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AROMATIC HYDROXYLATION OF BENZYLAMIDES BY POTASSIUM SUPEROXIDE

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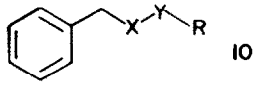
Abstract—N-benzylamides react with potassium superoxide in benzene in presence of 18-crown-6 ether to give *ortho* and *para* hydroxylated products. A mechanism is proposed for this reaction, involving the nucleophilic attack of superoxide anion to amide carbonyl and hydrogen abstraction from benzyle methylene by the substrate-superoxide adduct.

Superoxide anion is a wisespread species in biochemical systems, whose presence and behaviour have been largely detected and clarified by many groups of research.[1] There is growing interest in the reactivity of this species with simple molecules, these studies can be useful models for understanding the interactions between oxygen metabolites and more complex biochemical systems. One of the aims of such research is to explain the mechanism by which oxygen, or its metabolites, are toxic to aerobic organisms. The enzymes catalases, peroxidases, and superoxide dismutases may protect these organisms from oxygen metabolites. Superoxide is often produced by electron transfer between molecular oxygen and a radical intermediate formed during biochemical processes such as some peroxidase catalysed oxidations[2] and some xanthine oxidase catalysed reactions.[3]

We have shown that tertiary aromatic amines generate superoxide anions when they undergo horseradish peroxidase-catalysed oxidative dealkylation with hydrogen peroxide.[4] The investigation of the reactivity of superoxide anion with nitrogen containing compounds is interesting, and one of the first reactions is performed with simple amides. It was known that potassium superoxide reacts in benzene in the presence of 18-crown-6 ether with carboxylic esters to yield the corresponding alcohol and carboxylic acid.[5] A mechanism had been proposed whereby hydrolysis is accounted for by nucleophilic attack of superoxide on carbonyl. Although with carboxylic esters yields are generally good, superoxide anion was reported not to hydrolyse nitriles and amides.[5] In our hands, N-methyl-acetanilide gave with superoxide under conditions in which esters are hydrolysed, the hydrolysed product, acetanilide, and aniline, deriving from N-demethylation, in very low yields. Demethylation did not occur when N-methyl-aniline was treated under similiar conditions with potassium superoxide. Since N-demethylation of tertiary amines is suggested to be correlated with the acidity of the H atom attached to the carbon α to nitrogen,[6] N-benzoylbenzylamine (**1**) was chosen to give better N-dealkylation yields. In this case no N-dealkylation was observed. The reaction mixture contained the *o*- and *p*-hydroxylated compounds (**2–3**):

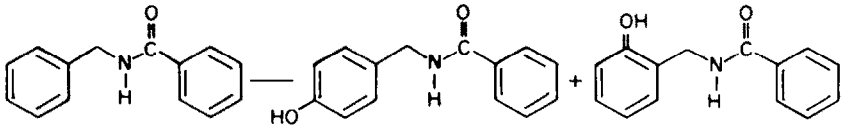
Thus a set of compounds was tested in order to obtain some mechanistic information concerning this new reaction. Results are collected in Tables 1 and 2. In control experiments (**1**) and (**4–7**) were treated with sodium peroxide in presence of 18-crown-6 ether. No reaction occurred. Thus the intervention of peroxides deriving from moisture-promoted dismutation of superoxide could be ruled out.

From the data collected in Tables 1 and 2 two main reactions can be recognised. The first occurs with the five tested acylamines (**1**) and (**4–7**). In these cases hydroxylation of the aromatic ring is always accompanied by hydrolysis of the starting substrate to yield carboxylic acid and benzylamine. Benzylamine could not be isolated from the mixture because it reacts further with potassium superoxide to yield a complex mixture of products (which however did not contain any hydroxylated product). The reaction of hydrocinnamamide (**8**) and hydrocinnamanilide (**9**) with $O_2^{\cdot-}$ gave neither hydroxylation nor hydrolysis. This suggests that these are two consecutive processes. Thus hydrolysis could occur by OH^- anions deriving from the reduction of superoxide (e.g. H_2O_2). Treatment of all these amides with KOH in benzene in presence of 18-crown-6 ether under the conditions used for superoxide reactions gave quantitative hydrolysis. The presence of a carboxybenzylamido group (**10**, X = NH, Y = CO) does not seem to be a necessary condition for the hydroxylation of the aromatic nucleus of benzylamine. Benzylphenylurea (**11**) still contains that group but does not react at all.



