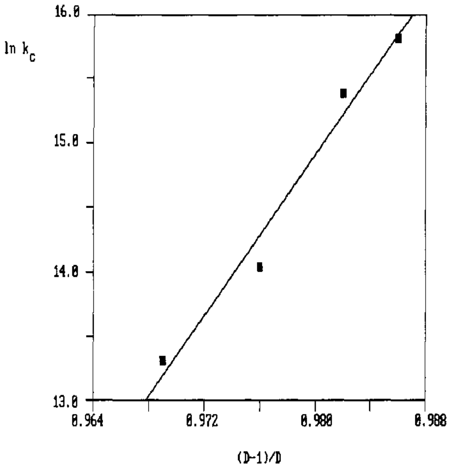

Figure 9. Dependence of the rate constant for cation formation, k_c, on solvent dielectric constant, D, as predicted by the Born equation.

equations based on the theory of Brownian motion predicting a linear relationship between the quantum yield of cage escape, Φ_{rf}, and the square root of inverse solvent viscosity, $(1/\eta)^{1/2}$. Figure 8 shows our data plotted accordingly. Even though the points show some upward curvature, they are within the error limits of the "best fit" straight line.

H. Conclusions. Photolysis of 9-fluorenol in methanol or aqueous methanol leads to the production of the fluorenyl radical as well as the fluorenyl cation. Both of these species are formed via the singlet excited state of 9-fluorenol. The partitioning between C–O bond homolysis and heterolysis is controlled by the medium dielectric. The rate constant for cation formation increases as the solvent dielectric constant increases as predicted by the Born equation. Thus, we conclude that the increase in yield of the fluorenyl cation with increasing amounts of water in the solvent mixture can be attributed to a lowering of the free energy necessary for ion solvation as the solvent becomes more polar.

The possibility of cation formation via electron transfer in the geminate radical pair cannot be ruled out. The oxidation potential of the fluorenyl radical in acetonitrile and the redox potential of OH/OH^- at pH = 7 are reported to have values of +0.52 mV vs NHE[37] and +1.89 V vs NHE,[38] respectively. Given these values, it is thermodynamically possible for electron transfer to occur. However, the observed rate constant for radical and cation production requires the sum of the decay rate constants for the geminate radical pair to be equal to or greater than that observed for the decay of the fluorenol singlet excited state.

Acknowledgment. This work was supported by the National Science Foundation (at the University of Texas) and by the Natural Sciences and Engineering Research Council of Canada (at the University of Victoria). The flash-photolysis and pulse-radiolysis experiments were conducted at the Center for Fast Kinetics Research, which is jointly supported by the National Institute of Health (RR00886-13) and by the University of Texas. We thank B. K. Naumann for assistance in the pulse-radiolysis experiments and Dr. M. A. J. Rodgers for a sample of *trans*-canthaxanthin.

Registry No. 1, 1689-64-1; **6**, 2299-68-5; **7**, 34985-70-1; **8**, 6630-65-5.

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Kinetic and Spectroscopic Studies on the Thermal Decomposition of 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one: Generation of Acetylketene[1]

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Contribution from the Eastman Chemicals Division Research Laboratories, Eastman Kodak Company, P.O. Box 1972, Kingsport, Tennessee 37662. *Received August 19, 1988*

Abstract: Acetylketene is shown to be a reactive intermediate in thermolytic reactions of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (the diketene–acetone adduct) via a series of kinetic studies. The uncatalyzed acetoacetylations of phenol, 1-butanol, and di-*n*-butylamine with the title dioxinone at 82–107 °C are first-order reactions in which the rate-limiting step is the formation of acetylketene and acetone, presumably via a retro-Diels–Alder reaction. Isopropenyl acetoacetate is not an intermediate in the aforementioned reactions but also provides acetylketene when heated. Acetylketene was observed by FT-IR spectroscopy in an argon matrix.

Acetylketene has been of interest since the beginning of this century, but its existence has not yet been rigorously established. Diketene was long believed to be acetylketene, and once the correct structure of diketene was established, acetylketene continued to be proposed as an intermediate in reactions of diketene and its derivatives.[2] Acetylketene (**2**) has recently been postulated as a reactive intermediate in the thermal decomposition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**), the "diketene–acetone adduct" (Scheme I).[3-5] This latter postulate is supported by various empirical observations which suggest that acylketenes are generated from the thermolysis of 1,3-dioxinones[6] and other pre-

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(1) Correspondence may be addressed to either author.

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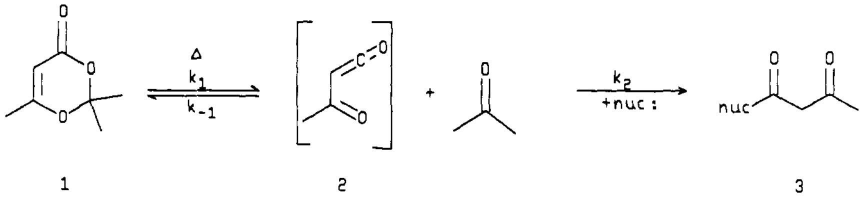
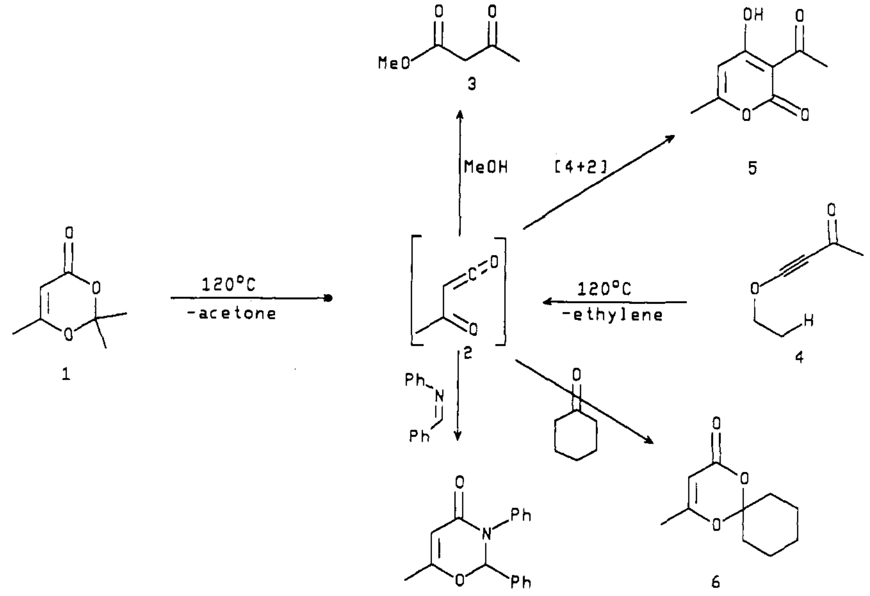
Scheme I



Scheme II



cursors.[7] The intermediacy of acylketenes in the thermolysis of 1,3-dioxin-4-ones has not, however, been rigorously established, and the assumptions regarding their existence have become increasingly important as new preparations[8] and synthetic applications[9] of 1,3-dioxin-4-ones have been developed. To more thoroughly analyze the issue of acylketene generation from 1,3-dioxin-4-ones, a detailed kinetic study of the thermal decomposition of the title 1,3-dioxin-4-one (**1**) was undertaken.

