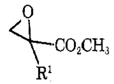
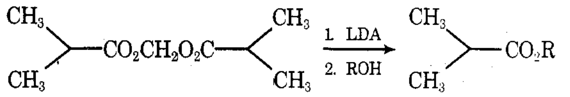
Table I
Preparation of 10 from 1 and 7 (R^2 = Br)

		% isolated yield	
No.	R^1	Fragmentation–recombination of 1 (R^2 = Br)	Methyl ester 7 (R^2 = Br) enolate trapping with formaldehyde
10a	CH_3	61	58
10b	CH_2CH_3	60	51
10c	$CH(CH_3)_2$	64	61

$OCOC_6H_5$) was isolated in 73% yield. Second, with methylene isobutyrate **8**, mainly isobutyric acid (**9a**) was isolated on quenching the LDA reaction with water and similarly methyl isobutyrate (**9b**) with methanol. These data indicate that nucleophilic attack of the ketene by methoxide precedes addition of formaldehyde (path b) and that, when the nucleophile generated in the fragmentation step is unreactive (isobutyrate), dimethyl ketene remains in solution to react with added water or methanol.



8

9a, R = H
b, R = CH_3

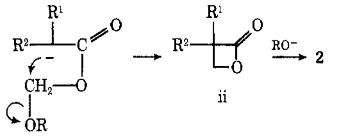
The viability of the second step in eq 2 (path b) was demonstrated by treatment of methyl ester lithium enolates (generated in the usual manner) with formaldehyde vapors and isolation of the corresponding hydracrylates **2** in yields comparable with those in the fragmentation–recombination process [**2**, $R^1 = R^2 = CH_3$, 60%; **6**, 60% (see Table I)]. Although the condensation of formaldehyde with regiospecifically generated ketone[9] and lactone[10] enolates has recently been reported, the analogous reaction described here with ester enolates seems not to have been previously cited. In any event, trapping ester enolates with formaldehyde and fragmentation–recombination of alkoxymethyl ester enolates should prove useful for preparation of many α,α-disubstituted hydracrylates.[11,12]

We also have shown that these two methods are especially attractive for preparation of glycidic esters **10** derived from formaldehyde and α-bromo esters (Table I). Because the standard Darsens reaction of α-halo esters with formaldehyde gives glycidic esters in low yield,[13] we feel that the methodology described here clearly represents a valuable alternative for preparation of these important synthetic intermediates.[14]

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. CA 16624-02).

References and Notes

(1) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(2) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(3) Significantly less than quantitative deuterium incorporation has been reported to occur on treatment of presumably pure ester enolates with D_2O; see ref. 1.
(4) L. L. Miller and J. R. Johnson, *J. Org. Chem.*, **1**, 135 (1936).
(5) Isolated by preparative gas chromatography on a 6 ft × ¼ in. aluminum column filled with 10% SE-30 on Chromosorb WAW, 80–100 mesh size. Occasionally, a minor and unidentified reaction component which eluted with **3** was detected.
(6) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(7) Here, the operationally indistinguishable mechanism involving cyclization of ester enolate **i** to a β-lactone **ii** followed by methoxide opening of **ii** to give **2** was excluded by failure to detect β-lactones in reactions



i

ii

of **1**, consideration of the highly unfavorable transition state required for closure **i** → **ii**, and further suggestive experimental results (vide infra).
(8) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).
(9) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974).
(10) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(11) Preliminary experiments indicate that α-monosubstituted hydracrylates may not be attainable by the fragmentation–recombination method; indeed, reactions of LDA with α-monosubstituted methoxymethyl esters have resulted in complex mixtures of products.
(12) Recent methods for synthesis of α-substituted hydracrylates are outlined in the following: P. E. Pfeffer, E. Kinsel, and L. S. Silbert, *J. Org. Chem.*, **37**, 1256 (1972), and J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 2429 (1973).
(13) M. S. Newman, *Org. React.*, **5**, 413 (1949). Darsens reaction to give the ethyl ester analog of **10a** has been reported to occur in 20–30% yield.
(14) Yields for all compounds reported in this paper are for isolated (distilled) material of near 100% purity (NMR and VPC analysis). Compounds previously reported are **2** ($R^1 = R^2 = CH_3$), J. Falbe and N. Huppes, *Brennst. Chem.*, **48**, 46 (1967); **10a**, R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962); **10b**, H. Loato and J. Ruohonen, *Suom. Kemistilehti* (*B*), **42**, 466 (1969).

