

Spin trapping of nitric oxide by nitrosoarenes, and new cupferron-like NO donors

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More than 30 years ago, it was shown by A. T. Balaban that nitrosoarenes can act as spin traps for nitric oxide yielding N-aryl-N-nitroso-nitroxides, which were characterized by EPR spectra (1-3). The same nitroxides could also be obtained via two other reactions, namely oxidation of ammonium N-nitroso-N-arylhydroxylamine salts (cupferron and its substituted derivatives), and decomposition of arenesulfonyl-aryl-nitroxides. It was found that the N-aryl-N-nitroso-nitroxides decomposed in solution in a few hours at room temperature affording diarylnitroxides, which were identified by their EPR spectra. Thus, it became evident that they were releasing nitric oxide.

Starting from these observations, we prepared a variety of over 25 ammonium N-nitroso-N-arylhydroxylamine salts (3)(aryl-NONO-ates, cupferron analogs) and investigated their activity as nitric oxide donors in vitro with a fluorescence analyzer. The results showed that the ortho-chlorophenyl and ortho-anisyl analogs of cupferron released NO with higher rates than the meta- or para-isomers at similar molar concentrations. X-Ray determinations indicated for these two compounds marked non-coplanarity between the aryl and NONO groupings. Quantum-chemical calculations support the hypothesis that unlike alkyl NONO-ates (studied by L. Keefer and coworkers), which release N₂O₂ that decomposes into 2 NO, in this case the cupferron analog is oxidized to the nitroxide, which undergoes a reverse spin-trapping affording NO and an arylnitroso compound.

We further tested the biological activity of cupferron analogs to induce smooth muscle relaxation via NO release in vitro and in vivo in a rat model of myometrial relaxation. Selected cupferron compounds exhibited marked relaxing ability on isolated uterine muscle strips in vitro. Moreover, when administered intraperitoneally to acutely instrumentized rats, such cupferron derivatives decreased intrauterine pressure significantly for a sustained period.

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