The products which result from heating dioxinone **1** in the presence of a variety of reagents strongly support the intermediacy of acetylketene (Scheme II).[3,4] Acetylketene (**2**) has been further implicated as the reactive intermediate in these latter reactions by its generation via an independent route. Thus, thermolysis of ethoxybutynone **4** in the presence of a variety of trapping agents provided identical product mixtures to those obtained with dioxinone **1**.[4]

Dioxinone **1** is a potent acetoacetylating reagent when heated and is more reactive than would be expected for an uncatalyzed bimolecular transesterification process. Acetoacetylation reactions effected with dioxinone **1** proceed efficiently with stoichiometric amounts of nucleophile and are less sensitive to steric effects than those of diketene.[5] The acetoacetylation of nucleophiles with dioxinone **1** therefore appeared to provide a relatively simple process with which to test the "acetylketene postulate" and simultaneously increase our understanding of this useful synthetic reaction.

Several reaction pathways can be postulated for the uncatalyzed reaction of dioxinone **1** with a nucleophile to provide acetone and an acetoacetic acid derivative (Scheme III). The two most plausible reaction mechanisms appeared to be a bimolecular process (path A) and a unimolecular decomposition to form a reactive intermediate, followed by the reaction of this intermediate with a nucleophile (path B). Earlier work suggested that acetylketene (**2**) was the most probable intermediate in this latter pathway (B), but it was also recognized that other intermediates, such as isopropenyl acetoacetate, needed to be considered (vide infra).

In the former of these two mechanistic extremes (path A), a rate-determining addition of the nucleophile to the dioxinone would give a tetrahedral intermediate, which could subsequently lose acetone to provide the acetoacetate. A reaction following this scheme would exhibit second-order kinetics as described by eq 1, with the observed rate constant being a combination of the microscopic rate constants k_1, k_{-1}, and k_2. The dissociative

$$\frac{\mathrm{d}[\mathbf{1}]}{\mathrm{d}t} = k_{\mathrm{obsd}}[\mathbf{1}][\mathrm{nuc}] \qquad k_{\mathrm{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2} \tag{1}$$

mechanism shown as path B would be described by the more

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(6) Acetylketene generation; see ref 3–5. Other acylketenes: Sato, M.; Ogasawara, H.; Komatsu, S. Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848–3856.

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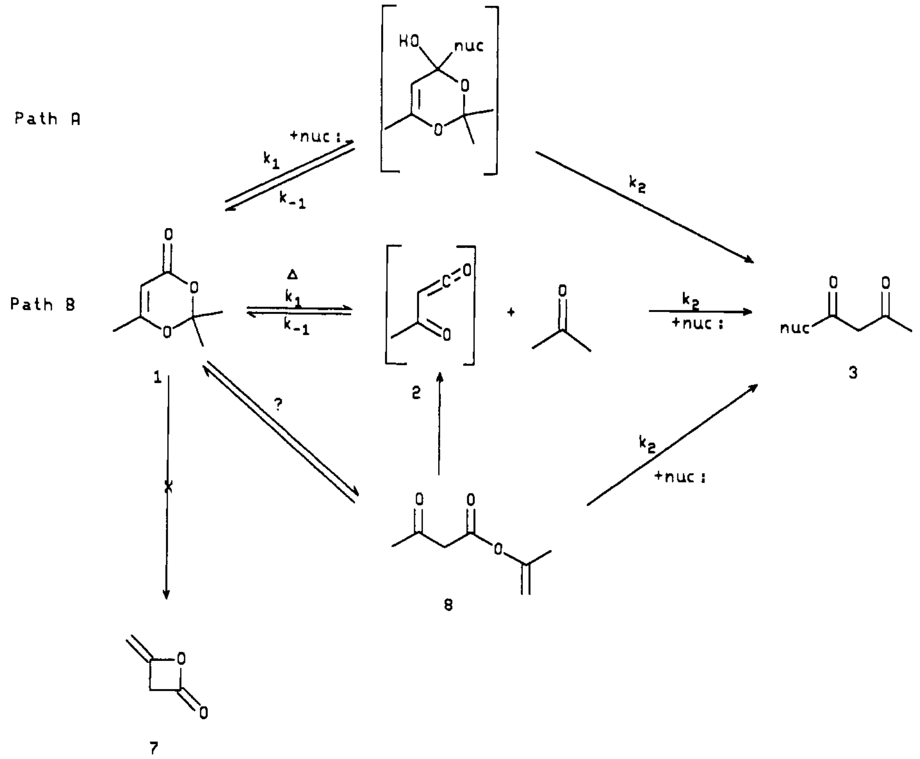
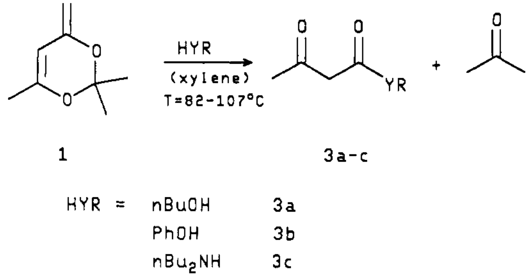
(9) These references include only those reactions which probably proceed via ketene intermediates. The (2 + 2) cycloaddition chemistry of 1,3-dioxinones is also extensive. (a) Baldwin, S. W.; Martin, G. F.; Jr.; Nunn, D. S. *J. Org. Chem.* **1985**, *50*, 5720–5723. (b) Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486–5489. (c) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823–2824. (d) Demuth, M.; Palomer, A.; Sluma, H. D.; Dey, A. K.; Kruger, C.; Tsay, Y. H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1117–1118. (e) Sato, M.; Ogasawara, H.; Kato, K.; Sakai, M.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 4300–4305. (f) Sato, M.; Ogasawara, H.; Yoshizumi, E.; Kato, T. *Heterocycles* **1982**, *17*, 297–300. (g) Seebach, D.; Zimmermann, J. *Helv. Chim. Acta.* **1986**, *69*, 1147–1152. (h) Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 2602–2608. (i) Sato, M.; Yoneda, N.; Kaneko, C. *Chem. Pharm. Bull.* **1986**, *34*, 621–627, 4577–4584. (j) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 106–116.

Scheme III



Scheme IV



complex kinetic eq 2, if the concentration of the intermediate acetylketene followed steady-state kinetics. Thus, the rate of

$$\frac{d[\mathbf{1}]}{dt} = \frac{k_1 k_2[\mathbf{1}][\text{nuc}]}{k_{-1}[\text{acetone}] + k_2[\text{nuc}]} \tag{2}$$

reaction could depend inversely on acetone concentration as well as on the concentrations of the dioxinone and nucleophile.[10a] If, however, the reaction of the nucleophile with the intermediate were much faster than the reverse reaction (k_2[nuc] ≫ k_{-1}[acetone]), first-order kinetics would be observed (eq 3). Such a situation was expected for a highly reactive intermediate such as acetylketene, based on the known rates of reaction of other ketenes with various nucleophiles.[10] In this latter extreme, the reaction rate would be independent of both the nature and the concentration of the nucleophile and would thus be differentiated from a process following path A.

$$\frac{d[\mathbf{1}]}{dt} = k_1[\mathbf{1}] \tag{3}$$

Table I. Effect of Concentration on the Observed First-Order Rate Constant for Reaction of Dioxinone **1** with Nucleophiles[a]

T (°C)	nuc	[**1**][b]	[nuc][b]	mol ratio nuc/**1**	$k_1 \times 10^4$ [c] (s^{-1})
91.7	Bu$_2$NH	0.120	0.307	2.6	0.97
91.7	Bu$_2$NH	0.121	0.135	1.1	1.16
91.7	nBuOH	0.128	0.137	1.1	1.11
91.7	nBuOH	0.172	1.854	10.8	1.00
91.7	PhOH	0.081	0.086	1.1	1.11
91.7	PhOH	0.089	0.873	9.8	1.09
106.7	nBuOH	0.125	0.181	1.5	6.60
106.7	nBuOH	0.033	0.324	10.0	5.61
106.7	PhOH	0.100	0.121	1.2	5.32
106.7	PhOH	0.033	0.338	10.3	6.93
106.7	Bu$_2$NH	0.130	0.161	1.2	6.08

[a] All reactions in xylene solvent. See supplementary material for a listing of all rate constants and relevant statistical parameters. [b] Initial molar concentration of dioxinone **1** and nucleophile, respectively. [c] First-order rate constant.

