Reactions of Carboxylic Acid Derivatives with Superoxide[1]

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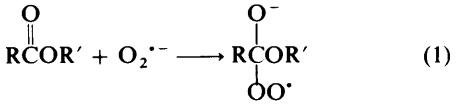
The mechanisms of the reactions of superoxide with carboxylic esters, acyl peroxides, and the acyl chlorides of α- and β-bromocarboxylic acids have been investigated. Experimental evidence is presented supporting the view that (*a*) conversion of an ester into its carboxylic acid does not proceed *via* the corresponding acyl peroxide; (*b*) conversion of acyl peroxide into carboxylic acid by superoxide involves either electron transfer to or an S_N2 reaction on the peroxidic group; (*c*) α-bromoacyl chlorides with superoxide give the corresponding aldehyde *via* a cyclic peroxidic intermediate.

The realisation[2] that superoxide is formed in many important biological processes and in particular during the 'respiratory burst' of stimulated neutrophils[3] has led to a remarkable growth of interest in its chemistry in both protic and aprotic media. Its reactions with carboxylic acid derivatives are well-known[4] but the exact ways in which they proceed have still to be fully elucidated. It was to this end that an investigation of the reactions of derivatives of *o*-phenylbenzoic acid with superoxide were undertaken.

Ester Hydrolysis.—Reaction of esters of carboxylic acids with potassium superoxide in aprotic medium-crown ether gives, after work-up, the corresponding carboxylic acid and alcohol or phenol.[5] Since the overall rate of reaction depends on the leaving group (OR′) the initial step [equation (1)] is considered to be nucleophilic addition of superoxide to the carbonyl group followed by loss of $^-OR'$ [Equation (2)]. The subsequent steps are usually depicted[4] as outlined in Equations (3)–(5) with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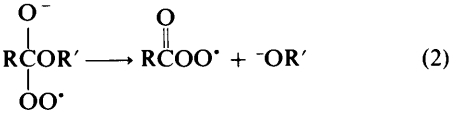
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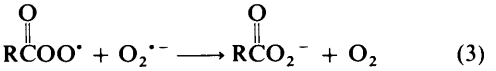
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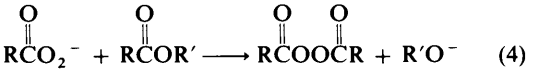
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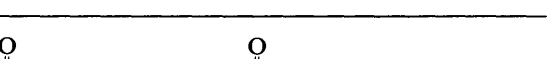
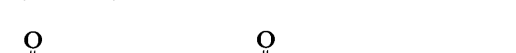


intermediate participation of diacyl peroxide although it is generally recognised that this may be an over-simplification. We have investigated this reaction using *o*-phenylbenzoate esters and have shown that the corresponding diacyl peroxide is not an intermediate *en route* to the acid and hence the sequence of reactions (3)—(5) is at best not general and at worst incorrect.

When ethyl *o*-phenylbenzoate in benzene–18-crown-6 was stirred with potassium superoxide (2.2 mol equiv.) for 24 h at room temperature the corresponding acid was formed in good yield (88%). No acyl peroxide was detected by t.l.c. during the course of the reaction. Conversion into the acid was faster when the reaction mixture was heated under reflux for 2 h and was complete when 3 mol equiv. of superoxide was used at room temperature or on heating. With 1 mol equiv. of superoxide about half of the ester was recovered (48%). Confirmation that the peroxide (**1**) was not an intermediate was obtained by examination of the products obtained when *o*-phenylbenzoyl peroxide (**1**) was treated with superoxide (2.2 mol equiv.) at room temperature. The main products were the parent acid (**3**) (52%) and, significantly, benzocoumarin (**4**) (44%) which was not a product of the ester-superoxide reaction. In the absence of superoxide the diacyl peroxide (**1**) in benzene at room temperature after 24 h gave only a trace of benzocoumarin (**4**).

