

Hypothesis

Thermodynamic considerations on the formation of reactive species from hypochlorite, superoxide and nitrogen monoxide

Could nitrosyl chloride be produced by neutrophils and macrophages?

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Abstract

Hypohalous acids are poor one-electron oxidizing agents, such that reactions with hydrogen peroxide to yield radical species are not feasible. However, the oxidation of superoxide by hypohalous acids can be a source of hydroxyl or haline radicals. The oxidation of nitrogen monoxide by hypochlorous acid is favourable, but in all likelihood cannot compete with the diffusion-controlled reaction with superoxide to yield peroxynitrite. The reaction of the latter with hypochlorous acid may lead to nitrosyl chloride, a strongly oxidizing agent [$E^{\circ}(\text{NOCl}/\text{NO}^{\bullet}, \text{Cl}) = 1.0 \text{ V}$] that is capable of nitrosylating organic compounds and thereby generating mutagens or promutagens.

Key words: Hypochlorite; Nitric oxide; Peroxynitrite; Nitrosyl chloride; Neutrophil; Macrophage

1. Introduction

The main microbial agent produced by activated neutrophils is hypochlorite, which is formed from chloride and hydrogen peroxide by the enzyme myeloperoxidase. Neutrophils also produce superoxide and nitrogen monoxide^{**}. These radical species react at a diffusion-controlled rate [2] to form peroxynitrite [$\text{O}=\text{NOO}^{\bullet}$, oxoperoxonitrate(1⁻)], a strongly oxidizing agent [3]. Evidence for formation of oxoperoxonitrate(1⁻) by macrophages [4] and neutrophils [5] has been presented. Gibbs energy changes for reactions between superoxide, hypochlorous acid and hydrogen peroxide were published [6]. There are two reasons for re-examining this study: (i) the discovery that nitrogen monoxide is formed in vivo [7,8] necessitates the inclusion of nitrogen containing compounds, and (ii) more accurate thermodynamic data are now available for inorganic radicals. I will show here that formation of nitrosyl chloride is energetically feasible, and that this compound is strongly oxidizing. Aside from this, nitrosyl chloride is known to

be a nitrosylating agent [9]. Currently, the only physiologically relevant mechanism to arrive at a nitrosylating species is via the autoxidation of nitrogen monoxide [10].

2. Thermodynamics

Standard Gibbs energies of formation were obtained from the literature [3,11–13], and Gibbs energies of solvation were added where appropriate such that all values, including reduction potentials, refer to 1 molal solutions. For this reason many of the reported values that pertain to gases are not standard values, and this is indicated by an apostrophe, as in $E^{\circ'}$. One- and two-electron potentials of the hypohalous acids are shown in Table 1. Three schemes have been constructed which show the energetics of hypohalous acids with superoxide and hydrogen peroxide. Nitrogen monoxide could react with a number of these compounds, and the Gibbs energy changes of these reaction have been collected in Table 2.

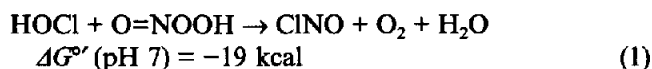
3. Discussion

Like hydrogen peroxide, the hypohalous acids are poor one-electron and strong two-electron oxidizing agents, as shown in Table 1. This explains why the oxidation of hydrogen peroxide to superoxide by the hypohalous acids is quite unfavourable, in contrast to the two-electron oxidation to dioxygen. Indeed, there is ex-

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^{**}Allowed names for chemical compounds are used. However, when the spelling of a name is uncertain (peroxynitrite or peroxonitrite) or when such a name is not recommended (nitric oxide), systematic names are used [1].

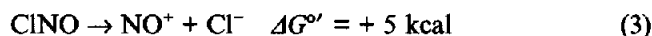
Compared to the various radicals that may be formed (see Schemes 1-3), hydrogen oxoperoxonitrate and hypochlorous acid are relatively stable compounds. One should consider, therefore, whether a reaction between these two species can occur that is analogous to the reaction between hydrogen peroxide and hypochlorite. The energetics indicate that singlet dioxygen is energetically not feasible, but, interestingly, nitrosyl chloride may be formed, as shown in Reaction 1:



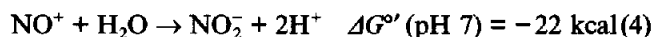
From the Gibbs energies of formation of nitrosyl chloride, the nitrosyl cation and chloride, one calculates that nitrosyl chloride is a strong oxidant:



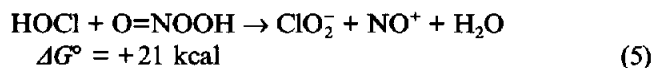
This reduction potential is similar to that of ozone [13], nitrogen dioxide [12,24], and chlorine dioxide [25,26]. bSince $E^\circ(\text{NO}^+/\text{NO}^\bullet)$ equals 1.21 V [12], dissociation is unfavourable (Reaction 3):



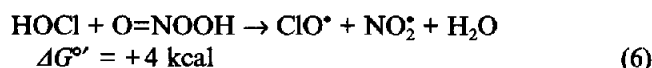
However, the subsequent hydrolysis, Reaction 4, is favourable, which may make Reaction 3 proceed in the direction indicated.



A reaction that results directly in dioxochlorate(1-) and the nitrosyl cation is unfavourable:



Similarly, the one electron oxidation of hypochlorous acid by hydrogen oxoperoxonitrate (Reaction 6) has a positive Gibbs energy change:



The small positive Gibbs energy is not likely to prevent this reaction from occurring, because the products, chlorine monoxide and nitrogen dioxide, disappear rapidly in subsequent reactions. Quantum mechanic studies appear to indicate that chlorine monoxide and nitrogen dioxide do not react to form $\text{O}=\text{NOOCl}$ [27]. While Reaction 6 cannot be excluded on thermodynamic grounds, it does not yield a nitrosylating species.

Nitrosyl chloride can nitrosylate organic compounds directly [9], and therefore its presence poses two dangers: first, it is a strong oxidant, and second, nitrosylation leads to compounds that are often mutagenic or promutagenic. N-Nitrosylation by activated neutrophils has been observed [28]. Hydrogen oxoperoxonitrate does not nitrosylate, but nitrates, aromatic compounds [29,30], and is therefore not directly responsible for the formation of nitroso compounds. Recently, we observed a

rapid reaction, comparable to that between hypochlorite and hydrogen peroxide [14], between hypochlorite and hydrogen oxoperoxonitrate with the help of the stopped-flow technique. We also obtained preliminary evidence for the formation of *p*-nitrosophenol from phenol, hypochlorite and oxoperoxonitrate(1-) (Bartlett, Ramezani and Koppenol, unpublished observations).

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