Table II. Effect of Temperature on Rate of Reaction of Dioxinone **1** with 1-Butanol in Xylene[a]

T (°C)	$k_1 \times 10^4$ (s^{-1})	T (°C)	$k_1 \times 10^4$ (s^{-1})
81.7	0.33	98.5	3.08
91.7	1.06	106.7	6.32

Activation Parameters[b]

log A (s^{-1})	E_a (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
14.7	31.1	30.4	6.4

[a] Average first-order rate constants obtained from at least two experiments per temperature. [b] Data obtained from weighted least-squares analysis (see Experimental Section). The standard deviations are as follows: log A = 0.70 s^{-1}; E_a = 1.1 kcal/mol; $\Delta H^{\ddagger}$ = 1.1 kcal/mol; $\Delta S^{\ddagger}$ = 3.0 eu; R^2 = 0.998 for both plots.

Results and Discussion

The rate of reaction of dioxinone **1** with three representative nucleophiles, 1-butanol, phenol, and di-*n*-butylamine (Scheme IV),

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[10] The exact nature and order of the reaction of various ketenes with nucleophiles is the subject of some debate (for example, see ref 10a,c,i). The reaction order in nucleophile could be first order or higher: the important point is that there would be a dependence on the nucleophile concentration. (a) Allen, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1987**, *109*, 2774–2780. (b) Bothe, E.; Meier, H.; Schulte-Frohlinde, D.; von Sonntag, C. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 380–381. (c) Poon, N. L.; Satchell, D. P. N. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1485–1490. (d) Lillford, P. J.; Satchell, D. P. N. *J. Chem. Soc. B* **1968**, 889–897. (e) Brady, W. T.; Vaughn, W. L.; Hoff, E. F. *J. Org. Chem.* **1969**, *34*, 843–845. (f) Tille, A; Pracejus, H. *Chem. Ber.* **1967**, *100*, 196–210. (g) Pracejus, H.; Samtleben, R. *Tetrahedron Lett.* **1970**, 2189–2194. (h) The reaction of acetylketene with a nucleophile to give **3** may, under certain conditions, be reversible. However, this process is slow relative to the rate of decomposition of dioxinone **1**. (i) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587–2613.

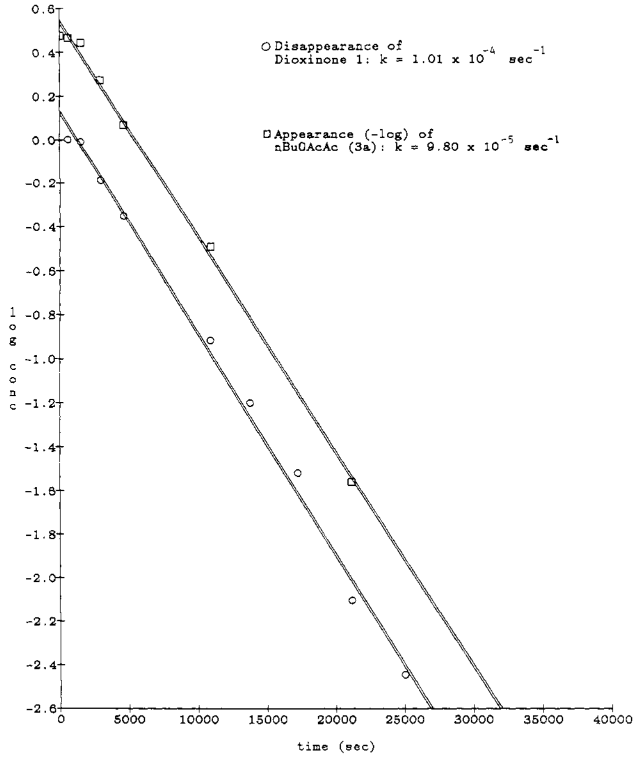

Figure 1. Reaction of Dioxinone **1** with excess 1-butanol at 91.7 °C.

in xylene solvent, was determined in a pressure bottle under a variety of conditions.[11] The concentrations of the nucleophile, dioxinone **1**, acetone, and the acetoacetate product were monitored over at least 3 half-lives (88% completion) via gas chromatography (see Experimental Section).

Figure 1 graphically depicts the uncatalyzed reaction of dioxinone **1** with 1-butanol at 91.7 °C; uniform, first-order rate constants were determined for the individual reagents and products, which also established that the acetone was retained in the reaction mixture. The observed first-order rate constants for reaction of dioxinone **1** with the three nucleophiles at various concentrations are summarized in Table I; the temperature dependence of the rate of reaction of dioxinone **1** with 1-butanol is shown in Table II. The first-order nature of these reactions is apparent from the excellent correlations observed ($R^2 > 0.98$), the independence of the observed rates on the nucleophile concentration, and by the fact that the rate constants for reaction of dioxinone **1** with all three nucleophiles are identical. This first-order behavior and independence of the nature of the nucleophile is consistent with a rate-limiting, unimolecular production of a reactive intermediate such as acetylketenes, as is presented in path B of Scheme III.

The fact that the rate constants determined for disappearance of **1** and for appearance of **3a–c** are equal provides further evidence that decomposition of **1** is rate-determining. This observation also demonstrates that the concentration of the reactive intermediate is low, thus verifying the steady-state hypothesis.

Table III summarizes several experiments which were designed to elucidate the effect of the reaction medium and various additives on the rate of reaction of dioxinone **1** with 1-butanol. Changing the solvent from xylene to the more polar DMSO had no effect on the reaction rate. Neither DABCO nor titanium isopropoxide had an appreciable effect on the observed rate constant, but a small (ca. 2-fold) rate acceleration was observed when 10 mol % (relative to the dioxinone) of *p*-toluenesulfonic acid was added. The rate of this latter process remained first-order in dioxinone and zeroth-order in butanol. A slightly smaller catalytic effect was also noted with trichloroacetic acid.[12]

Table III. Effect of Additives on the Rate of Reaction of Dioxinone **1** with 1-Butanol at 91.7 °C[a]

additive	[**1**][b]	[*n*BuOH][b]	$k_1 \times 10^4$ (s^{-1})[c]	mol ratio *n*BuOH/**1**
DMSO (solvent)	0.150	0.194	1.03	1.29
DABCO (14 mol %)	0.148	0.180	1.05	1.22
$Ti(OiPr)_4$ (21 mol %)	0.140	0.188	1.23	1.35
pTSA (9.7 mol %)	0.123	0.140	2.20	1.14
Cl_3CCO_2H (9.7 mol %)	0.140	0.155	1.46	1.11
Cl_3CCO_2H (12.8 mol %)	0.142	0.182	1.88	1.28
acetone (1.071 M)[d]	0.088	0.114	1.08	1.28
acetone (1.646 M)[d]	0.043	0.063	1.15	1.46
acetone (3.400 M)[d]	0.010	0.004	1.29	0.40

[a] See supplementary material for a listing of all rate constants and relevant statistical parameters. [b] Molar concentration of dioxinone **1** and nucleophile, respectively. [c] First-order rate constant. [d] Molar concentration added acetone.