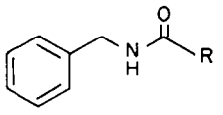
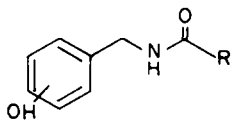
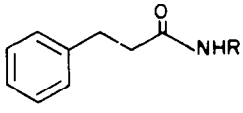
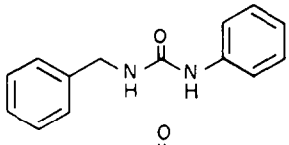
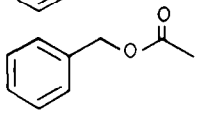
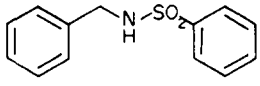
10

Furthermore substitution of N by O as the benzyl-acetate (**10**, X = O, Y = CO) (**12**) produces hydrolysis as usual[4] and no hydroxylation at the nucleus was noticed. Substitution of the CO with a sulphone group (**10**, X = NH, Y = SO_2) also results in suppressing reactivity, as shown by the inertness of N-benzyl-*p*-toluenesulphonamide (**13**). The last two examples rule out the possibility that the acidity of the hydrogen attached to the carbon α to nitrogen is responsible for the hydroxy-



1 2 3

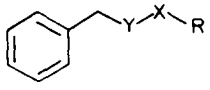
Table 1.

Substrate	Products (% yield)
	
1: R = Ph	R = Ph, 4-OH (58) R = Ph, 2-OH (4) starting product (28) benzoic acid (9)
4: R = 4-methylphenyl	R = 4-methylphenyl, 4-OH (38) R = 4-methylphenyl, 2-OH (2) st.p. (44) p-toluic acid (6)
5: R = 4-bromophenyl	R = 4-bromophenyl, 4-OH (61) R = 4-bromophenyl, 2-OH (4) st.p. (18) 4-bromobenzoic acid (17)
6: R = 4-nitrophenyl	R = 4-nitrophenyl, 4-OH (67) R = 4-nitrophenyl, 2-OH (4) st.p. (9) 4-nitrobenzoic acid (19)
7: R = Me	R = Me, 4-OH (12) R = Me, 2-OH (2) st.p. (67)
	
8: R = H	starting product
9: R = Ph	starting product
11 	starting product
12 	benzyl alcohol (68)[a] st.p. (27)[a]
13 	starting product

[a] after one day

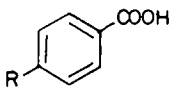
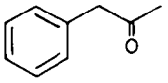
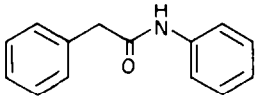
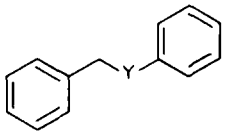
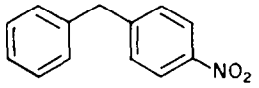
lation. If this is the case, the reaction should occur both with benzylamides and benzylureas, and even more promptly with benzenesulponamides, as sulphone is a more efficient electron withdrawing group.

A second group of results was obtained with compounds having a different arrangement (**14**):

 **14**

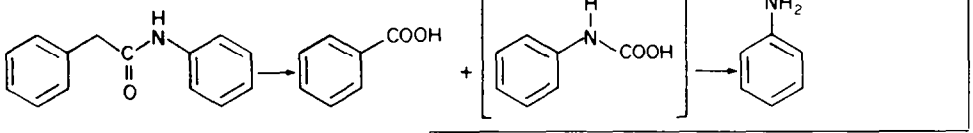
This reactivity occurs in compounds having Y = CO: phenylacetone (**15**) and phenylacetanilide (**16**). The for-

Table 2.

