the O_2/O_2^- couple (−330 mV)[1015] compared to that of the NOS Fe(III)−NO/Fe(II)−NO couple (−2 mV; both vs SHE).[1018] This equilibrium reaction could then be driven towards product formation if the subsequent reaction between the Fe(III)−NO complex and superoxide would be fast. This reaction, like mechanism 1 in Scheme 23, would similarly produce an Fe(III)−peroxynitrite intermediate. However, more recent work by Stuehr, Lehnert, and coworkers supports an inner-sphere mechanism via the N-bound Fe(III)−N(O)OO$^-$ intermediate as shown in Scheme 24.[1019] Using experimental studies on different NOS enzymes and DFT calculations, it was shown that the heme-thiolate active site of NOS enzymes can stabilize an N-bound Fe(III)−N(O)OO$^-$ intermediate (assisted by hydrogen-bonding from a water molecule; see Figure 58), which then rearranges to the energetically favored O-bound Fe(III)−OONO$^-$ complex,[1019] followed by isomerization to nitrate through a similar mechanism as the NOD reaction proposed for globins. In comparison, hemes with proximal His coordination like the globins have more positive Fe^{II}/Fe^{III} reduction potentials and cannot form the N-bound peroxynitrite complex, because electron transfer from the heme to the N(O)−OO ligand does not occur (Figure 59). Rather, the globins form an Fe(II)−NO—O_2 van-der-Waals adduct, and the reaction cannot proceed from there, in agreement with the experimental results (requiring NO dissociation as the first step of the ODN process in globins).[1019]

3. DINITROSYL IRON COMPLEXES (DNICS)

In this section, the discovery and major biological and synthetic advances in DNIC chemistry are discussed, including the involvement of [Fe−S] clusters as NO sensors, DNIC synthesis and electronic structure, reactivity of biomimetic DNIC complexes, and therapeutic applications of DNICs. Interested readers are referred to the cited reviews or accounts on the synthetic,[104,1020−1025] biological,[1021,1026−1028] biophysical,[1029−1031] and medicinal[107,1032] aspects of DNICs, as well as a recent 'viewpoint' article by Lu et al.,[106] for additional details.

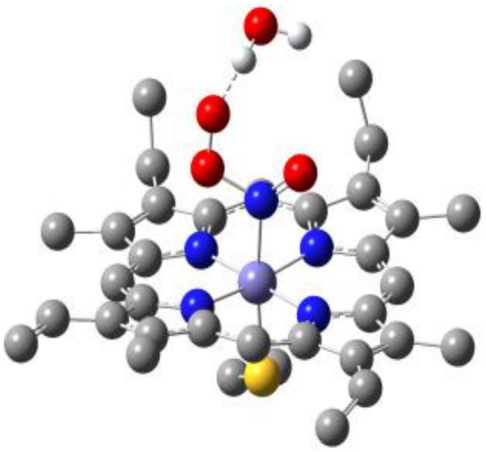

Figure 58. Fully optimized structure of the Fe(III)−**N** (O)OO$^-$/H_2O heme-thiolate complex (ON−OO distance = 1.508 Å). The two axial hydrogen-bond donors to the thiolate, the heme carboxylic acid side chains and all H atoms (except those of the H_2O molecule) have been removed for clarity.[1019]

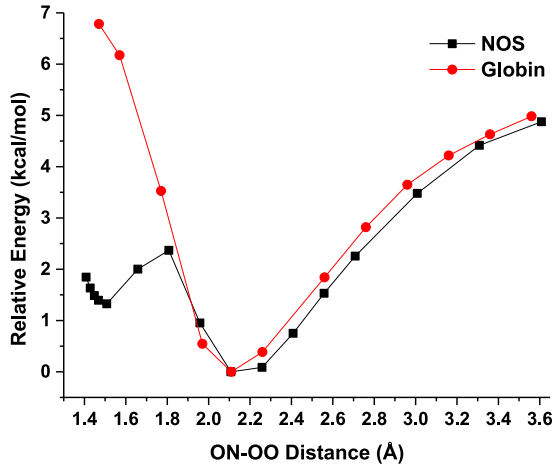

Figure 59. Comparison of the PES scan results for NOS and globin active site models. The relative energies were obtained from PES scans for the reaction of the respective Fe(II)−NO complex with $^3O_2$. Black line: the NOS active site model with a critical H_2O molecule as a hydrogen-bond donor. Red line: the globin active site model with the distal His reside (modelled as 5-ethylimidazole) included. Each point represents a fully optimized structure with only the ON−OO distance fixed. The minimum energy calculated for the Fe(II)−NO/O_2 van-der-Waals complex of each model was set to 0 kcal/mol to allow for a direct comparison of the relative energies for formation of the ferric peroxynitrite intermediate.[1019]

3.1. Discovery of DNICs

DNICs in biology were discovered well before the scientific community recognized nitric oxide as an important signaling molecule. In 1964, Anatoly Vanin observed the distinct DNIC electron paramagnetic resonance (EPR) signal at g_{av} = 2.03 while studying free radical chemistry in baker's yeast cells, *Saccharomyces cerevisiae* (Figure 60).[103,1033] Around that time, the Commoner group reported a similar g = 2.03 EPR signal from animal tissues in association with chemical carcinogenesis.[1034] Not until 1967 did Vanin identify the source for this distinct EPR signal to be from complexes best described as $[Fe(NO)_x(SR)_y]$,[1035] which was aided by the independent EPR studies of synthetic iron nitrosyl complexes from the chemistry community.[101,1036] The biological significance of DNICs was not fully understood until NO was recognized as an important signaling molecule in mammals (see Introduction).

Synthetic DNIC chemistry has a much longer history than biological DNICs. As introduced in Section 1.1, the French chemist Roussin reported the first DNIC, the 'red salt', in 1858 along with a bitter-tasting 'black salt' (Figure 60).[89] Subsequent studies by Pavel in Germany reported neutral 'ester' complexes in which the bridging sulfides of the red salt are alkylated (see Figure 8).[90] These early iron nitrosyl complexes are now referred to as Roussin's black salt (RBS) and Roussin's red salt (RRS), and Roussin's red esters (RREs). These complexes began experiencing a renaissance in the 2000s and the DNIC chemistry in this review mostly focuses on the work developed in the last 20 years. The earlier work on non-heme nitrosyls including DNICs has been previously reviewed by Butler and Megson in 2002.[1036] Within the past 60 years there has been incredible research conducted in biological and synthetic DNIC chemistry to better understand DNIC's role in nature, and how we can utilize their vast chemistry for further scientific advancements.

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