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THE ROLE OF SINGLET OXYGEN AS REAGENT IN THE DYE-SENSITIZED PHOTO-OXYGENATION OF α-KETOCARBOXYLIC ACIDS

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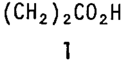
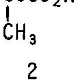
The oxidative decarboxylation of α-ketoglutaric acid by molecular oxygen is thought to be the key step in several dioxygenase-catalyzed hydroxylations.[1] In general, α-ketocarboxylic acids are unreactive towards ground-state molecular oxygen. However, we have reported that singlet oxygen, generated by dye-sensitization, gives carbon dioxide and the corresponding peroxy acid which instantaneously causes decarboxylation of the starting α-keto acid (eq. 1).[2] Subsequently, it has been suggested that the triplet-excited dye, rather than singlet oxygen, is the agent responsible since α-ketoglutaric acid (1) and its salts undergo dye-sensitized decarboxylation in the absence of oxygen.[3] We have examined this matter further by investigating several α-keto acids (1-4) and now report that photo-excited dyes alone bring about decarboxylation, but when oxygen is present, extra decarboxylation occurs which is due to singlet oxygen. Moreover, we find that the behaviour of α-ketoglutaric acid is atypical.

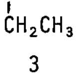
$$RCOCO_2H \xrightarrow{^1O_2} RCO_3H + CO_2; \quad RCO_3H + RCOCO_2H \rightarrow 2RCO_2H + CO_2 \qquad \text{(eq. 1)}$$


$\begin{array}{l} COCO_2H \\ | \\ (CH_2)_2CO_2H \end{array}$

1


$\begin{array}{l} COCO_2H \\ | \\ CH_3 \end{array}$

2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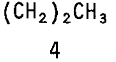
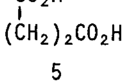
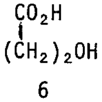
3


$\begin{array}{l} COCO_2H \\ | \\ (CH_2)_2CH_3 \end{array}$

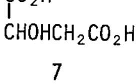
4


$\begin{array}{l} CO_2H \\ | \\ (CH_2)_2CO_2H \end{array}$

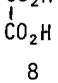
5


$\begin{array}{l} CO_2H \\ | \\ (CH_2)_2OH \end{array}$

6


$\begin{array}{l} CO_2H \\ | \\ CHOHCH_2CO_2H \end{array}$

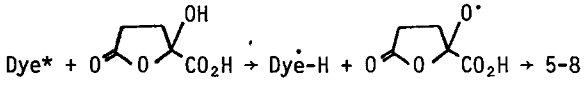
7


$\begin{array}{l} CO_2H \\ | \\ CO_2H \end{array}$

8

When oxygen is absent, acetonitrile-pyridine solutions of the acids 1-4 underwent bengal rose-sensitized decarboxylation accompanied by bleaching of the dye[4] (Table 1). Yields of carbon dioxide up to 90% were obtained with α-ketoglutaric acid (1) before the dye was completely bleached. On the other hand, the acids 2-4 gave yields of carbon dioxide which were never greater than 7%. Therefore, in some way α-ketoglutaric is different from the other acids.[5]

The exceptional behaviour of α-ketoglutaric acid is also seen when oxygen is present. Its pyridinium salt on bengal rose-sensitized photo-oxygenation evolved more than one equivalent of carbon dioxide and gave variable amounts of degradation products, namely succinic (5), β-hydroxypropionic (6), malic (7) and oxalic (8) acids. Under identical conditions, but in complete contrast, the pyridinium salts of the acids 2-4 liberated just one equivalent of carbon dioxide producing the corresponding carboxylic acids in accordance with equation 1. We believe that the anomalous behaviour exhibited by α-ketoglutaric acid lies in its tautomerization[6] to the lactol 9, which is preferentially oxidized by the excited dye. Subsequent reaction of the initially formed lactol radical 10 would account for the products 5-8 (eq. 2).



(eq. 2)

9 10

Table 1. Bengal Rose-Sensitized Decarboxylation of α-Keto Acids

Acid	Conditions[a]	Atmosphere	% CO_2[b]	Observations[c]
Ketoglutaric (1)	Solution	N_2	90	Bleaching[d]
	Solution	O_2	125	Succinic (5), hydroxypropionic (6), malic (7), oxalic (8)[e]
	Solid	N_2	0	No bleaching
	Solid	O_2	27	
	Solid (no dye)	O_2	16	
Pyruvic (2)	Solution	N_2	5	Bleaching[d]
	Solution	O_2	50	Acetic acid (50%)
Oxobutyric (3)	Solution	N_2	3	Bleaching[d]
	Solution	O_2	100	Propionic acid (100%)
Oxovaleric (4)	Solution	N_2	7	Bleaching[d]
	Solution	O_2	75	Butyric acid (75%)
	Solid	N_2	0	No bleaching
	Solid	O_2	30	Peroxybutyric acid[f]
	Solid (no dye)	O_2	0	

[a] Solution: in 100 ml acetonitrile/pyridine (50/50), keto acid; $2x10^{-2}$M, bengal rose; 10^{-3}M. 48 h illumination from two 500 W tungsten lamps. Solid: 1.4 mmol acid adsorbed on 4.8 g 70-230 mesh silica gel, bengal rose on IRA 401 ion exchange resin (ref. 10). Both solids were stirred in a pyrex vessel through which oxygen was passed. Illumination from a 500 W tungsten lamp for 68 h. [b] Calculated from weight of barium carbonate precipitated by passing exit gases through aqueous barium hydroxide. [c] Products were isolated and yields determined by NMR (or VPC of methylated) crude reaction mixtures. [d] Decolorization, not restored by oxygen. [e] Yields varied greatly from run to run. A typical reaction gave 5 (56%), 6 (12%), 7 (<5%) and 8 (< 5%). [f] Only product detected, epoxidizes cyclohexene. Yield not determined.

