

**Table I.** Equilibrium Constants for **1**  $\rightleftharpoons$  **2**

Temp, °C	193.4	201.7	209.7	217.9	226.5	235.5
<i>K</i>	6.04	5.89	5.63	5.48	5.32	5.10

**Table II.** Rate Constants for **1**  $\rightarrow$  **2**

Temp, °C	193.4	201.7	209.7	217.9	226.5	235.5
$10^5 k_1, s^{-1}$	2.13	4.44	8.79	17.4	31.6	66.2

analogously rearranges with an estimated  $E_a = 41.0$  kcal/mol (assuming  $\log A = 14.26$ ),<sup>10</sup> and 2,2,3,3-tetradeuteriomethylenecyclopropane (**5**) undergoes degenerate isomerization with an estimated  $E_a = 41.6$  kcal/mol.<sup>11,12</sup> It is thus apparent that the isomerization of **1** is *enhanced* substantially by the presence of the fluorine substituents. (Calculated relative rates of isomerization of **1**, **3**, **4**, and **5** at 210 °C are 3.8, 3.5, 2.3 and 1.0, respectively.) Much recent theoretical and experimental work on the structure of methylenecyclopropane and fluorinated cyclopropanes has appeared.<sup>6,13-15</sup> If the perturbation effects on cyclopropane of the fluorine substituents and of the methylene group are additive,<sup>14</sup> and it seems that they should be, then one would predict a *higher* activation energy for rearrangement of **1** than for methylenecyclopropane itself. The apparent incompatibility of our results with expectation (on the basis of the microwave data) might be able to be rationalized if a fluorine substituent were to stabilize a radical site.<sup>16</sup> However, that data which exists points neither to stabilization nor destabilization of a radical site by fluorine.<sup>4,18</sup> It does appear that the effect of fluorine substituents on a cyclopropane should not, thermochemically, be thought of as a simple "strain" effect,<sup>4</sup> since the various C-C bonds seem to be affected to different extents, with the opposite bond appearing to be more dramatically affected.

The preference of **2**, with vinylic CF<sub>2</sub> over **1** in the equilibrium was foreshadowed by the fluorobullvalene work.<sup>2,3</sup> The deleterious thermodynamic effect of fluorine on a vinylic site is fairly well documented. While tetrafluoroethylene is enhanced in its addition and dimerization reactions by ~16 kcal/mol<sup>18,20</sup> over those of ethylene, the heats of hydrogenation of trifluoroethylene and 1,1-difluoroethylene reflect smaller degrees of enhanced reactivity, i.e., 8 and 4 kcal/mol, respectively.<sup>21</sup> Butadiene-cyclobutene equilibria also indicate a nonlinear relationship between numbers of fluorine substituents and  $\pi$ -bond reactivity.<sup>22,23</sup>

Additional systematic equilibrium studies are needed to gain a firm quantitative insight into the incremental thermodynamic effect of fluorine substitution on double bonds. From our study we can unambiguously state that a vinylic *gem*-difluoro group is 1.9 kcal/mol more stable than a CF<sub>2</sub> group which is incorporated into a cyclopropane ring.

Interestingly, the analogous 2,2-dichloromethylenecyclopropane has been examined and shown to rearrange virtually quantitatively to dichloromethylenecyclopropane, indicating a much greater propensity for chlorine to exist in the vinylic position.<sup>24</sup> Uncertainties relating to both kinetic and thermodynamic effects of cyclopropyl-, vinyl-, and alkyl-bound fluorine still are prevalent. Further research is in progress to elucidate such effects.

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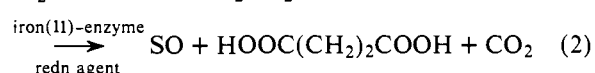
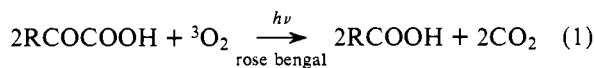
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## Dioxygen Fixation. Oxene Transfer in the Reaction of Singlet Dioxygen with $\alpha$ -Keto Acids