Arthur G. Schultz,* Mitchell H. Berger
Department of Chemistry, Cornell University
Ithaca, New York 14853

Received November 4, 1975

Cleavage of Esters by Superoxide[1]

Summary: The reaction of carboxylic esters with potassium superoxide in benzene in the presence of 18-crown-6 ether produces, upon aqueous work-up, the corresponding carboxylic acid and alcohol in good to excellent yields by a process which appears to involve an initial nucleophilic attack of O_2^- at the carbonyl carbon and by the subsequent formation of intermediate peroxo species.

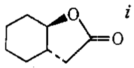
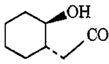
Sir: The beneficial and deleterious effects of superoxide in biological systems have become increasingly evident in recent years.[2] However, until recently,[3,4,5] virtually nothing was known of the reactivity of superoxide with common biological substrates.[6] Ester and peptide bonds are ubiquitous functionalities in biological systems. Here we wish to report that esters, but *not* amides or nitriles, undergo a reaction with superoxide which results in the cleavage of the ester functionality. Aqueous work-up affords the corresponding carboxylic acid in generally high yield. A summary of the results obtained on treatment of various representative substrates is given in Table I.

$$RCO_2R' \xrightarrow[2.\ H_3O^+]{1.\ KO_2\text{-18-crown-6, }C_6H_6} RCO_2H + R'OH \qquad (1)$$

In a typical experiment, a mixture of methyl octanoate (0.529 g, 3.34 mmol) and 18-crown-6 ether[7] (0.264 g, 1.00 mmol) dissolved in dry benzene (20 ml) was added to 0.710 g (10.0 mmol) of powdered potassium superoxide.[8] The resulting mixture was vigorously stirred for 24 h, then cautiously poured into 25 ml of water. The mixture was acidified with 6 M HCl and the organic layer separated. The remaining aqueous phase was extracted with an additional 25 ml of ether and the combined extracts dried ($MgSO_4$). GLC analysis indicated a 98% yield of *n*-octanoic acid.

The cleavage of carboxylate esters by superoxide seems applicable to a spectrum of esters including those of pri-

Table I
Reaction of Potassium Superoxide with Various Esters[a]

Substrate[b]	Product(s) (%)[c]	Reaction time, h
1-$C_7H_{15}CO_2CH_3$	1-Octanoic acid (98) (68)[d]	24
$(CH_3)_3CCO_2CH_3$[e]	Pivalic acid (81)	72
1-$C_7H_{15}CO_2CH_2C_6H_5$	1-Octanoic acid (100) Benzoic acid (55)[f]	24
$C_6H_5CO_2CH_2CH_3$	Benzoic acid (88)	24
1-$C_7H_{15}CO_2CH(CH_3)_2$	1-Octanoic acid (98)	72
$CH_3CO_2CH(CH_3)C_6H_{13}$	2-Octanol (89)	72
1-$C_9H_{19}CO_2C_6H_5$	1-Decanoic acid (84) Phenol (70)[g]	8
1-$C_7H_{15}CO_2C(CH_3)_3$[h]	1-Octanoic acid (96)	140
 [i]	 (85)[j]	28
1-$C_7H_{15}C(O)SC_4H_9$	1-Octanoic acid (93) 1-Butyl disulfide (33)[k]	8
$C_6H_5CH_2CH(NHCOCH_3)CO_2CH_2CH_3$[l]	*N*-Acetylphenylalanine (56)[m]	24
$(C_6H_5O)_3P(O)$	Phenol (30)[g]	24
$(1\text{-}C_8H_{17}O)_3P(O)$	1-Octanol (<1)[n]	72