The effect of added acetone on the observed rate constant was also examined to see if the reaction could be shifted into a second-order reaction manifold. It was found that addition of ca. 10–360-fold excess acetone had no effect on either the observed rate constant or the reaction order, which indicates that k_2 is at least 500 times that of k_{-1}. Even under conditions of high dilution and low 1-butanol concentration, no second-order behavior was noted. Under these conditions, dioxinone **1** continued to decompose to unknown materials once the alcohol was consumed. Finally, dioxinone **1** was heated in xylene in the absence of a nucleophile, with the expectation that dehydroacetic acid would be formed from the dimerization of the reactive intermediate. Thermolysis of concentrated solutions of **1** in xylene provided only low yields of dehydroacetic acid (**5**, Scheme II); the small amount of acetone which was coproduced suppressed the rate of acetylketene dimerization.[13] This latter result suggests that the generation of the reactive intermediate is reversible as suggested in Scheme I. The reversibility of dioxinone decomposition was further probed by heating a toluene solution of dioxinone **1** to 91.7 °C in the presence of a 5-fold excess of hexadeuterioacetone. The incorporation of the hexadeuterioacetone moiety into the starting dioxinone, with no deuterium scrambling, was demonstrated by ^1H NMR and mass spectral analysis of the reaction products. The rate of this deuterium incorporation at 91.7 °C under pseudo-first-order conditions was found to be the same as that for reaction of dioxinone **1** with the nucleophiles listed in Table I (1.14×10^{-4} s^{-1}), thus demonstrating that this process occurs on a time scale similar to that for formation of **3a–c**.

The kinetic data clearly established that thermal acetoacetylation reactions of dioxinone **1** proceed via a rate-determining unimolecular decomposition to afford a reactive intermediate, but did not rigorously establish that acetylketene was the intermediate. Other possible intermediates were therefore considered. Diketene (**7**) was thought to be an unlikely intermediate for thermochemical reasons, but was conclusively eliminated because it does not react with acetone at an appreciable rate in the absence of an acidic catalyst. The lack of any solvent effect on the reaction rate makes ionic intermediates quite unlikely. Isopropenyl acetoacetate (**8**), which has been implicated as an intermediate in the formation of dioxinone **1** from acetone and diketene under acidic conditions,[13] appeared to be a plausible alternative to acetylketene. A priori, it was anticipated that isopropenyl acetoacetate would react with butanol in a second-order process at a slower rate than dioxinone **1** and could thus be eliminated from further consideration. Isopropenyl acetoacetate (**8**) was prepared by the method of Hyatt[14]

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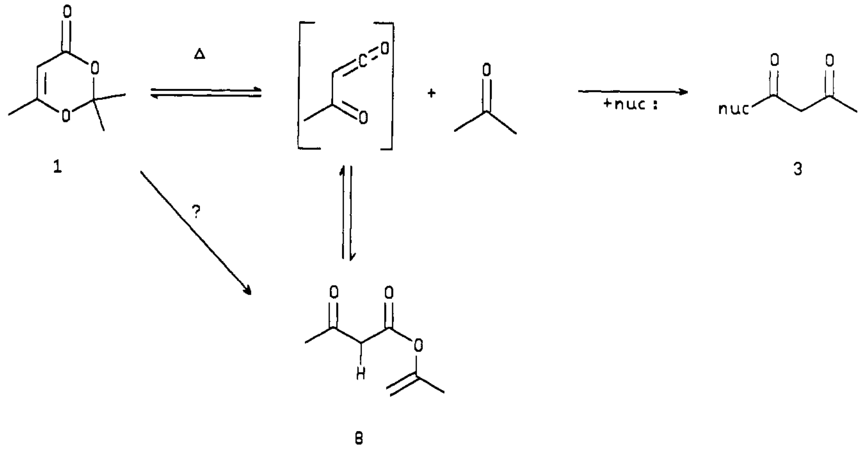
(11) A complete listing of the individual rate constants is provided as Supplementary Material.

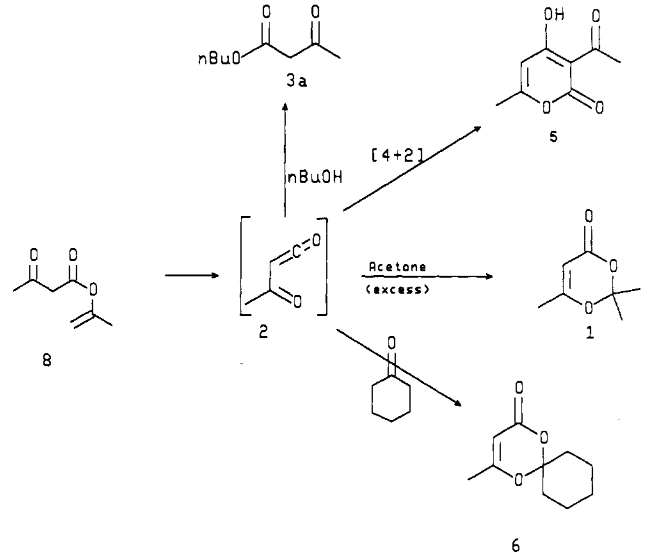
(12) The acid-catalyzed process appears to be first-order in the acid, but this relationship was not rigorously established. In another experiment a sample contaminated with ca. 9% dehydroacetic acid (**5**), a common impurity in **1**, showed a 45% rate enhancement. In this work great care was taken to make sure that the material used was not contaminated with **5** (see Experimental Section).

(13) The rate of this process appeared to slow appreciably after ca. 5–10% of the dioxinone was consumed. The yields of product were poor; thus, the rate constant for this process cannot be determined with any degree of confidence.

