Copper(II) mediated Aromatic Hydroxylation by Trimethylamine *N*-Oxide

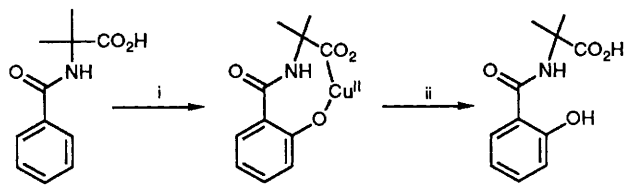
Olivia Reinaud,* Patrice Capdevielle, and Michel Maumy

Laboratoire de Recherches Organiques de l'ESPCI, associé au CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Quantitative orthohydroxylation of *N*-benzoyl-2-methylalanine (**1**) occurs through its copper(II) salt oxidation by trimethylamine *N*-oxide; transitory formation of a Cu^{III} species is proposed.

Hydroxylation of aromatic compounds[1] by H_2O_2 either through electrophilic (H_2O_2/BF_3[2] or HF[3]) or free radical processes (Fenton's[4] or Udenfriend's[5] reagent) is usually not selective (partly because the introduction of an OH group activates the ring to further oxidation), except in the case of intramolecular processes leading to stable chelates ('oxidative coppering').[6] On the other hand, pyrolysis of copper(II) benzoates into salicylates,[7] which seems to occur *via* nucleophilic attack, is limited by a poor conversion ratio and drastic experimental conditions. In recent years, some examples of oxidation of copper ligands have indicated that the association of copper(I) ions with molecular oxygen[8] or iodosylbenzene[9] or copper(II) ions with H_2O_2[10] can promote highly selective aromatic hydroxylation. In earlier papers,[11] we have shown how copper(III) species are responsible for various selective oxidations through their intramolecular evolution. We present here some preliminary results dealing with the interaction between copper salts and trimethylamine *N*-oxide (TMAO) as a new source of copper(III) entities and its application to selective and quantitative hydroxylation of aromatic derivatives.

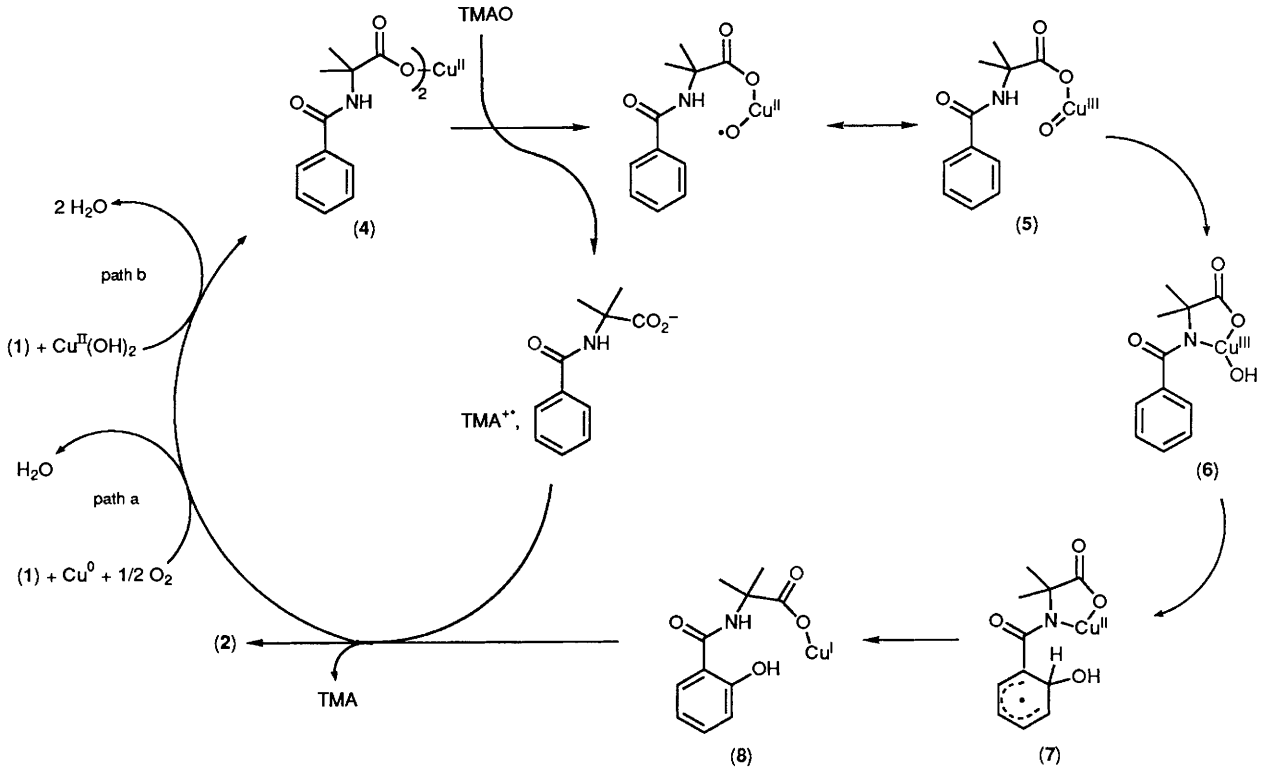
N-Benzoyl-2-methylalanine (**1**),[12] when heated in dry acetonitrile under an oxygen atmosphere with metallic copper powder (1 equiv.) and TMAO (5 equiv.), is quantitatively converted into the blue copper(II) salt (**2**) of *N*-(2-hydroxybenzoyl)-2-methylalanine (**3**) which has been identified† after



(1) (2) (3)

Scheme 1. Phenyl orthohydroxylation of (**1**) by the Cu^0/O_2/trimethylamine *N*-oxide system. *Reagents and conditions*: i, Cu^0/O_2/TMAO, MeCN, 6 h, 75 °C; ii, HCl (0.5 M); ~100%.