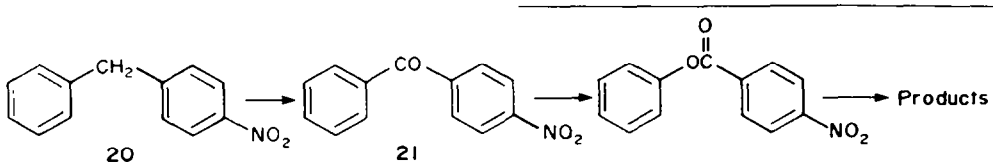
Substrate		Products (% yield)
		
(15)		R = H (95)
(16)		R = H (96) aniline (85)
		
(17)	Y = SO_2	R = H (42)
(18)	Y = SO	benzenesulphonic acid[a]
(19)	Y = S	starting product st.p.
(20)		R = NO_2 (72) phenol (22)

[a] essayed only qualitatively

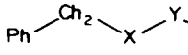
mer is cleaved by superoxide anion to benzoic and acetic acid as previously reported.[7] The latter, which is an isomer of N-benzoylbenzylamine derived by inversion of the amino and carbonyl groups, gives benzoic acid and aniline. This could be caused by decarboxylation of the intermediate carbamic acid:



The same reaction pattern is found when CO is replaced by sulphone (**14**, Y = SO_2) but not sulphide or sulphoxide (Y = S or SO). Benzylphenylsulphone (**17**) is cleaved along the C–S bond. No reaction occurred with the corresponding sulphide (**18**) and sulphoxide (**19**). The same reaction occurs with 4-nitrodiphenylmethane (**20**) which is oxidised by superoxide anion to give 4-nitrobenzoic acid, phenol, and tars probably due to further oxidation. The reaction may take place through formation of 4-nitrobenzophenone (which however was not detected in the mixture) and successive Bayer–Villiger-like oxidation with HOO^- derived from superoxide and hydrolysis:[8]



Two main pathways are apparent from the data shown in Tables 1 and 2. Some substrates undergo aromatic *ortho* and *para* hydroxylation (path *a*) and some other compounds are oxidised to the benzyl carbon with subsequent Bayer–Villiger-like reaction (path *b*). These two reactions seem to be correlated with different structural requirements. In a molecule with general formula **23**



(23)

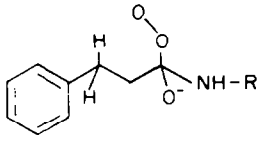
the hydroxylation *ortho* and *para* in the phenyl ring occurs only if the group Y is a CO and the group X is NH. Moreover, the inertness of hydrocinnamamides suggests that hydrolysis to benzoic acid observed with N-benzylamides (**1**) and (**4–7**) is subsequent to the O_2^- reaction and could be due to OH^- anions derived from O_2^- consumption in the primary process. The nuclear hydroxylation seems to be correlated with the inductive electron withdrawing effect exerted by the carboxyamido

group on the adjacent benzyl carbon, as occurs in most benzyl carbon oxidations.[9] Reinforcement of this effect by using substrates having the arrangement $-CH_2-NH-CO-NH-$ or $-CH_2-NH-SO_2-$ did not give positive results. This fact suggests that this reaction was better correlated with the possibility of a nucleophilic attack at the CO group X effected by superoxide. Moreover the yield of hydroxylation of compounds **1** and **4–6** follow the electron withdrawing power of the aromatic substituent on the acid moiety of the molecule. This is supported by the fact that yields after a fixed time (one week) are not compromised by any loss of material (Table 1), and may therefore represent an indirect measure of reactivity. This observation also is consistent with the hypothesis of a nucleophilic attack at the amide CO. These remarks could explain why the urea (**11**) and the sulphonamide (**13**) do not react. The alkaline hydrolysis of ureas is in fact much slower than that of amides,[10] and sulphonamides are not satisfactorily hydrolysed basis conditions.[11] When this structural requirement is not met in the substrate, then benzylic oxidation occurs (path *b*).

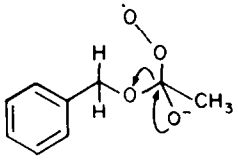
In this case the electron withdrawing effect of the groups attached to the benzyl carbon is important. In fact benzylphenylsulphone (**17**) is attacked but the sulphoxide (**19**) and sulphide (**18**) are not. The interpretation of this behaviour of superoxide may be valid since this reagent is both a powerful nucleophile and a powerful hydrogen abstractor.[12] Thus, the hydroxylation may be correlated with the nucleophilic character, and the benzyl fission to its hydrogen abstracting properties. Path *a* could occur through the mechanism depicted in Scheme 1.