How then is the acid formed? Peroxy acids appear to react with superoxide in aprotic media to give the parent acid. For example, *m*-chloroperoxybenzoic acid with superoxide (2 mol equiv.) gave *m*-chlorobenzoic acid (95%) after aqueous work-up. However, this result is misleading since a high conversion (90%) of peroxy acid into acid can be achieved simply by shaking for 15 min a solution of *m*-chloroperoxybenzoic acid with aqueous potassium superoxide. Hence, the superoxide, which disproportionates according to Equation (6), is simply a source of hydroxide ion[4] which displaces hydroperoxide-anion as indicated in Equation (7).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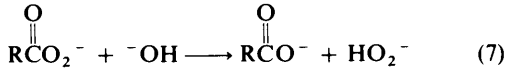
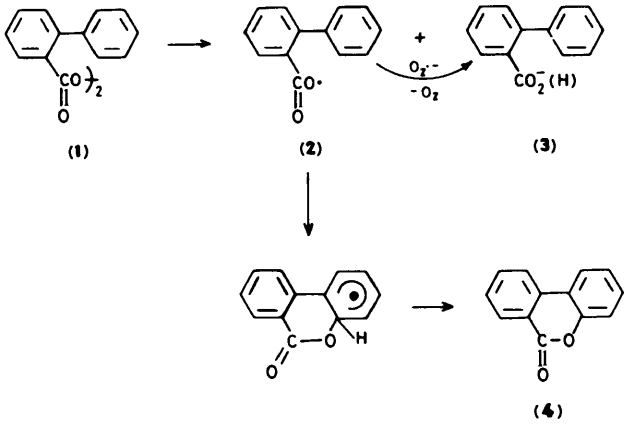
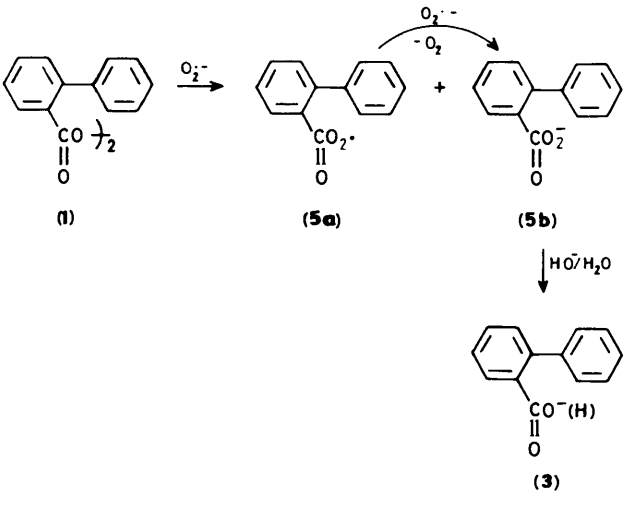

(7)

Peroxide Decomposition.—Benzocoumarin (**4**) is a known decomposition product of *o*-phenylbenzoyl peroxide[6] and is formed by intramolecular cyclisation of *o*-phenylbenzoyloxyl radicals (**2**). We have confirmed this by heating a solution of the peroxide in benzene under reflux and isolating benzocoumarin (**4**) (34%), biphenyl, 2-phenylbiphenyl (combined 6%) and *o*-phenylbenzoic acid (**3**) (16%) from the product mixture. Three different mechanisms have been considered[7a] for the conversion of acyl peroxides into carboxylic acids. (i) *Electron transfer* from superoxide to the peroxy linkage of (**1**) (Scheme 1) would certainly account for benzocoumarin formation *via* *o*-phenylbenzoyloxyl radicals (**2**). However, electron transfer from superoxide to other peroxy bond (H_2O_2, R_2O_2, RO_2H) has few if any precedents and is considered unlikely by some.[7a] (ii)



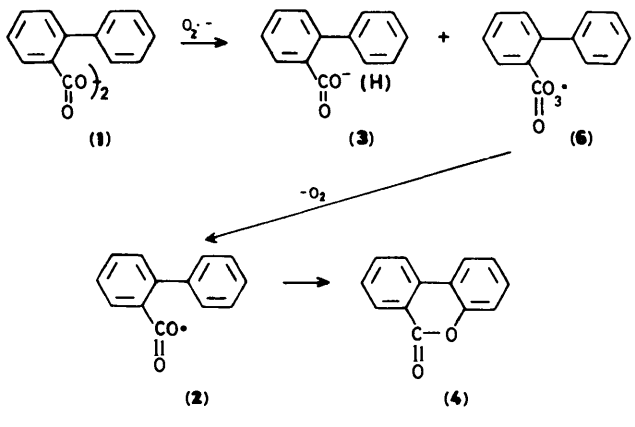
Scheme 1.

