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First, Serendipitous and Intriguing Hydrolysis of a Tertiary Nitroalkane

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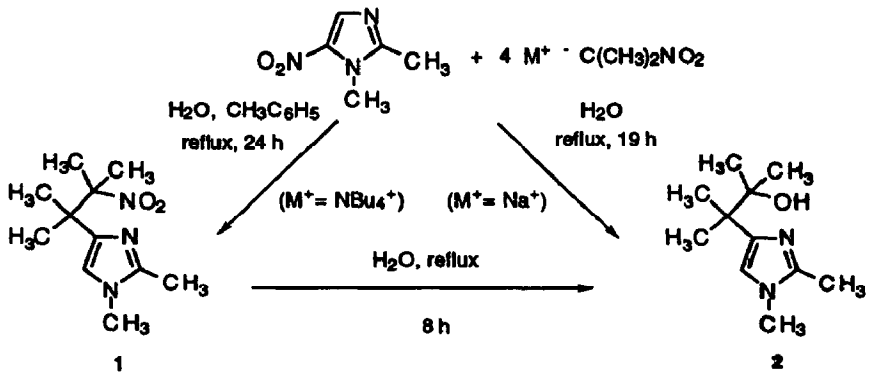
Abstract: *The hydrolysis of 1,2-dimethyl-4-(1,1,2-trimethyl-2-nitropropyl)imidazole which leads to two tertiary alcohols formed respectively by C-NO_2 and C-C bond fission, is the first example of hydrolysis of a tertiary nitroalkane. It might be explained by an intramolecular nucleophilic catalysis favored by a double gem-dimethyl effect and a possible anchimeric assistance by imidazole group.*

As a part of our program directed toward the study of electron transfer reactions to synthesize new biologically active 5-nitroimidazoles,[1] we have shown that 1,2-dimethyl-5-nitroimidazole (dimetridazole) reacts with 2-nitropropane anion to give, via cine-substitution and $S_{RN}1$ substitution, the new 4-highly branched imidazole derivative **1** with the histamine skeleton.[2] If the reaction is carried out in water, we have obtained the serendipitous formation of the corresponding tertiary alcohol **2**, formed by hydrolysis of the tertiary nitro group, which is a useful synthon in the preparation of new 4-substituted-5-nitroimidazole.[3] When the tertiary nitroalkane **1** is heated in water at reflux, it also leads mainly to the tertiary alcohol **2**, whose structure has been confirmed by X-ray spectroscopic data.[4]



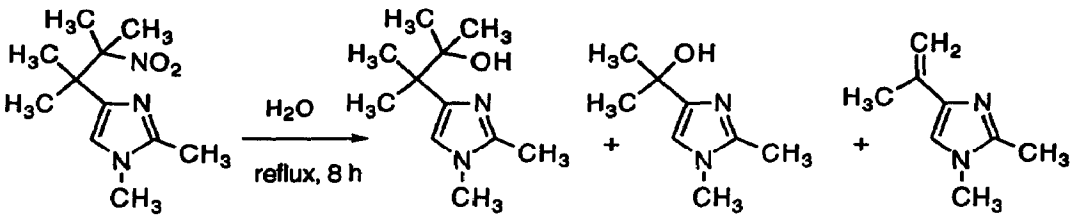
This first example of hydrolysis of a tertiary nitroalkane is amazing because Cundall and Locke[5] have shown

that "*nitroalkanes are not hydrolysed to any measurable extent by the action of water alone*" and further that "*secondary and tertiary nitroalkanes are stable to hydrolysis by hot mineral acids*".

The molecular structure of **1** shows particular features: a tertiary nitro group, two *gem*-dimethyl groups and an imidazole group. *Gem*-dimethyl effect is known to exhibit dramatic rate accelerations of intramolecular reactions. For example, tetramethylsuccinanilic acid undergoes hydrolysis 1,200 times faster than unsubstituted succinanilic acid.[6] The imidazole group is in excellent position to establish a link with the reacting center and to provide anchimeric assistance to the reaction. Many examples of intramolecular catalysis of hydrolysis by an imidazole group have been described and several mechanisms of enzymatic reactions have been formulated around the involvement of the imidazole group of a histidine residue.[7] The imidazole group can act as a catalyst in nucleophilic catalysis, general-base catalysis, general-acid catalysis and general-acid-base catalysis.[8]

On the other hand, the tertiary nitro group is a rather unreactive group because C-NO_2 bond is relatively strong so that reactions involving C-N bond fission are limited to those taking place under extreme conditions *e.g.* thermally and photochemically. Nevertheless different types of reactions involving C-NO_2 bond fission are known: elimination of nitrous acid with systems bearing acid β-hydrogen atoms,[1] thermally- or photochemically-induced rearrangements of C-nitro compounds to C-nitrites,[9] free radical reductions and electron transfer substitutions.[10]

In order to understand the mechanism of this intriguing reaction, we have studied in detail the hydrolysis of 1,2-dimethyl-4-(1,1,2-trimethyl-2-nitropropyl)imidazole **1**, which gives in fact two alcohols, **2**[4] (57% yield) and **3**[11] (38% yield), and the ethylenic derivative **4**[2] (4% yield).



1 **2** **3** **4**

The fact that the reaction is favored by an intramolecular process has been demonstrated by reacting in refluxing water 2,3-dimethyl-2,3-dinitrobutane with an excess of 1,2-dimethylimidazole during 24 h. This tertiary nitro compound, which has a structure similar to **1**, the second nitro group miming in part steric and electronic effects of the imidazole group, is recovered unchanged under these experimental conditions.