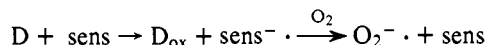
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The mechanism of dioxygen activation in iron-containing oxygenases such as cytochrome P-450 has been discussed in terms of an oxenoid intermediate.<sup>1-5</sup> Some chemical systems function apparently as oxenoid oxygen transfer agents, notably pyridine *N*-oxide,<sup>6</sup> the oxidant from low temperature ozonation of alkynes,<sup>7</sup> and iodobenzene.<sup>8</sup>

We report now that the <sup>1</sup>O<sub>2</sub> oxidative decarboxylation of  $\alpha$ -keto acids (eq 1)<sup>9</sup> proceeds via an intermediate which is capable of oxygen transfer to unsaturated substrates. This result also enables us to suggest a role for the hitherto unexplained function played by  $\alpha$ -ketoglutarate in  $\alpha$ -ketoglutarate dependent oxygenases<sup>10,11</sup> (eq 2).



A central point in the reaction presented in eq 1 is the role of dioxygen. It has been shown that  $\alpha$ -ketoglutaric acid upon irradiation in the presence of methylene blue, but in the absence of dioxygen, undergoes decarboxylation.<sup>12</sup> Furthermore, the  $\alpha$ -ketoglutaric acid can undergo photodecarboxylation.<sup>13,22</sup> Also superoxide anion-radical formation from the sensitizer may occur:



The basic question is whether the reaction in eq 1 is a reaction of singlet dioxygen. Accordingly we generated singlet dioxygen

**Table I.** Reaction of  $\alpha$ -Ketoglutarate with Singlet Oxygen under Various Conditions

$^1\text{O}_2$ source	temp, $^\circ\text{C}$	alkene	$\text{CO}_2$ , %	succinic acid, %	epoxide, <sup>a</sup> %
$(\text{C}_6\text{H}_5\text{O})_3\text{P}-\text{O}_3$	-24		24	24	
microwave <sup>b</sup> discharge $^3\text{O}_2$ at 5 mmHg	25		26	30	
rose bengal <sup>c</sup> - $^3\text{O}_2$ , $h\nu$	25	TCNE	15	18	15 <sup>d</sup>
rose bengal- $^3\text{O}_2$ , $h\nu$	-100 <sup>e</sup>	cyclohexene	26	21	18 <sup>f</sup>
rose bengal- $^3\text{O}_2$ , $h\nu$	-100	styrene	23	22	19 <sup>g</sup>
rose bengal- $^3\text{O}_2$ , $h\nu$	-100	<i>trans</i> -stilbene	24	24	14 <sup>h</sup>
rose bengal- $^3\text{O}_2$ , $h\nu$	-100	<i>tert</i> -butylphenol	22	20	10% <i>tert</i> -butylcatechol <sup>i</sup>
$^3\text{O}_2$ , $h\nu$	-100	<i>trans</i> -stilbene	~4	~4	none
$^3\text{O}_2$ , $h\nu$	-100	cyclohexene	~4	~4	trace, <1%

<sup>a</sup> Yield of oxide was calculated by wt of alkene oxide/theoretical wt of alkene oxide  $\times 100$  / (yield of  $\text{CO}_2$  + yield of  $\text{HOOCCH}_2\text{CH}_2\text{COOH}$  / 2).

<sup>b</sup>  $\alpha$ -Ketoglutaric acid was absorbed on silica gel (60–200 mesh). The reaction time was 20 h. Oxygen atoms were removed by a mercury reservoir. In a control experiment <3% decarboxylation was observed under these conditions with  $^3\text{O}_2$ . <sup>c</sup> The sensitizer is partially protonated in methanol. No bleaching of the sensitizer occurred during the course of the reaction. <sup>d</sup> TCNE-oxide.<sup>19</sup> <sup>e</sup> The photooxygenation apparatus containing a solution of 0.009 mol of  $\alpha$ -ketoglutaric acid and 132 mg of rose bengal in 120 mL of  $\text{CH}_3\text{OH}$  was immersed in a Dewar flask with dry ice–diethyl ether. Liquid nitrogen was circulated through the inner cooling jacket. <sup>f</sup> Cyclohexene oxide (see D. Swern, "Organic Reactions", Vol. VII, Wiley, New York, N.Y., 1953, p 378). Under our conditions the oxide undergoes methanolysis and is isolated as *trans*-1-hydroxy-2-methoxycyclohexane. <sup>g</sup> Styrene oxide (see H. Hibbert and P. Burt, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 494). <sup>h</sup> *trans*-Stilbene oxide (see D. Reif and H. House, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 860). No evidence for this *cis* isomer was obtained. <sup>i</sup> Identified by comparison with a purified commercially available sample.

chemically from the triphenyl phosphite–ozone reaction.<sup>14</sup> The results indicate that the same products in comparable yields are obtained.