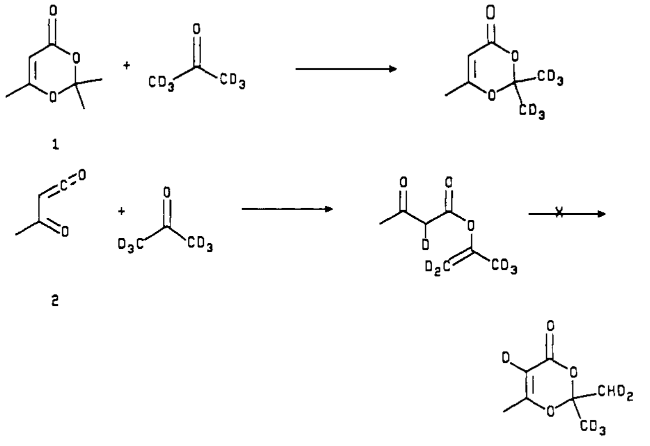
Scheme V



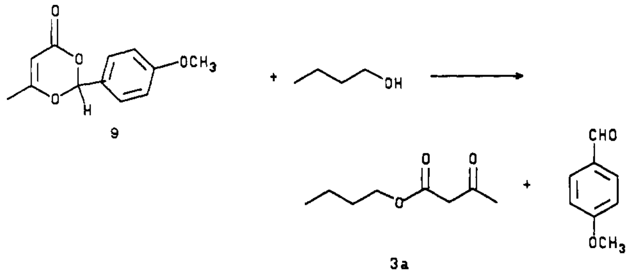
Scheme VI



Scheme VII



Scheme VIII



and was treated with 1-butanol at 91.7 °C as described above; the reaction was found to be first-order in the acetoacetate **8** and zeroth-order in the alcohol, with a rate 5–12 times greater than that of the dioxinone **1**. Since the reactive intermediate of Scheme III, path B would have provided *n*-butyl acetoacetate via a bimolecular process, it was clear that isopropenyl acetoacetate (**8**) could not be the reactive intermediate instead of acetylketene. However, because isopropenyl acetoacetate could produce acetylketene via the oxy analogue of a retro-ene reaction (Scheme V), the intermediacy of isopropenyl acetoacetate (**8**) in the formation of acetylketene (**2**) from dioxinone **1** had to be considered. In an experiment aimed at further establishing that isopropenyl acetoacetate (**8**) does provide acetylketene when heated, a solution of **8** was heated to 91.7 °C in a 100-fold excess of acetone and found to produce dioxinone **1** in quantitative yield in less than 1 h (Scheme VI). Similarly, heating **8** in the presence of cyclohexanone gave the cyclohexanone–diketene adduct **6**, while heating isopropenyl acetoacetate in an open flask afforded dehydroacetic acid (**5**) and dioxinone **1** (along with other products). Isopropenyl acetoacetate does not appear to be an additional reactive intermediate during the formation of acetylketene from dioxinone **1** for several reasons. First, the absence of deuterium scrambling during the equilibration of dioxinone **1** and hexadeuterioacetone (vide supra)[15] is consistent only with the direct production of acetylketene from **1** (without involving isopropenyl acetotacetate) (Scheme VII). Secondly, the *p*-anisaldehyde adduct of diketene (**9**, Scheme VIII), which could not produce an enol acetoacetate, produces butyl acetoacetate (**3a**) when subjected to the reaction conditions which produce **3a** from dioxinone **1**. Thus, isopropenyl acetoacetate (**8**) is an independent precursor to acetylketene (**2**) but is not an intermediate in the formation of **2** from dioxinone **1**.[14]

The activation energy for the retro-Diels–Alder reaction of dioxinone **1** is some 30–38 kcal/mol below that for the corresponding processes for cyclohexene and its substituted derivatives.[16] This reflects the much more favorable heat of reaction for the former process relative to the latter. Thus, while thermolysis of cyclohexene to produce butadiene and ethylene and is endothermic by 39.4 kcal/mol, the disassociation of **1** to give acetone and acetylketene is 23 kcal/mol less endothermic (vide supra). This is a consequence of the higher bond energy associated with a carbonyl π bond relative to a C–C σ bond. The log A ($\Delta S^{\ddagger}$) values for reactions of **1** are also less than those for the retro-Diels–Alder reaction of cyclohexene and its derivatives. This observation is

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[14] Hyatt, J. A. *J. Org. Chem.* **1984**, *49*, 5102–5104.

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[16] (a) Tsang, W. *Int. J. Chem. Kinet.* **1973**, *5*, 651–662. (b) Limmie, J. *Int. J. Chem. Kinet.* **1978**, *10*, 227. (c) Tsang, W. *J. Chem. Phys.* **1965**, *42*, 1805–1809.

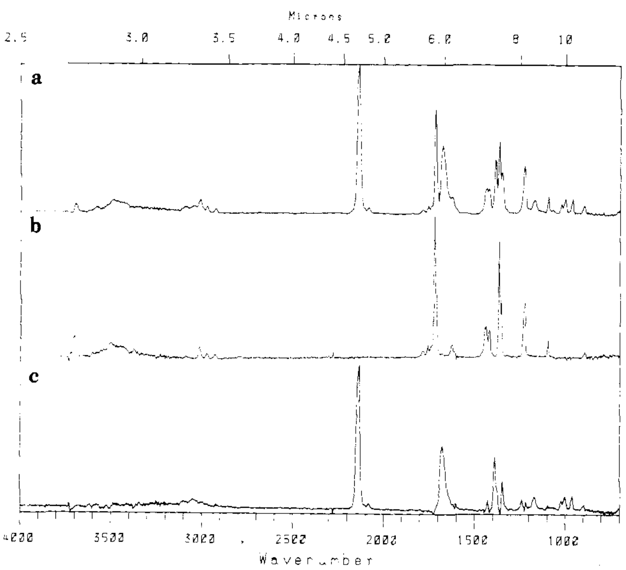


Figure 2. Matrix IR spectrum of acetylketene: (a) acetylketene and acetone as produced in GC; (b) acetone; (c) acetylketene with acetone subtracted.

consistent with the transition state for reaction of **1** being more reactant-like, as would be expected from the Hammond postulate.

Spectroscopic Observation of Acetylketene. In the course of analyzing the aforementioned reactions, we found that dioxinone **1** could be pyrolyzed in the transfer line of a GC-IR and the resultant products trapped in an argon matrix at 5 K. The spectrum obtained from this experiment is given in Figure 2. The strong ketene infrared absorption band at 2137 cm^{-1}, the acetyl carbonyl absorption at 1676 cm^{-1}, the CH deformations at 1386 cm^{-1}, and the sp^2 CH stretch in the 3150–3000-cm^{-1} region are consistent with acetylketene. The absorption bands at 1716, 1367, and 1217 cm^{-1} in this spectrum are due to the acetone coproduced by the retro-Diels–Alder reaction of **1**. The 2137-cm^{-1} absorbance is similar to that noted by Kato[3b,c] in a crude spectrum of dioxinone pyrolysis products. The ketene carbonyl stretch at 2137 cm^{-1} is similar to that of ketene (2142 cm^{-1})[17a] and greater than that of vinylketene (2118 cm^{-1}),[17b] while the 1676-cm^{-1} absorption frequency attributed to the acetyl carbonyl group is similar to the corresponding absorption in (2-oxocyclopentyl)ketene.[17c] When the acetylketene was sufficiently dilute in the argon matrix, it was possible to resolve two ketene bands, one at 2135 cm^{-1} and one at 2142 cm^{-1}. These two absorbances may reflect the presence of the s-cis and s-trans rotamers of acetylketene.[18] In another experiment it was found that pyrolysis of isopropenyl acetoacetate (**8**) and subsequent matrix isolation produced a material with an IR spectrum identical with that in Figure 2.