(1) The nucleophilic attack of $O_2^{\cdot-}$ at the CO group of the amide yields a tetrahedral intermediate, such as proposed in the initial step of ester hydrolysis by potassium superoxide.[5]

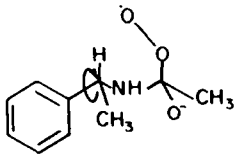
(2) The oxygen centered radical abstracts an H atom attached to the C α to nitrogen to yield a carbon radical. This step is favoured by a 6-membered cyclic transition state. Also hydrocinnamamate could give a 6-membered cyclic transition state. The fact that these compounds do not undergo hydroxylation suggests that the inductive



effect of the carboxyamido group is necessary to weaken the benzyl C–H bond. In the case of benzylacetate a higher rate for the elimination of benzyl alcohol prevents any hydrogen abstraction from the benzyl position.

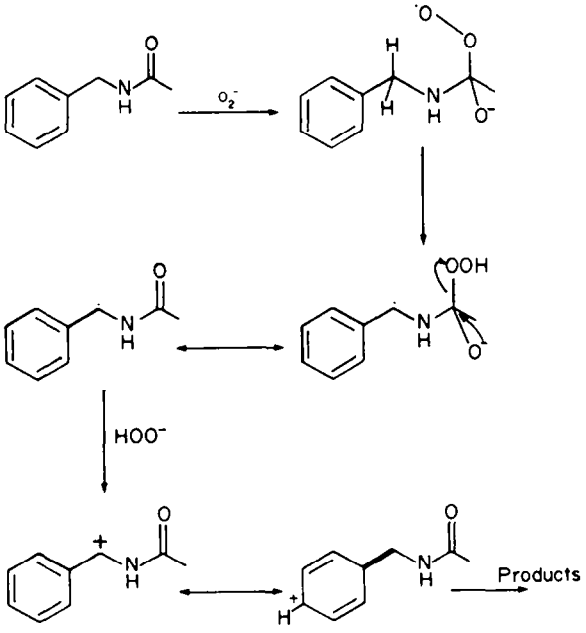


α-Phenylethylacetamide was reported not to react under our conditions.[4] This is in accord with the hypothesis of a cyclic transition state: both for statistical reasons (only one benzyl hydrogen is available) and for steric factors, in this case the abstraction of hydrogen could be much slower.



(3) A peroxide anion is eliminated from the rearranged tetrahedral intermediate.

(4) The resulting carbon radical is oxidised by a peroxide species. Steps 3 and 4 could be also concerted. The oxidation yields OH anions which can react both in the following step and in the hydrolysis (in presence of 18-crown-6 ether) of the starting amide.



Scheme 1.

(5) The cation binds an OH ion. Successive rearomatisation of the adduct yields the hydroxylated product.

The distribution of *ortho* and *para* hydroxylated isomers seems to rule out any concerted migration of an O atom within any superoxide-substrate adduct, and is similar to other hydroxylations due to the OH^- attack on dihydroaromatic cations.[13] The mechanism proposed is different from that invoked in the photooxidation[14] and the peroxydisulphate oxidation of amides.[15] In these cases the abstraction of an α H atom is performed by a radical initiator or the sulphate radical anion $SO_4^{\cdot-}$ respectively. The resulting carbon radical reacts with molecular oxygen to give a hydroperoxyl radical; the subsequent hydroperoxide can yield either imides or dealkylated amides.

$$R\text{-}CH_2\text{-}NHCOR' \rightarrow R\text{-}\underset{\displaystyle O\text{-}O^{\cdot}}{\overset{\displaystyle |}{CH}}\text{-}NHCOR' \rightarrow R\text{-}\underset{\displaystyle O\text{-}O^{\cdot}}{\overset{\displaystyle |}{CH}}\text{-}NHCOR \rightarrow \text{products}$$

In the case of superoxide oxidation two features seem to determine a different reactivity: the nucleophilic character of the reagent, which can interact directly with CO, and the presence as an intermediate of a strong oxidant such as H_2O_2 (or $HOO^{\cdot}$) derived from superoxide consumption, which can oxidise the carbon radical intermediate. In conclusion, this reaction could have a heuristic value in the study of some aspects of biochemical behaviour of carboxyamido and peptidic groups in presence of a widespread biochemical species such as superoxide anion.