[a] Unless otherwise indicated, all reactions were carried out at ambient temperature by adding a solution of ester (3.33 mmol) and 18-crown-6 ether (1.0 mmol) in dry benzene (20 ml) to powdered potassium superoxide. Vigorous stirring was maintained during addition and throughout the course of the reaction. [b] All esters, unless otherwise indicated, were prepared by adding the corresponding acid chloride to a solution of the appropriate alcohol or thiol in dry pyridine. [c] Yields were determined by GLC using a 6 ft × 0.25 in. column of 20% ethylene glycol adipate polyester–4% H_3PO_4 on Gas-Chrom Z [L. Metcalfe, *J. Gas Chromatogr.*, 1, 7 (1963)]. Yields are based on ester and were determined by the internal standard technique with response factors obtained from authentic samples. [d] Carried out in dry Me_2SO. [e] Purchased from Aldrich Chemical Co. [f] Control experiments established that under the reaction conditions, benzyl alcohol is oxidized to benzoic acid by superoxide in 62% yield. [g] Control experiments suggest that the low yield of phenol in this experiment results from the fact that this substance undergoes a subsequent reaction with an as yet undetermined reaction intermediate. [h] Prepared according to a procedure outlined by C. R. Hauser, B. E. Hudson, and B. Abramovitch, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 142. [i] M. S. Newman and C. A. VanderWerf, *J. Am. Chem. Soc.*, 67, 233 (1945). [j] Isolated yield after recrystallization from ethyl acetate–hexane, mp 105.0–105.5°C (lit.[i] 105.8–106.6°C). [k] Control experiments establish that superoxide reacts rapidly with alkyl thiols under these conditions. The resulting product, obtained in yields ranging from 60 to 75%, is the corresponding disulfide, RSSR. [l] Purchased from Sigma Chemical Co. [m] Isolated yield, after recrystallization from ethyl acetate, mp 151–153°C (lit.[18] 150–151°C). [n] Unreacted ester was recovered in 96% yield.

mary, secondary, and tertiary alcohols, as well as phenol and thiols. The use of dimethyl sulfoxide (Me_2SO) as a solvent resulted in shorter reaction times but reduced yields (cf. Table I). Reactions carried out in Me_2SO in the absence of 18-crown-6 ether were slower than those performed in its presence. In all instances, ester cleavage is accompanied by the evolution of oxygen.

Although our understanding of the detailed course of this reaction is still incomplete, several observations allow a description of its general features. First, in view of the substantial nucleophilic character of the superoxide radical anion,[4] the possibility of oxygen–alkyl cleavage resulting in the nucleophilic displacement of a carboxylate anion was considered as a plausible pathway.[9] This mechanism is precluded, however, at least for esters of secondary and presumably other alcohols, by the fact that the reaction of superoxide with the acetate ester of (−)-(*R*)-2-octanol (α^{20}_{589} − 7.79°) yields (−)-(*R*)-2-octanol (α^{20}_{589} − 7.61°), corresponding to 99% net retention of configuration at the chiral carbon.

Second, an alternative mechanism involving the SN2 addition of O_2^- to the carbonyl carbon remains reasonable and, moreover, is consistent with the apparent influence which the structure of the departing group exerts on the rate of reaction,[10] i.e., R' = Ph > primary > secondary > tertiary, as indicated by a comparison of the half-life for reaction of phenyl, methyl, isopropyl, and *tert*-butyl *n*-octanoate under comparable conditions: $t_{1/2} \approx 1$, 8, 15, and 26 h, respectively. Under similar conditions, the half-life of the reaction of potassium superoxide with the *n*-butanethiol ester of octanoic acid was 3 h. Understandably, the rate of these reactions can be enhanced by increasing the ratio of macrocyclic polyether to potassium superoxide. For example, the half-life for the reaction of *tert*-butyl *n*-octanoate decreased from 26 to 5 h when the ratio of 18-crown-6 ether to potassium superoxide was increased from 1:10 to 1:1.

Third, in addition to carboxylic esters, certain phosphate esters are also cleaved by superoxide. Thus, the reaction of triphenyl phosphate with potassium superoxide in benzene, in the presence of 18-crown-6 ether, proceeds to completion in less than 24 h. In contrast, tri-*n*-octyl phosphate showed no appreciable reactivity (96% recovery) after 72 h. Presumably this result is, at least in part, a reflection of the different leaving-group ability of phenoxide and *n*-alkoxide.

Finally, simple amides and nitriles seem largely unaffected by superoxide under conditions equivalent to those employed for ester cleavage.[11] As an example, benzamide and *N*-(α-phenylethyl)acetamide were recovered, respectively, in 84 and 99% yield after 8 days of treatment. Similar treatment of benzonitrile led to its recovery in 93% yield after 2 days. This yield was diminished to 73% when the reaction time was extended to 8 days.