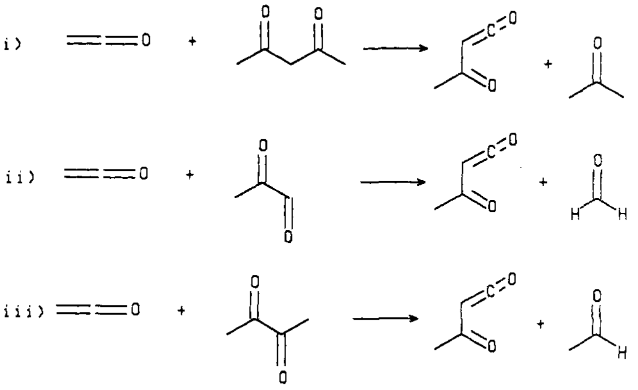
Several attempts were made to further characterize acetylketene (**2**) via mass spectroscopy, by generating **2** in the transfer line of a GC-MS.[19,20] Although less rigorous than the kinetic data and IR observations, mass spectroscopic evidence for the intermediacy of **2** was obtained by using the ammonia CI gas as a trap. The mass spectrum of **1** obtained under ammonia chemical ionization conditions with a 180 °C transfer line showed peaks at m/z = 143 (MH^+) and m/z = 160 ($M + NH_4^+$) amu. When the temperature of the transfer line was increased to 250 °C, additional species with m/z = 102 and 119 were also observed. These masses correspond to protonated acetoacetamide and a protonated acetoacetamide–ammonia adduct, respectively, which are presumably formed from acetylketene.

Table IV. Experimental and Calculated Heats of Formation

compd	calcd[a] $\Delta H_f°$ (kcal/mol)	exptl[b] $\Delta H_f°$ (kcal/mol)
*n*BuOH	−66.4	−65.8
nBu_2NH	−37.9	−37.5
PhOH	−22.3	−23.1
MeOH	−48.0	−48.2
EtOH	−56.5	−56.3
dioxinone **1**	−118.5	
acetone		−51.9
2,5-pentanedione		−91.0
pyruvic aldehyde		−64.8
2,3-butanedione		−78.2
formaldehyde		−26.0
acetaldehyde		−39.7
acetylketene (**2**)[c]	−50.4 (i), −50.2 (ii), −49.9 (iii)	
PhOAcAc (**3b**)	−103.3	
*n*BuOAcAc (**3a**)	−152.0	
nBu_2NAcAc (**3c**)	−128.7	
EtOAcAc	−142.1	−145.6[d]
MeOAcAc	−133.6	−140.8[e]
ketene		−11.4[f]

[a] All calculated values by Benson group additivity (ref 21a) unless otherwise noted. Values calculated at 298 K and are for the material in the gaseous phase. [b] Experimental $\Delta H_f°$'s from ref 21b unless otherwise noted. [c] Calculated by thermodynamic cycles, number in parentheses indicates the cycle used (see text). [d] Reference 21d. [e] Reference 21e. [f] Reference 21f.

Scheme IX



Thermochemical Analyses. In order to compare the reactivity of dioxinone **1** and acetylketene (**2**) with other species, it is necessary to have an estimate of the heats of reaction involved in formation of acetoacetic acid derivatives **3a–c** from **1** and **2**. The determination of these heats of reaction requires estimations of the heats of formation of the various species. The heats of formation of compounds **1** and **3a–c** can be estimated with the Benson group additivity method. For compounds **3a–c**, these calculations are straightforward. Table IV lists the calculated and experimental heats of formation of various relevant compounds. The agreement between the experimental and calculated

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(17) (a) Moore, C. B.; Pimental, G. C. *J. Chem. Phys.* **1963**, *38*, 2816. (b) Maquestiau, A.; Pauwels, P.; Flammang, R.; Lorenčak, P.; Wentrup, C. *Org. Mass Spectrum* **1986**, *21*, 259–265. (c) Wentrup, C.; Gross, G.; Berstermann, H.-M.; Lorenčak, P. *J. Org. Chem.* **1985**, *50*, 2877–2881.

(18) (a) Semiempirical (MNDO) calculations predict that the s-trans form of **2** is more stable. Hyatt, J. A.; Foster, C. H., personal communication. (b) Other explanations for these two bands are possible; additional work is being conducted in this area. (c) The IR absorption frequency for ketene is known to be sensitive to the surrounding medium. See ref 17a and Gano, J. E.; Jacob, E. J. *Spectrochem. Acta* **1987**, *43A*, 1023–1025. Arendale, W. F.; Fletcher, W. H. *J. Chem. Phys.* **1957**, *26*, 793–797.

(19) The mass spectrum of acetylketene has been difficult to obtain (and to reproduce), perhaps due to ion-molecule reactions of **2** with other materials. One one occasion, using a hot (T = 250 °C) transfer line, a mass spectrum was obtained from dioxinone-d_6 **1** which had a molecular ion at m/z = 84 amu, which is consistent with $(2)^{\bullet+}$. Other fragments included m/z = 69 ($2\text{-}CH_3$), m/z = 64 (acetone-d_6), m/z = 46 (acetone-d_6–CD_3) and m/z = 43 ($2\text{-}C_2HO$). This mass spectrum was very different from that of **1**, as obtained either on a solid probe or via a GC-MS with a transfer line kept below 180 °C.

(20) One interesting observation made during the course of these studies was that thermolysis of **1** via a hot GC injector port (T = 250 °C) and/or hot transfer line produced, besides dehydroacetic acid (**5**), the 2,4,6-heptanetrione, which is isomeric with **1**. 2,4,6-Heptanetrione is also formed in low yield upon thermolysis of isopropenyl acetoacetate (**8**) (see Experimental Section). (Isopropenyl acetate rearranges to give 2,4-pentanedione upon thermolysis.)

Table V. Heats of Reaction for Various Processes Involving Dioxinone **1** and Acetylketene (**2**)

reaction	ΔH_{rxn}[a] (kcal/mol)
1 → **2** + acetone	+16.4
2 + *n*BuOH → **3a**	−36.0
2 + PhOH → **3b**	−30.0
2 + Bu_2NH → **3c**	−41.0
1 + *n*BuOH → **3a** + acetone	−19.7
1 + PhOH → **3b** + acetone	−13.6
1 + Bu_2NH → **3c** + acetone	−24.6

[a] Heats of reaction calculated by using experimental $\Delta H_f°$'s when available and estimated values otherwise. Median value for acetylketene used (−50.2 kcal/mol).

heats of formation for methyl and ethyl acetoacetate suggests that the Benson method gives acceptable values for acetoacetic acid derivatives. Calculating the $\Delta H_f°_{298}$ of dioxinone **1** is slightly more complicated, since the ring, or strain, energy of this material must be estimated. This was done by assuming various effects to be additive. Thus, comparison of the Benson correction factor for tetrahydropyran to that of dihydropyran suggests that 0.3 kcal/mol additional strain is imparted by the C–C double bond. This value is included with the 1,3-dioxane, cyclohexanone, and C···C gauche correction factors to give a total strain energy of 8.0 kcal/mol for **1**. This 8 kcal/mol correction is included in the $\Delta H_f°_{298}$ value given in Table IV.