Nucleophilic addition to carbonyl carbon, by analogy with reaction of esters would lead to the peroxycarboxyl radical (**5a**) and anion (**5b**). Although the benzocoumarin precursor (**2**) could be formed from (**5a**) by dimerisation to a tetraoxide followed by fragmentation this process would have to compete with an electron transfer[7b] process [(**5a**) ⟶ (**5b**)] favoured by the relatively high concentration of superoxide. There is no evidence for the conversion of peroxycarboxylate anions into carboxyl radicals and certainly none occurred with *m*-chlorobenzeneperoxycarboxylate. On this basis we consider that the sequence of reactions in Scheme 2 is an unlikely route to

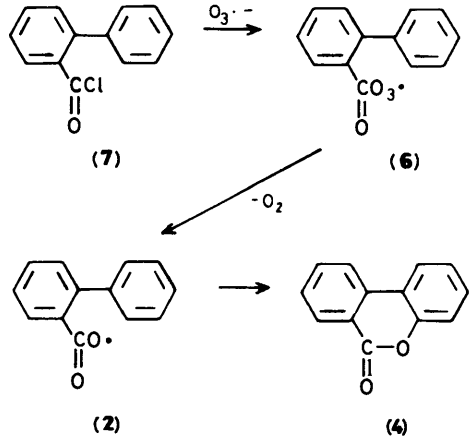


Scheme 2.

benzocoumarin. (iii) *Nucleophilic substitution* at the peroxy oxygen would give an acyltrioxyl radical (**6**), loss of oxygen from which leads to the immediate precursor (**2**) of benzocoumarin (Scheme 3). We have attempted to test the feasibility of Scheme 3 by generating the acyltrioxyl (**6**) by an independent route. Potassium ozonate ($K^+O_3^{-\bullet}$) was prepared as an orange solid by ozonisation of potassium superoxide at low temperature in Freon-12 presaturated with ozone.[7] The potassium ozonate was stabilised by mixing (adsorption) with dried silica gel. Bright orange solutions of ozonate were obtained by dissolving the solid in benzene–18-crown-6. Addition of *o*-phenylbenzoyl chloride to such solutions followed by aqueous work-up after loss of the orange colour gave only small amounts of benzocoumarin (2%). The main product was the carboxylic acid (**3**) (35%) with smaller amounts



Scheme 3.



of the corresponding anhydride and acyl peroxide (**1**). A complicating factor in ozonate chemistry[8,9] is its spontaneous and relatively rapid ($k = 7.18 \times 10^{-3}$ s^{-1} at 0 °C) decomposition to the oxide radical-anion in solution at room temperature. Hence, reaction with acid chloride would have had to be fast relative to reaction (8) if substantial quantities of

$$O_3^{-\bullet} \longrightarrow O^{-\bullet} + O_2 \qquad (8)$$

benzocoumarin were to be formed. Clearly this was not the case and Scheme 3 cannot be discounted on the basis of this result. Hence, our results exclude Scheme 2 but cannot distinguish between Schemes 1 and 3 for the reaction of superoxide with acyl peroxides.

Peroxide Formation.—Although the diacyl peroxide (**1**) is not formed by reaction of ester with superoxide under the conditions employed, its formation from the corresponding acid chloride is not in doubt.[10] Thus, the peroxide (**1**) (33%), accompanied by benzocoumarin (**4**) (6%) and *o*-phenylbenzoic anhydride (13%), is readily obtained from acid chloride (**7**) and superoxide in benzene–18-crown-6 at room temperature. It follows that the course of reaction of acid derivatives with superoxide depends upon the rate of reaction (4). If this is fast then acyl peroxide is formed which may react further if sufficient superoxide is present to give carboxylic acid. With alkyl esters, at least, it is slow and reductive hydrolysis prevails (after work-up) to give carboxylate anion [Equation (7)].

