Sirt2, Sirt6, Sirt7), cytoplasm (Sirt1, Sirt2), and mitochondria (Sirt3, Sirt4, Sirt5). The sirtuins serve as key regulators of many important cell processes, including metabolism of glucose, secretion of insulin and adaptation to oxidative stress and hypoxia. For example, Sirt1 produces structural changes in chromatin that activate the synthesis of protective proteins, including antioxidant enzymes, and increase the number of mitochondria in the cells.[33] Some data indicate that Sirt1 and, possibly, other sirtuins regulate the amplitude and duration of the expression of circadian genes (metabolic clock).[34] All these proteins are NAD^+-dependent deacetylases/ADP-monoribosyltransferases. Moreover, it has been shown that expression of the sirtuin genes depends on the redox state of their intracellular environment.[35–37]

It stands to reason that $O_2^{\bullet-}$, as a powerful reducing agent, would significantly affect the redox ratio [NADH]/[NAD^+] and, thus, provoke undesirable changes in expression of the sirtuin genes in the cells that perform the supervisory functions over the organism's repair and renewal processes, be it the suprachiasmatic nucleus of the hypothalamus or another kind of "longevity-assurance structures". The evident consequence of this will be accumulation of free-radical products and other metabolic slag in peripheral cells and tissues with the resulting impetus to autophagic or apoptotic cell death and age-associated clinical disorders. As a matter of fact, the radicals are targeted onto the [NADH]/[NAD^+]-dependent sirtuin system that performs, in its turn, the function of the biological amplifier of $O_2^{\bullet-}$.

8.4 Extension of Lifespan by Antioxidants

8.4.1 Antioxidants: Radical Chemistry Standpoint

In chemistry, antioxidants are compounds, synthetic and natural, capable of terminating branching chain oxidation. These are mainly derivatives of phenols, secondary aromatic amines, organic phosphites and sulfides whose valence-saturated molecules containing an active hydrogen atom (InH) react with an active free radical $R^\bullet$ or $RO_2^\bullet$, that runs the oxidative chain, to give radical ($In^\bullet$) of the antioxidant:

$$R^\bullet + InH \Rightarrow RH + In^\bullet \quad (8.6a)$$

$$RO_2^\bullet + InH \Rightarrow ROOH + In^\bullet \quad (8.6b)$$

The relatively unreactive free radical $In^\bullet$, thus formed, cannot participate in chain propagation reactions and is destroyed upon collision with another radical or the vessel wall. The most common antioxidants are phenolic derivatives in which the OH group is shielded, the so-called "sterically hindered phenols" (see ref. 38–40).

Some of the synthetic antioxidants are depicted in Scheme 8.1. The antioxidant 2,6-di-*tert*-butyl-4-methylphenol, called butylated hydroxytoluene (BHT) in English-language literature or ionol or dibunol in Russian