Group additivity cannot be used to calculate the heat of formation of acetylketene due to the fact that the appropriate molecular group parameters have not been determined. To estimate this value, thermodynamic cycles which relate **2** with materials which have known heats of formation were constructed.[21c] The thermodynamic cycles used involved the exchange of ketene, the heat of formation of which has been determined by reaction calorimetry,[21f] with various mono- and diketones (also with known $\Delta H_f°$'s). The thermodynamic cycles shown in Scheme IX were used.[21g] The heats of formation calculated by this method are in good agreement with each other: $\Delta H_f° = -50.42$ kcal/mol (eq i), $\Delta H_f° = -50.20$ kcal/mol (eq ii), $\Delta H_f° = -49.9$ kcal/mol (eq iii); $\Delta H_f°$ calculated by MNDO[18a] (−47.56 kcal/mol). With these thermochemical values available, the heats of reaction for formation of **3a–c** from **1** and **2** as well as the ΔH_{rxn} for formation of **2** from **1** can be determined. These values are given in Table V. Examination of the data in Table V suggests that formation of **3c** from either **2** or **1** is the most exothermic of the three processes. This thermochemical data has experimental basis, since treatment of **3a** with dibutylamine at 92 °C produces **3c** in good yield. Further investigation of these exchange reactions is planned.

Conclusions

The reaction of dioxinone **1** with three nucleophiles, which cover a large range of acidity, nucleophilicity, and ΔH_{rxn}, is a first-order process. The rate-determining step in these reactions is a reversible, unimolecular loss of acetone to provide a reactive intermediate, presumably via a retro-Diels–Alder reaction. The chemical and spectroscopic data demonstrates that this reactive intermediate is acetylketene (**2**). While the general kinetic description for the proposed mechanism has only been shown to fit eq 2 in the limiting case of $k_2[\text{nuc}] \gg k_{-1}[\text{acetone}]$, the acetone exchange experiments and the spectroscopic data suggest that the mechanism given in path B of Scheme III best explains all relevant experimental results. Isopropenyl acetoacetate does not appear to be involved in the uncatalyzed, thermal acetoacetylation reactions of dioxinone **1**; it does, however, serve as another precursor to acetylketene.

The current work also has synthetic relevance, since the activation parameters obtained for the decomposition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to form acetylketene can be used to calculate the time necessary for complete reaction of dioxinone **1** at a given temperature. The half-life for this process is a surprisingly short 4–5 min at 120 °C, which suggests that even somewhat sensitive molecules may be amenable to thermal reactions with dioxinones. Also, since the decomposition of dioxinone **1** is reversible, acetone is a competitor with other trapping reagents for acetylketene; the need to remove the acetone must be examined in this perspective. Thus, while the rates of reaction of acetylketene with the nucleophiles in the current work precluded the need to remove the acetone, this is presumably not the case in exchange reactions of dioxinone **1** with other ketones or in the dimerization of **1** to form dehydroacetic acid (**5**).

Experimental Section

Materials. All reagents were obtained commercially (Eastman); *p*-xylene and dibutylamine were distilled prior to use; phenol, butanol, and *p*-dichlorobenzene were used as purchased. Dioxinone **1** was twice distilled through a wiped-film evaporator (0.1 Torr, 100 °C walls) and subsequently cooled to 0 °C and allowed to slowly solidify; after ca. 90% of the colorless liquid had solidified, the remainder was discarded.

Apparatus. Reactions were run in a 6-oz Fischer–Porter pressure bottle equipped with an inlet valve for an inert gas, a pressure gauge for monitoring internal pressure, and a dip tube for sampling aliquots while the reaction was in progress. The entire apparatus was oven dried and purged with nitrogen prior to use. The reaction vessel was immersed in a well-stirred constant temperature bath (±0.05 deg C) whose temperature was maintained with a Yellow Springs Instruments temperature controller. Temperature was measured by using an NBS thermometer. Analyses were performed on a Hewlett Packard HP5890 GC with flame ionization detector on a 30 m × 0.25 mm DB-5 capillary column (180 °C injector, oven 70 °C/2 min hold time; +10 deg C/min to 240 °C). Samples were injected via an HP 7673A autoinjector and integrated with an HP 3393A autointegrator. Chromatographic analyses were performed in duplicate, and the results were averaged. Due to the thermal lability of **1**, it is essential that the injector temperature be kept at 180 °C (or less) to prevent artifacts in the analysis. ^{1}H NMR spectra were obtained on Varian EM-360 and JEOL GX-400 spectrometers with tetramethylsilane as an internal standard; mass spectra were recorded on a VG-ZAB mass spectrometer in the EI or CI modes, as individually noted.

Data Analysis. Rate constants were obtained from linear least-squares analysis of first-order plots of the concentrations of the various reagents and products vs time. The statistical routines which were used (RS/1 from BBN Corporation) included an analysis of variance which provided a standard deviation of the individual rate constants. The best correlation coefficients were obtained from plots based on dioxinone disappearance. Similar rate constants were also obtained for acetoacetate (acetoacetamide) appearance and from monitoring the rate of appearance of the acetone or of disappearance of nucleophile. The t = infinity value for appearance of *N*,*N*-dibutyl acetoacetamide was extrapolated due to a secondary (slow) reaction of this material with amine to produce the enamine. The identity of this product was demonstrated by GC-MS and by independent synthesis. The concentration of **3a** as determined by GC has a greater error associated with it, due to problems obtaining reproducible integrals of this broad GC peak. It was not possible to determine the rate of appearance of phenyl acetoacetate (**3b**) by GC due to its instability during GC analysis. The rate of reaction of this material was determined by following the disappearance of the dioxinone. The validity of this approach was verified by 400 MHz ^{1}H NMR analysis of the phenyl acetoacetate/dioxinone **1** ratio of selected reaction aliquots. The activation parameters given in Table II were obtained by a weighted least-squares fit of $1/T$ (K) vs log k (Arrhenius parameters) or vs log (kh/Tk_b) (Eyring equation). The weighting factors used were the inverse of the absolute value of the residuals obtained from a standard least-squares fit.

Typical Kinetic Procedure. Dioxinone **1** (0.500–1.1 g), *p*-dichlorobenzene (0.400–1.2 g), and the nucleophile (1–10 equiv) were weighed into a 50-mL volumetric flask and diluted to 50.0 mL with solvent. The solution was placed in the pressure bottle, purged with nitrogen, and pressurized to 13–17 psi. The bottle was immersed in the constant temperature bath such that the liquid level in the reaction vessel was at least 2.5 cm below the oil level in the bath. Aliquots (1 mL) were

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(21) (a) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279. (b) *Thermochemical Data of Organic Compounds*; Pedley, J. B., Naylor, R. D., Kirby, S. P., Eds.; Chapman and Hall: 1986. (c) Deming, R. L.; Wulff, C. A., In *The Chemistry of Ketenes Allenes and Related Compounds*; Patai, S., Ed.; John Wiley and Sons: 1980; Vol 1, pp 155–164. (d) Vilcu, R.; Persianu, S. *Rev. Roum. Chim.* **1979**, *24*, 237. (e) Qunchant, M. *Ann. Chem.* **1918**, *10*, 30. Nuttall, R. L.; Laufer, A. H.; Kilday, M. V. *J. Chem. Thermodyn.* **1971**, *3*, 167–174. (g) These thermodynamic cycles assume that the heat of reaction for the exchange process is zero (ref 21c). The similarity of the values obtained from the three cycles suggests that this assumption is valid.

periodically withdrawn from the reaction vessel (after a forerun was taken) into a cold vial which was immediately capped. All samples were analyzed within 24 h of collection, and control experiments established that the reaction did not proceed at a measurable rate (at 25 °C) during this time period. It was later shown that, for acetoacetylation reactions with alcohols and amines, similar kinetic data could be obtained from experiments which were run in a round-bottomed flask equipped with a reflux condenser.