The reactivity of acid anhydrides towards nucleophiles is intermediate between those of esters and acid chlorides and so it was of interest to examine the course of the reaction of *o*-

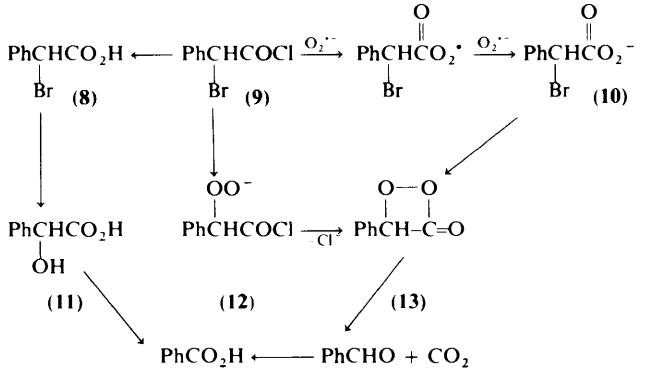
Table. Yields (%) of products from *o*-Phenylbenzoic acid derivatives with superoxide[a]

Substrate	KO_2 (mol equiv.)	Products: Acid (3)	Peroxide (1)	Benzocoumarin (4)	Anhydride
Acid chloride (7)	1.25	*ca.* 50	33	6	13
Acid chloride (7)	5	*ca.* 70	20	1	10
Ethyl ester	1.1	52			
Ethyl ester	2.2	88			
Ethyl ester[b]	2.2	91			
Ethyl ester	3.3	100			
Peroxide (1)	2.2	52		44	
Peroxide (1)	1.0	*ca.* 50	26	27	
Anhydride	2.2	81		16	
Anhydride	1.1	50	9	4	13
Acid chloride[c]	1.0	35	3	2	4
Peroxy acid[d]	2.0	95[e]			

[a] Product yields evaluated by separation and isolation; peroxides also estimated by iodometric titration. [b] Heated under reflux in benzene for 2 h; others stirred at room temperature for 24 h. [c] Reaction with potassium ozonate. [d] *m*-Chloroperbenzoic acid. [e] *m*-Chlorobenzoic acid.

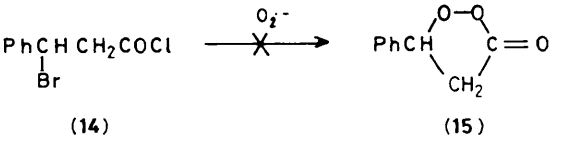
phenylbenzoic anhydride with superoxide. Using a mole ratio of anhydride (1 mol equiv.) to superoxide (2.2 mol equiv.) under previously described conditions the acid (**3**) (81%) and benzocoumarin (**4**) (16%) were obtained. Acyl peroxide (**1**) was detected (t.l.c.) as an intermediate in this reaction and the yield of benzocoumarin (**4**) is a measure (25% corresponds to complete reaction) of the extent to which reaction proceeds *via* the acyl peroxide (**1**) (Table).

Reaction of Superoxide with 2-Bromophenylacetyl Chloride (**9**).—The above acid chloride also reacts anomalously with superoxide. Thus when (**9**) was treated with superoxide (2.2 mol equiv.) at room temperature in benzene–18-crown-6 no acyl peroxide was formed. Instead, the main products were benzaldehyde (7%) and benzoic acid (36%) accompanied by small amounts of mandelic acid (**11**) and 2-bromophenylacetic acid (**8**). Higher yields of benzoic acid (65%) and benzaldehyde (17%) were obtained when the mole ratio of superoxide to acid chloride was increased to 4:1. Superoxide would be expected to react at the carbonyl group of (**9**) to give acyl peroxycarboxylate (**10**) in the usual way. However, an alternative to reaction (4) must be followed at this stage. By analogy with the mechanism