The influence of the imidazole group has been shown by different experiments. The analog of **1** bearing a nitro group at position 5 is recovered unchanged after 144 h under these experimental conditions. The nitro group has a dramatic effect on the p*K*a of imidazole[12] (1-methylimidazole: p*K*a = 7.30; 1-methyl-5-nitroimidazole: p*K*a = 2.13) and then the imidazole group is no more an effective catalyst. It is the same for the methyl iodide salt of **1** and the hydrochloride of **1**. The fact that **1** is recovered unchanged in acidic medium also is an indication against a general-acid catalysis of imidazole.

A possible mechanism for the formation of **2** is a nitro-nitrite rearrangement followed by a homolytic fission of the O-N bond and hydrogen transfer or hydrolysis of nitrite. When the reaction is performed in dry toluene at reflux during 24 h, **1** is recovered unchanged. The formation of **2** is not a thermally-induced nitro-

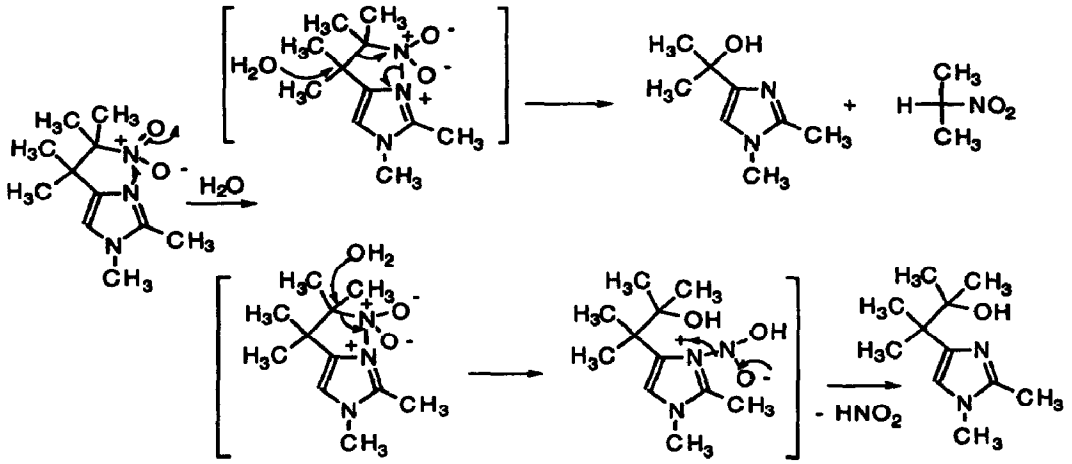
nitrite rearrangement. If **1** is reacted in the dark (cooking foil), the formation of the products is observed showing that the reaction is not photochemically-induced. Finally, we have shown that the oxygen atoms of the alcohols **2** and **3** come from water by the use of 10% $^{18}OH_2$. In that case, mass spectrometry of **2** and **3** shows ^{18}O incorporation whereas recovered **1** does not contain ^{18}O in the nitro group.

Different photo-induced electron transfer reaction from amines to nitro compounds have been proposed.[9] A such intramolecular process with **1** seems very disfavored considering the oxidation potential of the imidazole group of **1** (E_pOx = 1.4 V / SCE) and the reduction potential of the nitro group of **1** (E_pRed = -1.65 V / SCE). When the reaction is performed in the presence of one equivalent of TEMPO, the coupling product which might result of the trapping of the radical formed by an electron transfer is not observed.

An other possible mechanism for the formation of **2** and **3** is hydration of the corresponding ethylenic derivatives with water and an acid catalyst.[13] The mechanism is electrophilic and begins with attack by a proton and a carbocation is formed. In the presence of different alcohols, no change has been observed and when D_2O is used, there is no deuterium incorporation in one of the methyl groups of **2** or **3**. On the other hand in D_2O, there is no significant isotope effect on the rate of the reaction, whereas isotope effect of 2 to 4 are measured in general-base catalysed hydrolysis by imidazole.[14] If the absence of such a deuterium isotope effect does not rule out general-base catalysis, we have observed that addition of 1 to 4 equivalents of hydroxide anion in the reaction has very few effect.

The anchimeric assistance of imidazole group by nucleophilic catalysis might explain the formation of **2** and **3**, if it is accepted that an intermediate can be formed from **1** by attack of the nitro group by imidazole and that water (or hydroxide anion) can react by S_N2 reaction on a tertiary carbon atom as described in the following Scheme.

Scheme.



Examples of S_N2 reactions at tertiary centers are rare, but few cases have been reported[15] with $^-N_3$ and ^-SCN anions. If the reaction of **1** in refluxing water is performed in presence of 4 equivalents of KSCN, the expected products are not observed.

A mechanism, in which hypothetical acetone would be formed from nitronate anion and might lead to **2**, can be rejected by the negative result obtained in conducting this reaction in the presence of an excess of

methylethylketone.

In conclusion, we have shown for the first time that a tertiary nitro group and 2-nitropropan-2-yl group can be substituted by water to give the corresponding tertiary alcohols. If the mechanisms of these intriguing hydrolysis remain unclear and would necessitate other studies out of our reach, an anchimeric assistance of imidazole as known in enzymatic systems can only explain the extraordinarily acceleration of these reactions which are impossible in intermolecular reactions. The extension of these hydrolysis to other imidazole derivatives to examine the scope of these reactions is in progress and will be reported in the near future.

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