Exchange of Dioxinone 1 with Hexadeuterioacetone. A solution of dioxinone **1** (2.241 g, 15.6 mmol) and acetone-d_6 (5 g, 78 mmol) was diluted to 50 mL with toluene, placed in the pressure bottle under 15 psi of N$_2$, and heated to 91.7 °C. The progress of the reaction was monitored as described in the general kinetic protocol, since the undeuterated and hexadeuterated materials were surprisingly easily separated by GC (t_r = 9.16 min for **1**-d_6 vs 9.24 min for protiated **1**). The rate was plotted as a function of time vs the logarithm of the percent of theoretical maximum deuterium incorporation (83.3%). The data were corrected for the slow decomposition of the dioxinone; approximately 8% of the dioxinone was lost to byproducts after 24 h at 91.7 °C. Dioxinone-**1**-d_6: MS, m/z = 148 (M$^{\bullet+}$, 22), 86 (72), 84 (51), 69 (53), 64 (37), 46 (98), 43 (100). Dioxinone **1**: MS, m/z = 142 (M$^{\bullet+}$, 16), 85 (60), 84 (28), 69 (32), 59 (19), 43 (100). Analysis of the reaction product (after concentration in vacuo) showed a reduction in the area of the integral associated with the methyl groups at C-2 (1.69 δ), confirming the incorporation of the CD$_3$ unit. No reduction (or D–C–H coupling) was noted for the proton resonance at C-5 or the protons on the methyl group at C-6.

Conversion of Isopropenyl Acetoacetate (8) to Dioxinone 1. In a 10-mL, round-bottomed flask was placed isopropenyl acetoacetate (0.030 g, 0.211 mmol), acetone (1.18 g, 21.1 mmol), and 3 mL of *p*-xylene. The flask, was tightly stoppered and immersed in the bath at 91.7 °C. Analysis by GC after 1 h showed complete conversion to dioxinone **1**.

Reaction of Isopropenyl Acetoacetate (8) with 1-Butanol. In a dry, 25-mL flask equipped with a condenser, a nitrogen inlet, and a stoppered sidearm was placed a solution of isopropenyl acetoacetate (62 mg, 0.436 mmol), 1-butanol (37 mg, 0.492 mmol), and *p*-dichlorobenzene (36 mg, internal standard) in 10 mL of *p*-xylene. This flask was immersed in a 91.7 °C constant temperature bath, and the reaction was monitored by GC as described above. After 1 h GC indicated complete conversion to **3b**. After correcting the data for the time the solution required to reach the elevated temperature, a rate constant of 9.2×10^{-4} s^{-1} was estimated for the process. This is in agreement with the 8.8×10^{-4} s^{-1} rate constant which was noted for a similar experiment which utilized 0.457 mmol of isopropenyl acetoacetate and 5.466 mmol 1-butanol. In a third experiment, isopropenyl acetoacetate (32 mg, 2.335 mmol), 1-butanol (208 mg, 2.870 mmol), and *p*-dichlorobenzene (284 mg) were diluted to 50 mL with *p*-xylene, placed in the pressure bottle, purged with nitrogen, and immersed in the 91.7 °C constant temperature bath. A value for k_1 was estimated from four data points to be 7.27×10^{-4} s^{-1} (standard deviation = 3.9×10^{-5}). The uncertainties associated with these rate constants are considerably greater than those for dioxinone **1** due to the faster rate of reaction and the larger experimental errors associated with the GC analysis of **8**.

Reaction of Isopropenyl Acetaoacetate (8) with Cyclohexanone. In a 10-mL, round-bottomed flask was placed 30 mg of isopropenyl acetoacetate (0.211 mmol), 200 mg of cyclohexanone (2.11 mmol), and 5 mL of xylene. The solution was immersed in the bath at 91.7 °C for 15 min. Analysis by GC showed complete conversion to the diketene–cyclohexanone adduct.

Reaction of Isopropenyl Acetoacetate (8) To Give Dehydroacetic Acid (5). In a small tube was placed 69 mg of isopropenyl acetoacetate (0.486 mmol), 52 mg of *p*-dichlorobenzene, and 0.15 mL of *p*-xylene. The solution was heated at 91.7 °C for 45 min. Analysis of the reaction mixture by GC and using response factors for **1** and **6** indicated **1** had been formed in 15% yield and **6** in 14% yield. GC/MS analysis suggested that 2,4,6-heptanetrione (**10**) and 2,6-dimethyl-4-pyrone were also present in the reaction mixture.

Reaction of 1-Butanol with 2-(4-Methoxyphenyl)-6-methyl-4*H*-1,3-dioxin-4-one (the Diketene–Anisaldehyde Adduct, 9). In a nitrogen-purged, 2-necked flask equipped with a condenser and thermocouple temperature regulator (Omega controller) was placed 25 mL of toluene. The toluene was heated to 91 °C, and a solution of the dioxinone (0.346 g, 1.57 mmol) and 1-butanol (315 mg) in 10 mL of toluene was added. Analysis by 60 MHz ^{1}H NMR spectroscopy showed ca. 50% conversion to butyl acetoacetate after 25 min and ca. 85% conversion after 50 min.

Spectroscopic Observation of Acetylketene. The apparatus consisted of a Mattson Cryolect Matrix Isolation GC-IR. This apparatus allows the effluent from an HP5890 GC to be trapped in an Ar matrix on a cold (5–12 K) gold-coated disk, from which the infrared spectrum is subsequently obtained. The GC conditions used were identical with those used in the kinetic experiments, and the transfer line between the GC and the cold disk was heated to 180–240 °C. The carrier gas contained approximately 1% Ar to provide the matrix medium. Under all conditions, acetylketene was observed. To increase the dilution of the acetylketene in the matrix, the split ratio was increased from ca. 20:1 to 100:1. This gave spectra which showed two distinct ketene absorption bands at 2142 and 2135 cm^{-1}.

Acknowledgment. We appreciate the many helpful suggestions provided by Prof. J. Peter Guthrie and Drs. John Hyatt and Dale Van Sickle. Dr. Rick Zimmerman provided expert technical assistance in isolating and observing acetylketene via GC-IR.

Registry No. 1, 5394-63-8; **2**, 691-45-2; **8**, 93304-66-6; **9**, 83559-41-5; butanol, 71-36-3; phenol, 108-95-2; dibutylamine, 111-92-2.

Supplementary Material Available: Tables that summarize the reaction conditions used in each individual experiment, the rate constants thus obtained, and an analysis of variance for each rate constant (4 pages). Ordering information is given on any current masthead page.

A Stereoselective Totally Synthetic Route to Methyl α-Peracetylhikosaminide

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New Haven, Connecticut 06511. *Received June 22, 1988*

Abstract: A synthesis of the title system from D-galactose has been achieved. The racemic galactose 1,2,3,4-bisacetonide is expanded to a C$_7$ heptulose, which is then extended to an undecose by a Lewis acid catalyzed cyclocondensation reaction. Racemic galactose was synthesized from furfural by a similar cyclocondensation reaction.

Hikizimycin (or anthelmycin **1**)[1a,b] (Figure 1) was isolated from the fermentation broths of a strain of *Streptomyces longissimus* and from *Streptomyces A-5*. While hikizimycin exhibits broad antibacterial properties, its potency is too weak to be of importance.[2] Of greater interest are its anthelmintic properties against a variety of common parasites. The synthesis of antiparasitic substances has been one of the concerns of our laboratory.[3]

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