rate limiting (see W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, p 551.
(9) (a) W. D. Griffiths and M. L. Bender, *Adv. Catal.*, **23**, 209 (1973); (b) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley-Interscience, New York, N.Y., 1971, Chapter 11.
(10) K. Fiohr, R. M. Paton, and E. T. Kaiser, *Chem. Commun.*, 1621 (1971).
(11) Y. Iwakura, K. Uno, F. Toda, S. Onozuka, K. Hattori, and M. L. Bender, *J. Am. Chem. Soc.*, **97**, 4432 (1975).
(12) R. Hershfield and M. L. Bender, *J. Am. Chem. Soc.*, **94**, 1376 (1972).

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Reaction of Singlet Oxygen with α-Ketocarboxylic Acids. Oxidative Decarboxylation and Peroxyacid Formation

Sir:

An important class of monooxygenases are those which require α-ketoglutarate as cofactor.[1] Biological oxidation is catalyzed by the metalloenzyme so that hydroxylation of a substrate (SH) is effected by half a mole of molecular oxygen, while the other half is taken up by α-ketoglutarate which acts as reductant (Scheme I). The details of the general scheme are presently not known.[2] However, the ingenious and mechanistically plausible suggestion has been made that α-ketoglutaric acid (**1**) is converted by oxygen to persuccinic acid (**3**) which subsequently brings about oxidation of the substrate (Scheme II).[3] Direct reaction of singlet α-keto acid and triplet oxygen is spin-forbidden and in fact does not take place. Consequently, the role of transition metal complexation has been invoked to render molecular oxygen acceptable to the α-keto acid function.[3] However, it occurred to us that the plausibility of this idea depends largely on whether singlet oxygen itself is reactive towards α-ketocarboxylic acids.[4] We now report the first examples of this new reaction.

A selected range of α-keto acids and similar structures was submitted to photogenetic singlet oxygen[6] (Table I). For those acceptors which possess a ketonic carbonyl group, singlet oxygen was consumed steadily, carbon dioxide was evolved, and the corresponding carboxylic acids were obtained (entries 1, 2, 3, 4, 5, 12; Table I). Singlet oxygen appeared to be the reagent responsible as omission of any one

Scheme I

$$\underset{\text{1}}{\text{SH} + \text{O}_2 + \text{HO}_2\text{C(CH}_2)_2\text{COCO}_2\text{H}} \xrightarrow[\text{ascorbic acid}]{\text{enzyme}} \underset{\text{2}}{\text{SOH} + \text{HO}_2\text{C(CH}_2)_2\text{CO}_2\text{H} + \text{CO}_2}$$

Scheme II

$$\underset{\text{3}}{\text{1} + \text{O}_2 \longrightarrow \text{HO}_2\text{C(CH}_2)_2\text{CO}_3\text{H} + \text{CO}_2}$$

$$3 + \text{SH} \longrightarrow \text{SOH} + 2$$

of the three components, light, oxygen, or dye, stopped the reaction. The addition of DABCO unexpectedly did not dampen the reaction, but accelerated it.[7] This was attributed to the greater reactivity of the carboxylate anion, which was confirmed by the similar behavior of the sodium salt (entries 3, 4; Table I). On the other hand, progressive addition of β-carotene slowed, but did not halt the reaction.[8]

Reactivity depends on electronic effects which are as yet difficult to completely evaluate. Electron withdrawing groups attached to the α-carbonyl group manifestly stabilize the α-keto acid. Moreover, oxalic acid and its derivatives are inert. The stability of phenylglyoxalic acid (entries 10 and 11) seems to be electronic in origin and not simply due to the absence of a β-hydrogen atom, as *tert*-butylglyoxalic acid is extremely reactive (entry 12).

Although the signs were there, namely the coloration of starch-potassium iodide paper, it was not possible to isolate peracids even at temperatures as low as −78 °C. We believe that as fast as the peracid was formed, it was decomposed by further reaction with the parent α-ketocarboxylic acid.[9] Indeed, the mixing of equimolar amounts of perbenzoic and α-ketovaleric (**4**) acids resulted in *instantaneous* decarboxylation to give butyric acid (**5**) in quantitative yield (Scheme III). Phenylglyoxalic acid behaved similarly with perbenzoic acid. We decided to take advantage of the latter reaction to demonstrate the intermediacy of singlet-oxygen-generated peracid. Phenylglyoxalic acid (**7**) (3.34 mM) and α-ketovaleric acid (**4**) (3.9 mM) in 30 ml of acetonitrile were photooxygenated at 5 °C for 24 h. Carbon dioxide was evolved in 45% yield. The reaction mixture was then methylated with excess diazomethane in ether, and analyzed.[11] In addition to starting material, methyl benzoate and butyr-

