
Marcelo Mota Reginatoa, Derisvaldo Rosa Paiva a, Fabrício Ronil Sensatoa, Hugo Pequeno Monteiro b, Adriana Karla Cardoso Amorim Reisa

a Department of Chemistry, Institute of Environmental, Chemical and Pharmaceutical Sciences, Universidade Federal de São Paulo – Campus Diadema, Brazil
b Department of Biochemistry, Center for Cellular and Molecular Therapy, Universidade Federal de São Paulo – Campus São Paulo, Brazil

Abstract

The conformational study on the new S nitrosothiols esters (SNO-ESTERS): para-substituted (X = H, OMe, Cl and NO2) 5 nitrosothiol derivatives 2 methyl 2 (sulfanyl)propyl phenylacetates (R1), 2 (4 isobutylphenyl)propanoate (ibuprofen, R2), and 2 (4 isobutylphenyl)propanoate of 2 methyl 2 (nitrososulfanyl)propyl (naproxen, R3) was performed using infrared spectroscopy (IR) in solvents with increasing polarity (CCl4, CH3Cl and CH3CN), and theoretical calculations, to determine the preferential conformer and the potential of these compounds to release nitric oxide (NO). S Nitrosothiols were synthesized by esterification reactions, using chlorides of the corresponding carboxylic acids, with good yields (~60%). IR results showed that these compounds presented only one conformation, and the experimental data were supported by the theoretical results obtained by density functional theory (DFT) calculations using the 6311+G (2df, 2p) basis set. The calculations revealed that all S nitrosothiol presented one preferential antiperiplanar (ac) geometric conformation, which agrees with the data obtained experimentally in CCl4. These conformers are stabilized by intramolecular hydrogen bonds. Examination of the geometry with regard to the R–SNO group revealed that these compounds are preferentially in the trans (unit) conformation. The calculation of the orbital interactions using the Natural Bond Orbital (NBO) method showed that the nO(N–O) → σ(S–N) hyper-conjugative interaction increases the S–N bond length. The strong nO → nO(N–O) interaction and electronic delocalization induces a partial π character to the S–N bond. The weak σ(S–N) bond indicates strong delocalization of the electron pair in O (NO) by the nO(N–O) → σ(S–N) interaction, thereby increasing the capacity of NO release from SNO-ESTERS.

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occurring via both cyclic GMP-dependent and -independent mechanisms. Human studies have shown that, while NO aspirin maintains its anti-thrombotic activity, it spares the GI tract. The use of NCX-4016 results in a 90% reduction of the gastric damage caused by equimolar doses of aspirin [10,11].

S Nitrosation, the NO-mediated modification of sulfhydryl residues of peptides and proteins has been associated with the anti-inflammatory actions of NO aspirin and NO naproxen [12,13]. Furthermore, recent studies have shown that S nitrosation of the signaling proteins Src, EGFR, and Ras generating their S nitrosothiols derivatives, regulates pathways associated with cell survival and proliferation (reviewed in [14]).

In addition to NO-NSAIDs, S nitrosothiols are a class of NO donors that under appropriate conditions decompose to liberate NO. They decompose by thermal and photochemical reactions to give the corresponding disulfide and NO. It was proposed that the photolytic decomposition of S nitrosothiols is a two-step process: the first step being the homolytic dissociation of the S=N bond to form •NO and RS• radicals, followed by dimerization of RS• forming the disulfide RSSR [15]. On the other hand, in aqueous buffers at physiological pH, S nitrosothiols decompose in the presence of trace transition metal ions generating NO and RSSR. In this process RS• radicals are not formed [16].

By the reasons explained above, addition of an S nitrosothiol moiety to NSAIDs may prove to be advantageous to these molecules. However, syntheses of these derivatives have been scarcely reported [17].

Theoretical approaches combined with experimental approaches, provide a new and consistent picture of the conformational behavior of S nitrosothiols. The combination of methodologies also provides information on how the conformational behavior influences S nitrosothiols spectroscopic and chemical properties. For instance, to assign the structure of S nitroso methanethiol, reported calculations showed for B3LYP/6-311+G* calculation minima for the syn and anti conformations (the former possessing an eclipsed C=H bond). MP2/6-311+G* geometry optimizations and QCISD (T)/6-31+G* single-point calculations further confirm the syn preference. Also of note is the preferred eclipsing of an R-CH and anti-clinal orientation of the alkyl chain with respect to the SNO moiety in syn exclusively in the anti-orientation [18].

The reliability and accuracy of the conventional electron correlation methods MP2 and QCISD, and the density functional theory methods B3LYP and B3P86, to obtain optimized structures and homolytic bond dissociation energies S—N of a range of S nitrosothiols, has been investigated. A variety of model RSNOs (HSNO, CH3SNO, C2H5SNO, C3H7SNO, C4H9SNO, and CysSNO (S nitroso cysteine) have been used. For all methods considered, optimized S—N bond lengths were found to be highly dependent on the basis set being employed. In general, to obtain convergence in the r(S—N) values of RSNO for a given method, the 6-311+G*(2df,p) or larger basis set was required [19].

The combination of IR spectroscopy and theoretical calculations has been extensively employed in conformational studies of carbonyl compounds. Analysis of the carbonyl stretching frequencies (v(CO)) in solution determines the different conformations assumed by the compounds. The unusual solvent effect and v(CO) shifts for the conformers as compared to other α-hetero-substituted carbonyl compounds are interpreted in terms of a decrease in polarity [20–22].

The presence of carbonyls in the structure of an S nitrosothiol might interfere with its conformational behavior. However, potential interference of these groups on the conformational behavior of S nitrosothiols has not been evaluated.

In this work we synthesized the S nitrosothiols 2-methyl 2 (nitrososulfanyl) propyl phenylacetate para substituted R1, 2-methyl 2 (nitrosothio) propyl 2 (4 isobutylphenyl) propanoate R2 (derivative of ibuprofen), and 2 methyl 2 (nitrosothio) propyl 2 (6 methoxynaphthalen 2 yl)propanoate (derivative of naproxen) R3. A conformational study of the compounds was carried out using IR spectroscopy and theoretical calculations. This combination of experimental and theoretical approaches, allowed us to determine the most stable conformation they can assume in relation to the carboxyl group and their potential as NO releasing compounds.