The reactions with the acids absorbed on silica gel were informative. Under nitrogen, no decarboxylation occurred confirming that contact between sensitizer and acid is necessary for part of the photo-reaction. Under oxygen, where and when the sensitizer is immobilized, moderate decarboxylation (∿30%) occurred with both the atypical 1 and normal 4 acids. Always under oxygen, but omitting sensitizer, the normal acid 4 was inert, whereas α-ketoglutaric acid 1 still released carbon dioxide. Clearly, there is a second decarboxylation pathway which requires singlet oxygen for both normal 4 and atypical 1 acids, although the latter has available yet another reaction mode with triplet oxygen. Significantly, peroxybutyric acid was characterized as the sole product from oxovaleric acid (4).

Table 2. Relative Rates of Bengal Rose-Sensitized Decarboxylation of Pyruvic Acid in Oxygen-Saturated H_2O and H_2O/D_2O Mixtures

Run[a]	Mole fraction[b] D_2O	Predicted Rate[c] Enhancement	Measured Rate[d] Enhancement	Measured as % of Predicted Rate
1	0.871	4.63	1.80	38.9
2	0.900	5.26	2.12	40.3
3	0.854	4.32	1.74	40.3
4	0.838	4.07	1.58	38.7
5	0.831	3.97	1.56	39.3
6	0.814	3.74	1.70	45.5
7	0.864	4.50	1.64	36.4
8	0.835	4.02	1.35	33.7
10	0.900	5.26	1.99	37.9
11	0.854	4.32	1.32	30.6
12	0.838	4.07	1.19	29.3
13	0.831	3.97	1.33	33.5
14	0.814	3.74	1.45	38.8
15	0.864	4.50	1.42	31.6
16	0.835	4.02	1.17	29.2
Mean:				36.3
Standard deviation:				4.6

[a] Oxygen was continuously bubbled through solutions of pyruvic acid (5×10^{-2}M), bengal rose (10^{-3} M) and phosphate buffer (pH 7.0, 10^{-1}M) in pairs of identical pyrex tubes (sample and control) which were rotated on an externally illuminated carrousel submerged in a dual purpose cooling/UV filter bath of aqueous potassium chromate (10^{-1}M). [b] Determined by NMR using an internal standard. [c] Derived from the equation of Merkel *et al.*[8] for the prolongation of life-time of singlet oxygen in H_2O/D_2O mixtures cf. H_2O; $\Delta\tau = 1/(1.0-0.9 \times \text{mole fraction } D_2O)$. [d] Determined after 7 h photo-oxygenation by NMR comparison of CH_3 peaks of pyruvic and acetic acids.

Lastly, the observation of an important solvent isotope effect confirmed that singlet oxygen mediates the decarboxylation of the normal acids 2-4. For mixtures of H_2O/D_2O,[7] the life-time of singlet oxygen (τ) is prolonged,[8] thereby increasing its chances of reaction[9] when the mole fraction of the deuterated component is bigger. Ideally, a ten-fold rate enhancement would be expected in pure D_2O compared to H_2O. The evidence from 16 runs (Table 2) showed that the actual rate enhancement, on extrapolation to pure D_2O, was 3.63 ± 0.46, thereby indicating that a good part of the decarboxylation is due to the agency of singlet oxygen.

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4. By spectrophotometric studies we have discovered that the α-keto acids (1-4) completely protonate bengal rose. The resulting conjugate acid does not sensitize oxygen, hence the need for pyridine.
5. The small losses of carbon dioxide by acids 2-4 indicate stoichiometric reduction of dye (M. Koizumi & Y. Usui, Mol. Photochem. 4, 57 (1972)).
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7. The largest deuterium effects are found for D_2O/H_2O and CD_3OD/CH_3OH mixtures. The former mixture was preferred as hydrate concentrations are negligible at pH 7.0,[6] whereas we have detected substantial amounts of the methyl hemi-acetal of pyruvic acid in methanol by NMR spectroscopy of CD_3OD solutions.
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9. The life-times and quantum yields of formation of excited states of bengal rose are identical in both H_2O and D_2O (G.R. Fleming, A.W.E. Knight, J.M. Morris, R.J.S. Morrison & G.W. Robinson, J. Am. Chem. Soc. 99, 4306 (1977), R.S. Davidson & K.R. Trethewey, J. Chem. Soc., Perkin II, 173 (1977)). A secondary isotope effect is not possible as the methyl group of pyruvate does not exchange with D_2O. A primary isotope effect is also ruled out as pyruvid acid is > 99% dissociated at pH 7.0. The rate was found to be relatively insensitive to pH changes around pH 7.0.
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