Table I. Reaction of Some α-Ketocarboxylic Acids and Related Compounds with Singlet Oxygen[a]

Entry no.	Acceptor	Exptl conditions[b]	Reaction time (h)	% CO_2 evolved[c]	Products[c,d] (%)
1	$HO_2C(CH_2)_2COCO_2H$	A	19	45	$HO_2C(CH_2)_2CO_2H$ (45)
2	$CH_3(CH_2)_2COCO_2H$	A	40	51	$CH_3(CH_2)_2CO_2H$ (45)
3	$CH_3(CH_2)_2COCO_2H$[e]	A	8	35	$CH_3(CH_2)_2CO_2H$ (40)
4	$CH_3(CH_2)_2COCO_2Na$	B	23	30	$CH_3(CH_2)_2CO_2Na$ (29)
5	$HO_2CCH_2COCO_2H$	A	19	32	$HO_2CCH_2CO_2H$ (8)[f]
6	HO_2CCO_2H	A	19	0	None[g]
7	HO_2CCO_2H	C	19	0	None
8	$CH_3O_2CCO_2H$	A	19	0	None
9	NaO_2CCO_2Na	C	19	6	—[h]
10	$PhCOCO_2H$	A	19	0	None
11	$PhCOCO_2Na$	C	4	0	None
12	t-$BuCOCO_2H$	A	23	100	t-$BuCO_2H$ (95)
13	$CH_3(CH_2)_2(C{=}NOH)CO_2H$	A	24	0	None
14	$CH_2{=}CHCO_2H$	A	19	0	None

[a] Generated as previously described (ref 6). [b] 3 mM of acceptor and 5% methylene blue were dissolved in different solvents and photooxygenated at 5 °C: A = 30 ml acetonitrile; B = 30 ml methanol; C = 50 ml water and 25 ml acetonitrile. [c] Percentage yield based on acceptor. [d] Except for entry 5, in all cases the balance of material recovered is acceptor. [e] One equivalent of DABCO (1,4-diazabicyclo[2.2.2]octane) added. [f] Low yield of product due to cleavage via the presumed dioxetane of the enol form of the reactant; estimated as 60% present in the equilibrium mixture. The cleavage products were not identified. [g] None means no reaction of acceptor. [h] Very slight decomposition.

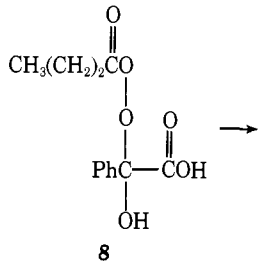
Scheme III

$$PhCO_3H + CH_3(CH_2)_2COCO_2H \longrightarrow \underset{4}{} PhCO_2H + CH_3(CH_2)_2CO_2H + CO_2$$
$$\underset{5}{}$$

Scheme IV

$$4 + {}^1O_2 \longrightarrow \underset{6}{CH_3(CH_2)_2CO_3H} + CO_2$$

$$6 + PhCOCO_2H \longrightarrow \underset{7}{} \underset{8}{} \longrightarrow 5 + PhCO_2H + CO_2$$



ate were found in 20 and 18% yields, respectively. We conclude that singlet oxygen oxidatively decarboxylates α-ketovaleric acid (**4**) to its peroxy derivative (**6**) leaving phenylglyoxalic acid (**7**) unchanged; however, the two acids rapidly form the appropriate Bayer–Villiger-type intermediate (**8**) which promptly fragments liberating carbon dioxide, benzoic, and butyric acids (**5**) (Scheme IV).

Since α-ketoglutaric acid (**1**) and the peroxyacid (**3**) are mutually destructible, it follows that for selective oxidation of a biological substrate the peracid must be discretely immobilized by being bound to an enzyme. Similarly, sequestering of the peracid should enable it to be identified. This was found to be the case. One gram of α-ketovaleric acid was absorbed on 6 g of anionic exchange resin.[12] The dried resin was suspended in 50 ml of methylene chloride and photooxygenated for 24 h.[13] Carbon dioxide was evolved in 40% yield. Next, the solvent was removed and the resin placed in 10 ml of formic acid and 4 g of cyclohexene. The suspension was heated under reflux for 6 h, cooled, and finally heated with 20 ml of 20% aqueous sodium hydroxide solution for 2 h. Extraction of the mixture with hot ethyl acetate gave 0.11 g of *trans*-cyclohexane-1,2-diol (12% yield).[14]

This work reveals an entirely new facet of singlet oxygen chemistry. It also provides an indication of how α-ketoglutarate-dependent monooxygenase systems may operate, at least in showing that when the spin restriction is removed, molecular oxygen may preferentially attack the α-ketocarboxylic function and not an inactive site on the substrate.