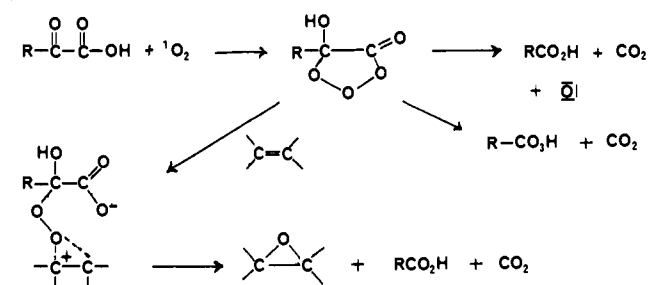
An even more straightforward demonstration of the role of singlet dioxygen in this process was achieved by the reaction of  $\alpha$ -ketoglutaric acid with singlet dioxygen formed by microwave discharge upon ground-state dioxygen (Table I). The observations<sup>9</sup> that (a) the  $\alpha$ -ketocarboxylate anion was more reactive toward  $^1\text{O}_2$  than the undissociated acid<sup>15</sup> and that (b) phenylglyoxalic and oxalic acid (compounds with, in the former, a deactivated ketonic carbonyl; and in the latter, no ketonic carbonyl group at all) did not undergo oxidative decarboxylation indicate (a) that the initial attack of the electrophilic  $^1\text{O}_2$  is at the nucleophilic carboxyl group and (b) the likelihood of a subsequent intramolecular nucleophilic attack upon the ketonic carbonyl group by the anionic oxygen occurs to form a trioxalane (Scheme I).

The cyclized form is probably more stable than the open form<sup>16</sup> and the structural analogy with cyclic trioxides proposed in alkene<sup>19</sup> and alkyne ozonation<sup>7</sup> is apparent.<sup>17</sup>

Among reactions open to the cyclic trioxide are loss of  $\text{CO}_2$  to yield a peroxy acid, a route which occurs if the  $\alpha$ -keto acid is sequestered on a resin,<sup>9</sup> or the trioxide could transfer "oxene" to an acceptor. We detected this possibility and differentiated it from the peroxy acid pathway, as follows. The photooxygenation at  $-100^\circ\text{C}$  for 10 h of  $\alpha$ -ketoglutarate was carried out. Then the system was flushed with  $\text{N}_2$  and tetracyanoethylene (TCNE) was added at  $-100^\circ\text{C}$ . The reaction solution was allowed to warm to  $-50^\circ\text{C}$  over a 3-h period and then at  $-50^\circ\text{C}$  excess diethyl sulfide was added and a 15% yield of TCNE oxide was obtained (Table I). This is a critical experiment since TCNE is not epoxidized by peroxy acids at  $<-25^\circ\text{C}$ .<sup>18</sup> Günther and Criegee<sup>19</sup> obtained TCNE oxide in a low temperature olefin–ozone reaction, presumably by oxygen transfer from an intermediary carbonyl oxide.

Next we tested the oxene transfer ability of the proposed trioxide toward other olefins. To distinguish this reaction from epoxidation by a possible peroxy acid, the photooxygenation was carried out at  $-100^\circ\text{C}$  during a 10-h period. Then the system was purged with nitrogen and the alkene (cyclohexene, styrene, or *trans*-stilbene) was added at  $-100^\circ\text{C}$ . The reaction was allowed to warm to  $-50^\circ\text{C}$  and kept at that temperature for 40 min, and then it was quenched by addition of a fourfold excess of diethyl sulfide. Yields of 14–19% of epoxides were obtained (Table I). In control experiments it was shown that

Scheme I



peroxyacetic acid did not effect oxidation of these olefins at  $-50^\circ\text{C}$ . Similar results were obtained with  $\alpha$ -ketobutyric acid under the same conditions.