proposed[7] for cleavage of 1,2-diketones to carboxylic acids a likely route is that shown, *i.e.* (**10**) ⟶ (**13**) ⟶ benzaldehyde ⟶ benzoic acid. Even if initial reaction occurred at the benzylic carbon the sequence (**9**) ⟶ (**12**) ⟶ (**13**) would lead to the same products. San Filippo and his co-workers[11] have shown previously that 2-bromophenylacetic acid (**8**) and mandelic acid (**11**) are converted into benzoic acid in high yield by reaction with an excess (4 mol equiv.) of superoxide but did not report benzaldehyde formation. Our conditions are milder than theirs and have allowed the intermediate aldehyde to accumulate rather than be completely converted into acid.[5,7] However, this may not be the only route to benzoic acid.

The intramolecular displacement of halide (**10**) ⟶ (**13**) appears to proceed relatively easily compared with that of the acid halide (**14**). Reaction of (**14**) with superoxide at room temperature gave a wide variety of products, all in low yield of which the cyclic peroxide (**15**) was not one. If this is formed it



(**14**) (**15**)

must decompose rapidly during reaction. Cinnamic acid and cinnamoyl chloride were detected (2—4%) but no styrene or other product which could be easily derived from the acyl peroxide corresponding to (**14**) or the cyclic peroxide (**15**) was identified. This result contrasts with the formation of a five-membered cyclic peroxide by reaction of a 1,3-dimesylate with superoxide.[12]

Experimental

I.r. spectra were measured as Nujol mulls or films (liquids) and n.m.r. spectra were measured for solutions in deuteriochloroform unless stated otherwise. Merck silica gel GF_{254} or HF_{254} was used for chromatographic separations. G.c. measurements were made using a Perkin-Elmer Model 8320 and an Alltech Durabond Column DB1701-30N.

Reactions of Methyl o-*Phenylbenzoate, Peroxide and* o-*Phenylbenzoic Anhydride with Potassium Superoxide: General Procedure.*—A solution of 18-crown-6 (0.11 mmol) in benzene (20 ml) was heated under reflux for 3 h, using a Dean Stark separator to remove water. The solution was evaporated and dry benzene (10 ml) was added to the residue. The substrate (0.05 mmol) and commercial potassium superoxide (0.11 mmol) (previously crushed in a dry box) were then added to the benzene–crown ether solution and the mixture was either stirred at room temperature for 24 h or heated under reflux for 2—3 h. This was followed by addition of water and extraction of the non-acidic products with ether. The aqueous alkaline solution

was made acidic and the acidic products were obtained by extraction of the aqueous acidic solution with ether. The non-acidic products were identified after chromatographic separation and yields obtained by (*a*) weighing separated components; (*b*) iodometric titration (peroxides). Yields of acidic products were obtained by weighing separated (t.l.c.) components (see Table).

Decomposition of o-*Phenylbenzoyl Peroxide.*—*o*-Phenylbenzoyl peroxide (0.11 g) in benzene (6 ml) was heated under reflux for 3.5 h and then diluted with benzene (15 ml). The benzene solution was extracted with saturated aqueous sodium hydrogen carbonate and dried ($MgSO_4$). Evaporation of solvent followed by chromatographic separation of the residue (t.l.c.) using benzene as eluant gave (*a*) benzocoumarin (0.034 g, 34%), (*b*) a mixture of biphenyl and *o*-phenylbiphenyl (0.006 g, 6%) M^+, 154 and 230, respectively. Acidification of the aqueous hydrogen carbonate gave *o*-phenylbenzoic acid (0.018 g, 16%). All products were identical (i.r., t.l.c.) with authentic samples.

Reaction of o-*Phenylbenzoyl Chloride with Potassium Ozonate.*—Potassium superoxide (0.22 g, 3.1 mmol) was converted into potassium ozonate by ozonation in dry Freon-12 as previously described[8] and stabilised by addition of silica gel (10 g).