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References and Notes

(1) B. Lindblad, G. Lindstedt, M. Tofft, and S. Lindstedt, *J. Am. Chem. Soc.*, **91**, 4604 (1969).
(2) For a review see M. T. Abott and S. Udenfriend, "Molecular Mechanisms of Oxygen Activation", O. Hayashi, Ed., Academic Press, New York, N.Y., 1974, p 167.
(3) G. A. Hamilton, *Prog. Bioorg. Chem.*, 1, 83 (1971).
(4) The organic chemistry of singlet oxygen has been amply reviewed (ref 5), however, no reactions have been reported so far with α-ketocarboxylic acids.
(5) K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968); C. S. Foote, *Acc. Chem. Res.*, **1**, 104 (1968); *Pure Appl. Chem.*, **27**, 635 (1971); D. R. Kearns, *Chem. Rev.*, **71**, 395 (1971); R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973).
(6) C. W. Jefford and A. F. Boschung, *Helv. Chim. Acta*, **57**, 2242 (1974).
(7) 1,4-Diazabicyclo[2.2.2]octane quenches singlet oxygen in its reactions with olefins (C. Ouannes and T. Wilson, *J. Am. Chem. Soc.*, **90**, 6527 (1968)). However, it acts here as a base. The acceleration was about four times.
(8) β-Carotene is an efficient quencher of singlet oxygen in biological systems (C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.*, **90**, 6233 (1968); *ibid.*, **92**, 5216, 5218 (1970).
(9) Hydrogen peroxide reacts readily with α-ketocarboxylic acid (see pp 132–133, ref 3, and pp 327 and 328, ref 10), but there is little or no mention of the reactions of peracids with them; however, a similar reaction course is to be expected.
(10) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972.
(11) Analysis was by gas liquid chromatography using a 1.5 m long 3.5% FFAP column at 60 °C Ethyl benzoate was used to calibrate the yields of methyl benzoate and butyrate.
(12) The resin, IRA-400 obtained from Fluka AG, CH-9470 Buchs, was washed with dry ethanol prior to use.
(13) Our general procedure (ref 6) was followed, but using tetraphenylporphyrin as sensitizer.
(14) The cyclohexanediol was identified with a genuine sample (A. Roebuck and H. Adkins, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 1955, p 217.

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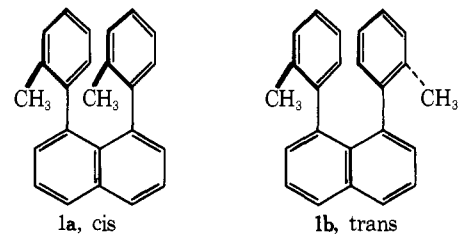
Stable Cis and Trans Rotational Isomers of 1,8-Di-*o*-tolylnaphthalene[1]

Sir:

Studies of CPK (Corey–Pauling–Koltun) or similar space-filling models suggest that there should be a very substantial barrier to a 180° rotation about the phenyl–naphthyl bonds in 1,8-diphenylnaphthalene derivatives. This leads to the expectation that such compounds with a substituent at one meta position of each phenyl ring should be expected to exist as stable cis and trans isomer pairs. However, House and co-workers[2] have shown that several such derivatives, including 1,8-bis(3-chlorophenyl)naphthalene and 1,8-bis(3-methylcarboxyphenyl)naphthalene cannot be resolved into stable configurational isomers. Further, proton NMR studies of these derivatives indicate that $\Delta G^{\ddagger}$ for rotation is 15–16 kcal/mol, which corresponds to rather rapid rotation in solution at room temperature.[3]



1a, cis **1b**, trans

The possibility of isolating stable cis and trans isomers of this type is an interesting one, and we now have found that 1,8-di-*o*-tolylnaphthalene (**1**) can be so resolved.

1,8-Di-*o*-tolylnaphthalene (**1**) was prepared by a direct coupling of *o*-tolylmagnesium iodide with 1,8-diiodonaphthalene with a nickel acetylacetonate catalyst.[4] The proton NMR spectrum of **1** showed two sharp singlets 1.85 ppm downfield from TMS, which were separated by 2 Hz at 60 MHz. The chemical shift of the methyl groups for **1** is decidedly upfield from the methyl signal of toluene (δ 2.32), presumably because of the ring-current effects of the adjacent phenyl and the naphthalene rings. Two isomers, **1a** and