These experiments demonstrate that (a) the oxidant is stable at  $-100^\circ\text{C}$  for a relatively long period of time (10 h), (b) oxygen transfer to the olefin occurs at  $-50^\circ\text{C}$  or below (and could not occur via a peroxy acid since epoxidation with this reagent does not take place at this temperature) and, finally, (c) because of the essential equivalence in yields of  $\text{CO}_2$ , succinic acid, and epoxides (Table I) the trioxide does not react with  $\alpha$ -keto acid to cause oxidative decarboxylation below  $-50^\circ\text{C}$ . Whether this reaction occurs at all is under investigation. Finally, *tert*-butyl phenol was converted in 10% yield to *tert*-butylcatechol, which is in agreement with an oxene mechanism.

We refer to this overall scheme as "dioxygen fixation" because a dioxygen molecule is incorporated into the  $\alpha$ -keto acid to form an unstable molecule which decomposes by formally cleaving the oxygen–oxygen bond of the original dioxygen molecule providing an oxidant at the oxidation level of an oxene species and oxygen with an octet of electrons (in the  $\text{CO}_2$ ).

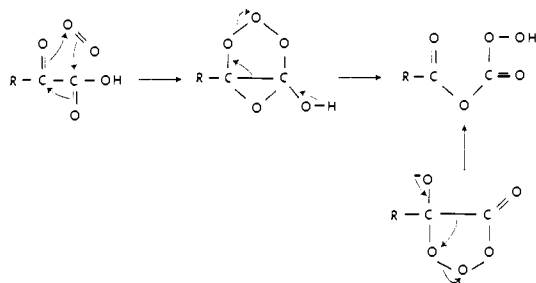
The above description is analogous to what may generally occur in enzymic activation of molecular oxygen in  $\alpha$ -ketoglutarate dependent oxygenases.<sup>10,11</sup> However, here we propose that the photochemical  $^3\text{O}_2 \rightarrow ^1\text{O}_2$  process discussed above has an analogy in the enzymic process:  $\text{Fe}^{11} + ^3\text{O}_2 \rightleftharpoons \text{Fe}^{11}\text{O}_2 \rightleftharpoons \text{Fe}^{11}\text{O}_2^-$ . Subsequent reaction with the  $\alpha$ -ketoglutarate may be quite similar, involving interaction of  $\text{Fe}^{11}$  with  $\alpha$ -ketoglutarate and the substrate, subsequent binding, and activation of dioxygen by one-electron transfer. The intermediary equivalent of a bound superoxide anion radical could add to the ketonic carbonyl of  $\alpha$ -ketoglutarate to yield a cyclic complex which then could lose  $\text{CO}_2$  donating two

electrons to give back Fe<sup>II</sup> and hydroxylated substrate or the iron-bound oxene. The relationship between the reaction of <sup>1</sup>O<sub>2</sub> and α-ketoglutarate and the enzymic reaction is that in each the keto acid is the intermediary dioxygen acceptor. The oxygen-oxygen bond cleavage is coupled with loss of carbon dioxide. This mechanism assigns a role for the hitherto unexplained action of the keto acid in the enzymic reaction.<sup>11</sup>

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these examples, a trioxide could form which is capable of yielding two atoms of oxygen. The trioxide proposed by us in the α-keto acid example could rearrange to a peroxy anhydride which could result from the bicyclic oxidotrioxide. We thank Professor H. H. Wasserman for calling our attention to the peroxy anhydride.

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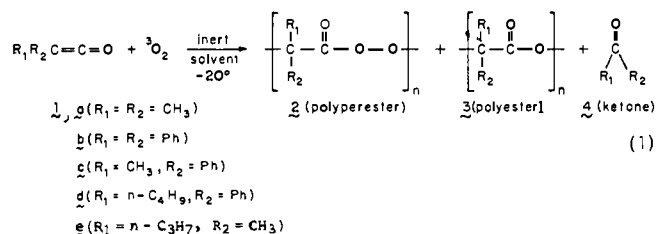
## Autoxidation of Ketenes. Diradicaloid and Zwitterionic Mechanisms of Reactions of Triplet Molecular Oxygen and Ketenes

Sir:

The reaction of ketenes with singlet molecular oxygen has recently been shown to yield α-peroxylactones in addition to

other products derived from zwitterionic or perepoxy intermediates.<sup>1</sup> Over 60 years ago, the autoxidation of ketenes was reported to result in an unusual copolymerization to produce polyester (arylketenes) or polyperester<sup>2</sup> (alkylketenes) as the major products. We have reinvestigated these autoxidations. In addition to confirming and expanding the earlier studies,<sup>2</sup> we provide evidence (a) for the occurrence of two distinct mechanisms (zwitterionic and diradicaloid) in the reaction of triplet oxygen with ketenes, (b) for the occurrence of a novel (overall) cycloaddition of triplet molecular oxygen to ketenes to form α-peroxylactones, and (c) for the intermediacy of trappable diradicaloid and zwitterionic transients.

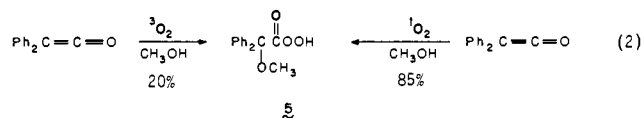
The autoxidation of dimethylketene<sup>3a</sup> (**1a**) was effected by bubbling oxygen gas through an ether solution (-20 °C) of **1a** (~0.1 M) for several hours. <sup>1</sup>H NMR analysis of the reaction demonstrated the formation of a major product (96%). A white precipitate developed which, after collection, washing with solvent and filtration (all manipulations at -20 °C), was assigned a polyperester structure (**2a**, eq 1) on the basis of the



following properties: (a) its tendency to undergo unpredictable, violent detonation as a dry solid; (b) its quantitative conversion<sup>4</sup> to acetone and CO<sub>2</sub> at temperatures >0 °C; (c) its spectral properties, especially <sup>1</sup>H NMR (δ<sup>Me<sub>4</sub>Si</sup>, CDCl<sub>3</sub>, -30 °C) 1.60 and IR (cm<sup>-1</sup>, CH<sub>2</sub>Cl<sub>2</sub>) 1775. The polyester **3a** is produced<sup>3b</sup> as a minor (~4%) product in the autoxidation of **1a**. No acetone is produced as a primary product of autoxidation of **1a** at temperatures below -20 °C. A similar course for autoxidation was found to occur for methyl-*n*-propylketene (**1e**).

The autoxidation of diphenylketene (**1b**)<sup>5</sup> leads to results that contrast sharply with those found for autoxidation of **1a**. The autoxidation of **1b** is much more sluggish and must be conducted at room temperature (benzene solvent) for over 3 days. The products of autoxidation of **1b** (~0.1 M, 1 atm of O<sub>2</sub>) are polyester<sup>6</sup> **3b** (~70%), **4b** (~30%), and CO<sub>2</sub> (~30%). No polyperester **2b** could be detected by IR analysis, even when the reaction was conducted at -78 °C (CS<sub>2</sub>). The infrared spectrum of polyester **3b** is experimentally indistinguishable from that of the polymer produced<sup>6a</sup> by reaction of **1b** with O<sub>3</sub>.

Autoxidation of **1a** or **1b** in methanol solvent again leads to contrasting results.<sup>7</sup> In the case of **1a**, the only significant autoxidation product is α-hydroperoxy methyl isobutyrate. In the case of **1b**, in contrast, α-methoxydiphenylperacetic acid (**5**, eq 2) is a significant oxidation product. The latter is also



the major oxidation product of reaction of <sup>1</sup>O<sub>2</sub> with **1b** in methanol.<sup>1</sup>

The autoxidation of **1a** (CS<sub>2</sub> solvent, -20 °C) was found to be strongly inhibited (~98%) by 2,6-di-*tert*-butyl-4-methylphenol (**6**), but autoxidation of **1b** (CS<sub>2</sub> solvent) was only partially (~85%) inhibited by **6**. The formation of **5** (CH<sub>3</sub>OH solvent) was not inhibited at all by **6**.

Autoxidation of phenylalkylketenes (**1c** and **1d**, 0.1 M) in benzene at room temperature produces polyesters **3c** (65%) and **3d** (40%) and ketones **4c** (35%) and **4d** (60%) as the major