† Spectral and analytical data are in agreement with the proposed structure as confirmed by comparison with an authentic sample (synthesized by condensing acetylsalicyloyl chloride with 2-methylalanine sodium salt).



Scheme 2. Proposed mechanism for (**1**) orthohydroxylation through the monoelectronic oxidation of its copper(II) salt (**4**) by trimethylamine *N*-oxide.

acid hydrolysis (Scheme 1). This orthoselective hydroxylation proceeds under mild conditions and constitutes the key step of a new route for transformation of benzoic acids into salicylic acids.

A series of control experiments according to the standard procedure demonstrates that each reactant is necessary for efficient operation: without Cu^0 or O_2, no reaction can be observed; without TMAO, (**1**) is converted into its green copper(II) salt (**4**) which, after acid hydrolysis, releases the starting compound (**1**). On the other hand, if TMAO is added to (**4**), hydroxylation proceeds as in the standard procedure together with the renewal of copper corrosion. These facts demonstrate that (**4**) does not evolve spontaneously and is inert toward O_2 but its association with TMAO produces the active species responsible for hydroxylation. This has been confirmed by another experiment: in similar conditions but under an inert atmosphere (N_2), the $Cu^{II}(OH)_2$/TMAO couple is also able to promote the hydroxylation of (**1**) into (**2**).‡

Our results can be rationalized as follows (Scheme 2): the copper(II) salt (**4**), produced either by copper corrosion with O_2 (path a) or reaction of $Cu(OH)_2$ with (**1**) (path b), is oxidized by TMAO. The intramolecular evolution of the resulting copper(III) species (**5**) is highly favoured by the proximity of the NH group, ionization of which allows the formation of the hydroxocopper(III) entity (**6**) according to the well known ability of amidic bonds to particularly stabilize Cu^{III} complexes.[13] This hypothesis is confirmed by the fact that the *N*-methyl derivative of (**1**) is not hydroxylated under such conditions.

When the starting benzamide (**1**) is 3′-fluoro-substituted, the regioselectivity of the hydroxylation gives an *ortho*/*para* ratio (relative to fluorine) of 0.41,§ which is quite in agreement with an HO· type attack and not an HO^+ type (Fenton's hydroxylation[14] and nitration[15] of fluorobenzene give, respectively, *o*/*p* 0.41 and 0.08). Therefore, the cleavage of the Cu^{III}–OH bond of (**6**) must be homolytic rather than heterolytic and the transfer of HO· is followed by the rapid intramolecular redox reaction (**7**) → (**8**). The copper(I) salt (**8**) is finally reoxidized by the aminium radical $TMA^{\cdot+}$ into (**2**) with concomitant liberation of trimethylamine (TMA) which has been trapped as its hydrochloride from gaseous effluents.¶

‡ This second method (Scheme 2, path b) is as efficient at the beginning of the reaction [(**3**) is the only product detected by HPLC] but very slow to reach completion. This can be attributed to the competition for complexation of (**4**) between TMAO and H_2O, the latter being here produced twice as much as in the corrosion system (path a, see Scheme 2). A similar effect is observed when H_2O is added to the reactive medium or when TMAO·$2H_2O$ is used (formation of a brown insoluble precipitate).

§ Determined by ^1H NMR spectroscopy (250 MHz, [$^2H_6$]DMSO) of the crude product obtained after acid hydrolysis (quantitative yield). *Selected data* for *N*-(3-fluoro-2-hydroxybenzoyl)-2-methylalanine: 1.49 (s, 6H, 2 Me), 6.88 (ddd, J_F 4.9, J_{H4} 8.1, and J_{H6} 8.0 Hz; H_5 arom.), 7.38 (ddd, J_{H5} 8.1, J_{H6} 1.0, and J_F 10.8 Hz; H_4 arom.), 7.80 (dd, J_{H4} 1.0 and J_{H5} 8.0 Hz; H_6 arom.), 8.90 (s. 1H, NH), 11.92 and 12.53 (2 br. s, 2H, 2 OH). *N*-(5-fluoro-2-hydroxybenzoyl)-2-methylalanine: 1.49 (s, 6H, 2 Me), 6.93 (dd, J_{H4} 9.0 and J_F 4.7 Hz; H_3 arom.), 7.26 (ddd, J_{H3} 9.0, J_F 8.5, and J_{H6} 3.1 Hz; H_4 arom.), 7.77 (dd, J_{H4} 3.1 and J_F 9.9 Hz; H_6 arom.), 8.87 (s, 1H, NH), 11.92 and 12.53 (2 br. s, 2H, 2 OH).

¶ Characterized by ^1H NMR spectroscopy and compared with an authentic sample.

The great stability of (**2**) in the experimental conditions accounts for the high yield obtained.

Together with the preceding Communication,[16] this is the first example of a copper(II) salt oxidation by an amine *N*-oxide‖ and it seems to proceed through a one-electron transfer, as has been observed in some cases with iron(III) porphyrin imidazole complexes.[17] This original reaction promises a number of developments, as much for elaboration of new chemical oxidizing preparative systems as for the studies of copper mono-oxygenases (phenylalanine hydroxylase[19] in particular) and their models.

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‖ To our knowledge, the only previous report of oxidative activity of the Cu/amine *N*-oxide couple describes an intramolecular diphenol oxidative coupling with copper(I) chloride.[18]