A solution of *o*-phenylbenzoyl chloride [prepared from the acid (0.6 g, 3.03 mmol) and thionyl chloride (1.2 ml)] and 18-crown-6 (0.08 g) in benzene (25 ml) was added to the ozonate-silica gel and the mixture was stirred for 5.5 h by which time the red colour of the ozonate had faded. The silica gel was collected and the filtrate was shaken with water and the two phases separated. Acidification of the aqueous phase gave *o*-phenylbenzoic acid (0.212 g, 35%). The organic phase was dried and an aliquot was used for peroxide estimation. The bulk of the solution was evaporated and the residue (0.096 g) was chromatographed using benzene as eluant to give (*a*) benzocoumarin (0.009 g, 2%), (*b*) *o*-phenylbenzoic anhydride (0.020 g, 4%), and *o*-phenylbenzoyl peroxide (0.007 g, 2%) (3% by iodometric titration).

Preparation of 2-*Bromophenylacetyl Chloride.*—This was prepared by bromination of phenylacetyl chloride in carbon tetrachloride under reflux.[13] It had b.p. 76—84 °C/0.01 mmHg; $\nu_{max.}$ 1 800 cm^{-1}; δ 5.7 (1 H, s, CHBr) and 7.3—7.6 (5 H, m, ArH); *m/z* 236, 234, 232 (*M*) (1%), 199, 197 (*M* − Cl) (8), 171, and 169 (*M* − Cl − CO) (100). The small peak at δ 5.63 was due to the presence of the corresponding acyl bromide but the fraction was used without further purification.

Preparation of 3-*Bromo*-3-*phenylpropanoyl Chloride.* This was prepared from 3-bromo-3-phenylpropanoic acid[14] by reaction with thionyl chloride.[15] It had b.p. 80—81 °C/0.1 mmHg, $\nu_{max.}$ 1 790 cm^{-1}; δ 3.8 (2 H, m, CH_2), 5.45 (1 H, m, CHBr), and 7.3—7.6 (5 H, m, ArH); *m/z* 184, 182 (1%) (*M* − HCl − CO), 171, 169 (1) (*M* − CH_2COCl), 13 (10) (*M* − HCl − Br), and 103 (10) (*M* − HCl − Br − CO).

Reaction with Potassium Superoxide.—(a) 2-*Bromophenylacetyl chloride.* A mixture of the acid chloride (0.5 g, 2.1 mmol), potassium superoxide (0.339 g, 4.78 mmol) on silica gel (5 g), and 18-crown-6 (0.128 g, 0.38 mmol) in dry benzene (20 ml) was stirred for 6 h at room temperature. Water (10 ml) was then added, the silica gel was collected and the aqueous and benzene layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were dried and evaporated. The residue (0.075 g) contained benzaldehyde (0.015 g, 7%) (g. c. analysis).

The aqueous alkaline layer was acidified and the acidic solution was extracted with ether. The ether extracts were dried and evaporated to give a residue (0.148 g) g. c. chromatographic analysis of which showed the presence of benzoic acid (0.072 g, 36%), mandelic acid (0.021 g, 6%), and 2-bromophenylacetic acid (0.015 g, 3%).

Repetition of the above experiment using bromophenylacetic acid (0.25 g, 1.07 mmol), superoxide (0.35 g. 4.93 mmol) on silica gel, and 18-crown-6 (0.13 g, 0.492 mmol) gave benzaldehyde (0.019 g, 17%), benzoic acid (0.083 g, 66%), mandelic acid (0.014 g, 8%), and 2-bromophenylacetic acid (0.009 g, 4%).

(b) 3-*Bromo*-3-*phenylpropanoyl Chloride.* Reaction of the acid chloride (0.48, 1.95 mmol), superoxide (0.13 g, 4.3 mmol) on silica gel (5 g), and 18-crown-6 (0.12 g, 0.44 mmol) in benzene (20 ml) for 2 h at room temperature gave 3-bromo-3-phenylpropanoic acid (0.071 g, 22%), cinnamic acid (0.014 g, 6%), and traces of cinnamoyl chloride and starting material.

Acknowledgements

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