EXPERIMENTAL

Products not commercially available were prepared by standard methods. Potassium superoxide was purchased from Pierce Inorganics B.V. Rotterdam. Mass spectra were obtained with a LKB (70 eV) instrument.

General procedure for superoxide reaction. Substrate (1 mmole) was dissolved in dry benzene (30 ml). Finely crushed potassium superoxide was added in excess (10 mmole). The suspension was stirred at room temp for a week, and during this period 3 portions of 18-crown-6 ether (20 mg) were added. 50 ml water was added to destroy the unreacted superoxide. The phases were separated and the aqueous layer was extracted with benzene (20 ml × 2). The aqueous layer was then acidified with conc HCl and extracted with benzene (20 ml × 2). The organic phases from acidic and basic extraction were dried and evaporated separately under reduced pressure. If necessary the residues were fractioned on a silica gel column. In the case of benzylphenylsulphone, after extraction the aqueous layer was evaporated under reduced pressure; benzenesulphonic acid in the residue was characterised as its benzylisothiouronium salt.

Alkaline hydrolysis of compounds **1** and **4–7** was performed by the same modalities substituting potassium superoxide with crushed pellets of potassium superoxide. Hydroxylation products were identified by comparison with samples obtained from nitration of the starting amide, reduction with tin and HCl, diazotisation and decomposition of the diaz compound in water, and by mass spectroscopy: N - benzoyl - 4 - hydroxybenzylamine, *m/e* 227, 211, 122; N - (4' - methylbenzoyl) - 4 - hydroxybenzylamine 241, 225, 135; N - (4' - bromobenzoyl) - 4 - hydroxybenzylamine 306, 290, 201; N - (4'-nitrobenzoyl) - 4 - hydroxybenzylamine 272, 256, 167.

REFERENCES

[1]A. M. Michelson, J. M. McCord, and I. Fridovich, *Superoxide and Superoxide Dismutase.* Academic Press, New York (1977).
[2]O. Hayaishi, *Molecular Mechanism of Oxygen Activation.* Academic Press, New York (1974).
[3]I. Fridovich and P. Handler, *J. Biol. Chem.* **237**, 916 (1962).
[4]G. Galliani and B. Rindone, *J. Chem. Soc.* Perkin II 1 (1980).
[5]J. San Filippo, L. G. Romano, C. I. Chern and J. S. Valentine, *J. Org. Chem.* **41**, 586 (1976).
[6]J. R. Lindsay-Smith and L. A. Mead, *J. Chem. Soc.* Perkin II 206 (1973).
[7]M. Lissel and E. V. Dehmlow, *Tetrahedron Lett.* 3689 (1978).
[8]Although phase transfer catalysis for Bayer-Villiger reactions is known, 18-crown-6 ether and sodium peroxide do not react in benzene with compound **21**.
[9]R. A. Stairs and J. W. Burns, *Can. J. Chem.* **39**, 960 (1961).
[10]A. I. Vogel, *A Textbook of Practical Organic Chemistry*, p. 1076. Longmans, London (1962).
[11]E. Dyer and G. W. Bartels Jr., *J. Am. Chem. Soc.* **76**, 591 (1954); J. H. Saunders Jr., S. Steingiser, A. S. Morecroft, P. G. Gemeinhardt, and E. E. Hardy, *Ind. Eng. Chem. Data Series*, **3**, 153 (1958).
[12]D. T. Sawyer and M. J. Gibian, *Tetrahedron* **35**, 1471 (1979).
[13]M. B. Dearden, C. R. E. Jefcoate and J. R. Lindsay-Smith, *Adv. Chem. Ser.* **77**, 260 (1968).
[14]W. H. Sharkey and W. E. Mochel, *J. Am. Chem. Soc.* **81**, 3000 (1959).
[15]H. L. Needles and R. E. Whitfield, *J. Org. Chem.* **29**, 3632 (1964).