

## A novel oxygen-dependent deoxygenation by nitric oxide

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A variety of aldoximes and ketoximes were oxidized to corresponding aldehydes and ketones by nitric oxide in the presence of oxygen. A presumed mechanism was suggested.

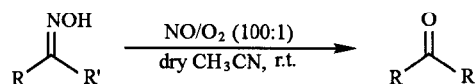
**Keywords** Nitric oxide, oxime, deoxygenation, carbonyl compounds

More and more attention to nitric oxide (NO) has been focused on its biological activities in a variety of biological processes<sup>1</sup> in the past decade. NO is again supposed to have cytotoxic effects when it exists in high concentration.<sup>2</sup> Intensive research has been carried out in the realm of biochemistry and physiology to clarify the mechanism of both the positive and negative actions of NO. Papers concerning the chemical reactivity of NO have been also growing at a rapid rate. Many reactions of NO have been reported in the absence or presence of an inert gas, such as NO with secondary amines,<sup>3</sup> olefins,<sup>4,5</sup>  $\alpha$ -tocopherol,<sup>6</sup> ethyl linoleate,<sup>7</sup> 2'-deoxyguanosine,<sup>8</sup> dihydropyridine, aromatic primary amines,<sup>9</sup> amides,<sup>10</sup> etc.

It was also reported that a potential intercellular nitric oxide carrier formed when *N*<sup>G</sup>-hydroxy-*L*-arginine exposed to nitric oxide in aerobic solutions.<sup>11</sup> The nitric oxide synthase (NOS) converts *N*<sup>G</sup>-hydroxy-*L*-arginine into *L*-citrulline and NO.<sup>10</sup> This led us to investigate the reaction of NO with oxime whose structure is partially similar to *N*<sup>G</sup>-hydroxy-*L*-arginine. Our results indicated that a variety of aldoximes and ketoximes were oxidized to corresponding aldehydes and ketones by NO in the presence of oxygen (Scheme 1). From a synthetic point of view, yields of this approach are not much higher than other deoxygenation methods.<sup>12</sup> However, it is certainly of biochemical significance.

In a representative experiment, 1 mmol of oxime was dissolved in 3 mL of dry CH<sub>3</sub>CN. A gas mixture of NO and oxygen (NO/O<sub>2</sub>  $\approx$  100:1 in vol.) was introduced to the solution for about 15 min. Subsequently, the reaction was quenched by water. Extraction with ether and purification by column chromatography afforded the corresponding ketones or aldehydes, which were identified by <sup>1</sup>H NMR and MS spectra. The conversion of various ketoximes and aldoximes to ketones and aldehydes is listed in Table 1.

### Scheme 1



The solvent effect was also studied by using piperonaloxime as the substrate. The yields in various solvents are shown in Table 2. It indicates that the protic solvents were totally ineffective on the reaction. However, the utilization of aprotic solvents, such as CCl<sub>4</sub>, CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, resulted in the formation of carbonyl compounds.

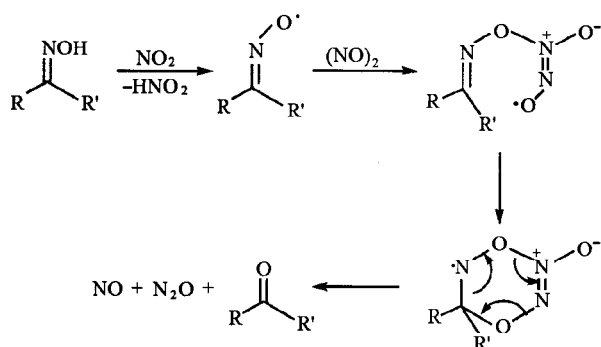
No deoxygenation reactions occurred in the absence of oxygen. This fact implies that the deoxygenation may be resulted from N<sub>2</sub>O<sub>3</sub>.<sup>13</sup> NO rapidly reacts with O<sub>2</sub> to give NO<sub>2</sub> and NO<sub>2</sub> thus formed is converted to N<sub>2</sub>O<sub>3</sub> in the presence of excessive NO. We rule out possibility of a nucleophilic attack on undissociated N<sub>2</sub>O<sub>3</sub>.<sup>13</sup> Both the constituents of N<sub>2</sub>O<sub>3</sub>, NO and NO<sub>2</sub>, may individually be responsible for the reaction.<sup>14</sup> It was also found that

\* Received March 28, 2000; accepted May 15, 2000.

Project supported by the National Natural Science Foundation of China (No. 2967201) and the Natural Science Foundation of Gansu Province.

*ortho*-methoxy benzylaldehyde 2,4-dinitrophenylhydrazone did not react with NO even though in the presence of oxygen. It may be due to the steric hindrance of groups or for reasons of difficulties in leaving 2,4-dinitrophenylhydrazinyl group. A presumed mechanism is suggested in Scheme 2.

Scheme 2



In comparison of the redox potential of the pair  $\text{NO}_2/\text{HNO}_2$  (+ 1.07 V)<sup>15</sup> with that of the pair  $\text{NO}/\text{HNO}$  (+ 0.71 V),<sup>15</sup> we believe  $\text{NO}_2$  abstracts a hydrogen atom from the substrate to form  $\text{HNO}_2$  more effectively than  $\text{NO}$  for  $\text{HNO}$ . As a result, iminoxy radical forms. It was reported that  $\text{N}_2\text{O}_4$  reacted with oximes and hydrazones at  $-40^\circ\text{C}$  in aprotic solvents, such as  $\text{CH}_3\text{CN}$ ,  $\text{THF}$ ,  $\text{CHCl}_3$ , and  $\text{CCl}_4$ , to afford the corresponding ketones.<sup>16</sup> Compared to this approach, conditions herein reported are quite mild and reactions may proceed via a different mechanism.

This work exhibits that ketoximes and aldoximes can be converted to corresponding ketones and aldehydes by NO in the presence of oxygen in aprotic solvents. Although it also offers a simple and effective synthetic approach of deoxygenation, the main point of this work, however, is mainly of its biochemical significance.

**Table 1** Oxidation of oximes to ketones and aldehydes with NO in the presence of oxygen ( $\text{NO}/\text{O}_2 \approx 100:1$ )

Entry	Oxime	Time (min)	Carbonyl compound <sup>a</sup>	Yield (%) <sup>b</sup>
1		8		95
2		8		72
3		15		85
4		15		75
5		15		85
6		15		75
7		15		70

<sup>a</sup> All products were identified by  $^1\text{H}$  NMR spectra and their comparison with authentic samples. <sup>b</sup> Isolated yield.

**Table 2** Solvent effect on the reaction of NO with piperonaloxime in the presence of oxygen (NO/O<sub>2</sub> ≈ 100:1)

Solvent	Time (min)	Yield (%)	Solvent	Time (min)	Yield (%)
CH <sub>3</sub> CN	15	70	CH <sub>3</sub> OH	20	0
CCl <sub>4</sub>	15	65	THF	20	0
CHCl <sub>3</sub>	15	68	Acetone	20	0
CH <sub>2</sub> Cl <sub>2</sub>	15	50	DMSO	20	0
C <sub>6</sub> H <sub>6</sub>	20	0			

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