Synthetically, the cleavage of carboxylate esters by superoxide is unexceptional since both we and others[12] have observed that under similar conditions, potassium hydroxide shows comparable reactivity. The significance of these observations, however, lies in their potential relevancy to the mechanism of certain biological oxidations. Thus, the observed cleavage of esters in these instances appears to involve nucleophilic substitution at the carbonyl carbon by O_2^- and, although the precise nature of the subsequent intermediates involved in this reaction sequence remains uncertain, peroxo compounds are strongly implicated.[13] Indeed, similar species have been proposed as the oxygen-fixing intermediates involved in several dioxygenase oxidations[14] and our own studies[15] show that the reactions of superoxide with such cosubstrates as, for example, α-ketoglutarate bear a resemblance to the action which certain dioxygenases have on these same substrates.[14]

References and Notes

(1) Supported by the Research Corporation, Rutgers Research Council, Charles and Johanna Busch Memorial Fund, and Biomedical Sciences Support Grant.

(2) B. M. Babior, R. S. Kipnes, and J. T. Curnutte, *J. Clin. Invest.*, **52,** 741 (1973); J. T. Curnutte and B. M. Babior, *ibid.*, **53,** 1662 (1974); B. H. J. Bielski and P. C. Chan, *Arch. Biochem. Biophys.*, **159,** 873 (1973); P. C. Chan and B. H. J. Bielski, *J. Biol. Chem.*, **249,** 1317 (1974); **250,** 318 (1975).

(3) J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.*, **97,** 224 (1975).

(4) J. San Filippo, Jr., C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, **40,** 1678 (1975); see also R. A. Johnson and E. G. Nidy, *ibid.*, **40,** 1680 (1975).

(5) For an application of these results to the synthesis of a naturally occurring prostaglandin, see E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).

(6) I. Fridovich, *Annu. Rev. Biochem.*, **42,** 877 (1973).

(7) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39,** 2445 (1974).

(8) Using a mortar and pestle and working in a glove bag under an atmosphere of dry nitrogen, lumps of potassium superoxide, purchased from K & K Chemicals, were ground to a fine consistency before use.

(9) Various nucleophilic reagents are capable of affecting *O*-alkyl cleavage of methyl and ethyl esters; see P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970), and references cited therein.

(10) A similar influence and order has been observed in the rate of ester saponification, a second-order reaction involving nucleophilic substitution at the carbonyl carbon; see E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1962, Chapter 9.

(11) This result is in strong contrast to the facile reaction that occurs between the hydroperoxide anion, HO_2^-, and nitriles; cf. K. Wiberg, *J. Am. Chem. Soc.*, **75,** 3961 (1953); **77,** 2519 (1955). This fact is surprising in view of the apparent nucleophilicity of superoxide. It may be a result of the considerable solvent differences (aprotic vs. protic) involved in these reactions.

(12) C. J. Pedersen, *J. Am. Chem. Soc.*, **89,** 7017 (1967).

(13) Several reaction sequences can be envisioned as pathways leading ultimately to the production of a carboxylate salt, for example

$$RCO_2R' + O_2^- \rightarrow RC(O)O_2\cdot + R'O^-$$

$$RC(O)O_2\cdot + O_2^- \rightarrow RC(O)O_2^- + O_2$$

$$RC(O)O_2^- \xrightarrow{H_2O} RCO_2^- \qquad \text{(ref 16)}$$

$$RC(O)O_2^- + RCO_2R' \rightarrow RC(O)O_2(O)CR + R'O^-$$

$$RC(O)O_2(O)CR + O_2^- \rightarrow RCO_2^- + RC(O)O_2\cdot + O_2 \qquad \text{(ref 17)}$$

(14) G. A. Hamilton, *Prog. Bioorg. Chem.*, **1,** 83 (1971).

(15) J. San Filippo, Jr., C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, submitted for publication.

(16) D. Swern, "Organic Peroxides", Vol. 1, D. Swern, Ed., Wiley, New York, N.Y., 1969, p 420.

(17) In this regard we have also noted that both acyl peroxides and peresters react readily with superoxide under the conditions cited in Table I. Thus, for example, reaction of benzoyl peroxide and *tert*-butyl perbenzoate with superoxide produced benzoic acid, isolated and recrystallized in yields, respectively, of 72 and 67% after 24 h.

(18) R. M. Herbst and D. Shemin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 491.

Joseph San Filippo, Jr.,* Louis J. Romano
Chuen-Ing Chern
School of Chemistry, Rutgers University
New Brunswick, New Jersey 08903
Joan S. Valentine
Department of Chemistry, Douglass College
Rutgers University, New Brunswick, New Jersey 08903

Received September 29, 1975