0.537
10	1f	$HC(iPr)_2$	0.083	(0.003)	1.046	0.477
11	1g	tAm	1.460	(0.07)	1.072	0.495
12	TKD(2)^d		1.07	(0.03)		

(a) First-order rate constant in sec^{-1}. (b) Standard deviation from ANOVA analysis. (c) Molar concentrations of n-BuOH and acetoacetate respectively. (d) See Reference 5c for a complete listing of kinetic parameters for this compound.

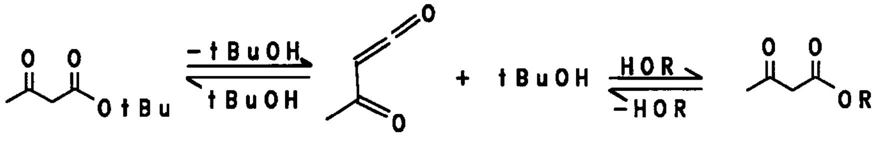
Table 2
Effect of Temperature on Rate of Reaction of Ethyl Acetoacetate (EAA)
and t-Butyl Acetoacetate (tBAA)

Temperature (C°)	EAA k(sec-1)x10$^{4(a)}$	tBAA k(sec-1)x10$^{4(a)}$
91.85	0.10	1.65
98.70	0.19	2.50
106.00	0.37	5.16

Activation Parameters

Acetoacetate	Log A^b (sec^{-1})	Ea (kcal/mol)^b	ΔH‡ (kcal/mol)^b	ΔS‡ (eu)
EAA	10.22	25.43	24.69	-14.2
tBAA	9.48	22.19	21.45	-17.6

(a) Average first-order rate constants. (b) Correlation Coefficient (R2) from ANOVA analysis =0.999 for EAA and 0.978 for t-BAA.



1a 3 1

Figure 2

Acetylketene has been similarly implicated in the reactions of dioxinone **2**.[6c] The fact that the reactive intermediate involved in this process is acetylketene rather than some other species has been demonstrated using matrix isolation-infrared spectroscopy. Thus, thermolysis of either ethyl or t-butyl acetoacetate in the transfer line of a GC-IR and trapping of the resulting effluent in an argon matrix at 6 K produced materials with IR spectra identical to that produced from thermolysis of dioxinone **2**,[6c] with characteristic infrared absorbances at 2137 and 1676 cm^{-1}. This spectroscopic data, along with the activation parameters (Table 2) and concentration dependence (Table 1) for transacetoacetylation of tBAA and EAA, suggest that while the rates of the two processes differ, the mechanisms of the two reactions are very similar and thus this proposed mechanism may, in fact, be quite general.

The formation of an acetylketene intermediate via an E1cB mechanism has been demonstrated by Bruice[7] in the base-catalyzed hydrolysis of variously substituted phenyl acetoacetates. These same workers suggested that a different process is operative in the analogous reactions of alkyl acetoacetates. The preceding results indicate that acetylketene can also be produced from acetoacetates under relatively mild thermolysis conditions without the intermediacy of anions or the use of base catalysts.

While the formation of the ketene intermediate in Figure 2 is unimolecular, the concentrations of the nucleophiles can become important in the transacetoacetylation reaction of acetoacetates, particularly during the latter part of the reaction when the concentration of the alcohol co-product becomes significant.[8a] This effect is much more pronounced for acetoacetates such as EAA than for tBAA; the latter displays first-order behavior out to at least 90-95% conversion.

The proposed mechanism explains the results discussed in this work as well as the observations of Bader,[3a,b] Taber[3c] and Gilbert.[3d] For example, the observation that 2,2-disubstituted acetoacetates do not undergo exchange reactions[3a,c,d] is readily attributed to the inability of these materials to form the corresponding ketenes. The fact that t-butyl acetoacetate (as well as other tertiary beta-ketoesters) cannot be prepared from either ethyl or methyl acetoacetate is presumably due to both the thermodynamic preference[8b] for the less sterically encumbered EAA or MAA as well as the significantly faster back-reaction for decomposition of the tertiary acetoacetate. This hypothesis can be tested by the transacetoacetylation of t-BAA with tertiary alcohols. If steric effects play an important role in this process, this reaction should be extremely sluggish. If, on the other hand, this reaction follows a mechanism such as that described in Figure 2, these reactions should proceed readily. The reaction of t-BAA with 1-methyl-cyclohexanol and 2-methyl-3-buten-2-ol produces the corresponding acetoacetates in 83 and 72 % yields respectively,[9] thus providing further evidence for the proposed mechanism.

The preceding results suggest that acetylketene is a far more ubiquitous intermediate than once thought. The kinetic studies demonstrate that the reagent of choice for the preparation of acetoacetates by the transacetoacetylation reaction is the more sterically encumbered t-butyl acetoacetate. The synthetic utility of this material will be discussed in a subsequent paper.[9]

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4). (a) Reactions were run in a 25 mL round-bottomed flask which had been immersed in a constant temperature bath maintained at the specified temperature +/-0.10 °C. Samples were periodically withdrawn, analyzed by gas chromatography and the rate constants determined using the protocols described in Reference 6c. The rate constants given for entries 1-4 and 11 of Table 1 were determined by following the reaction to at least 3 half-lifes, while those given in entries 5-10 were determined by following the reaction to approximately 30% completion. (b) All materials except 1f are known materials. Compound 1f was prepared by Reference 6a and was fully characterized by ^1H, ^{13}C NMR, IR, MS, HRMS and elemental analysis.

5). 5 mol % (relative to tBAA) of either DMAP or tetramethylguanidine results in only a slight (25 %) rate enhancement. Addition of 35 mol % $Ti(OiPr)_4$, a commonly used transesterification catalyst (see for example Seebach, D.; Hungerbuhler, E.; Naef, R.; Schurrenberger, P.; Weidmann, B.; Zuger, M. Synthesis 1982, 138) results in an approximate rate inhibition of 40%. No significant rate effect is observed if 1 mol % trichloroacetic acid is added to reactions using either EAA or tBAA as the acetoacetylating reagent.

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8). (a) "Instaneous" rate constants of 7.8×10^{-6}, 6.7×10^{-6} and 4.62×10^{-6} sec^{-1} respectively (vs 1.02×10^{-5} for 0-815 min) were obtained for reaction of 1b with 1.11 eq n-BuOH after times of 1418.2, 1913.2 and 2911.7 minutes respectively; while the experiment with 6 eq n-BuOH had instantanous rate constants in the same time period of 1.50×10^{-5}-1.7×10^{-5} sec^{-1} (vs. 1.36×10^{-5} sec^{-1} for the 0-800 min time period). (b) Preliminary equilibrium studies on the EAA/tBAA equilibrium at 106 °C indicated that this process favors EAA by between 15-22:1, reflecting a free energy difference (G^o) of 2.0-2.3 kcal/mol, which agrees well with the experimental difference in free energy of activation for the two materials.

9). Witzeman, J. S.; Nottingham, W. D. to be published.

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