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# QUENCHING OF SINGLET OXYGEN BY ELECTRON DONATING DERIVATIVES OF 1,4-DIHYDROPYRIDINE

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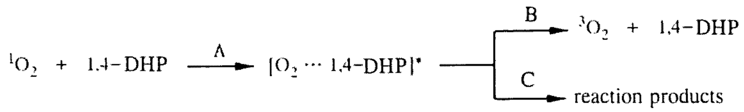
*It is shown that a series of derivatives of 1,4-dihydropyridine are capable of efficiently quenching singlet oxygen by a mixed quenching mechanism.*

Single oxygen ($^1O_2$), one of the active forms of oxygen, takes part in many biological processes, especially in photodynamic systems. $^1O_2$ is a very reactive species which efficiently initiates the peroxide oxidation of lipid and causes the degradation of proteins, nucleotides, and biomembranes. Consequently, the interest in compounds that deactivate $^1O_2$, thus protecting biological systems from decomposition, is understandable [1].

Derivatives of 1,4-dihydropyridine (1,4-DHP) attract attention as substances with a wide range of biological activity – antioxidant, cardiovascular, radioprotective, etc. Often, these properties are explained by the ability of 1,4-DHP to react with active forms of oxygen. Consequently, an investigation of the reactivity of 1,4-DHP with active forms of oxygen is of definite value in elucidating the mechanism of its biological activity. However, the reactivity of derivatives of 1,4-DHP with $^1O_2$ has seldom been investigated [2-4]. We have determined the overall quenching constants of $^1O_2$ ($k_q$) and the rates of chemical oxidation by $^1O_2$ ($k_{ox}$) of a series of derivatives of 1,4-DHP and 1,4-dihydroindeno[1,2-b]pyridines (1,4-DHIP) containing electron donor groups. The results obtained are collected in Table 1.

The results of the investigations show that some derivatives of 1,4-DHP are good quenchers of $^1O_2$ (compounds 1a and 1b), surpassing in activity the standard quencher – 1,4-diazabicyclo[2,2,2]octane. Comparing the quenching constants of the derivatives of 1,4-DHP, one can see that the replacement of a hydrogen atom in the 4 position of the 1,4-DHP ring causes a strong decrease in the quenching constants and rates of oxidation (compounds Ia, Ib, and compounds Ic-f). True, there is some increase in the quenching constants when the electron donor properties of the substituent in the 4 position is strengthened, e.g., the presence in this position of a phenyl or alkoxyphenyl substituent (compounds Id-f). Derivatives of 1,4-DHIP are more reactive towards $^1O_2$ than are those of 1,4-DHP (compare Ic and IIc). The mechanism of quenching $^1O_2$ obviously includes a chemical as well as a physical quenching of $^1O_2$, as shown by the scheme:



A is a reaction forming a collision complex or an exiplex, B is the reaction for the physical quenching of $^1O_2$, and C is the reaction for the chemical quenching of $^1O_2$.

Since 1,4-DHP derivatives are reducing agents and good electron donors, especially those unsubstituted in the 4 position, it is most likely that the physical quenching of $^1O_2$ takes place by a charge transfer mechanism, while the chemical quenching is an oxidation reaction giving the corresponding pyridine derivative or forming an addition product. It is known that the oxidation of NAD-H by photochemically generated $^1O_2$ gives about 80% $NAD^+$ and 20% products of an undeter

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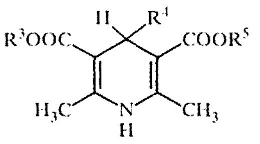
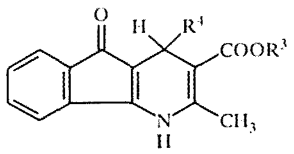
TABLE 1. Constants for the Quenching and Chemical Oxidation of Singlet Oxygen by Derivatives of 1,4-DHP and 1,4-DHIP



I



II

| Compound | $R^3 = R^5$ | R4 | $k_q, s^{-1}$ | $k_{ox}[^1O_2], s^{-1}$ |
|---|---|---|---|---|
| Ia | $C_2H_5$ | H | $1{,}6 \cdot 10^7$ | $7{,}6 \cdot 10^{-4}$ |
| Ib | $C_{10}H_{19}$ (menthyl-3′) | H | $3{,}5 \cdot 10^7$ | $3{,}1 \cdot 10^{-3}$ |
| Ic | $C_2H_5$ | $C_6H_5$ | $5{,}0 \cdot 10^4$ | $7{,}3 \cdot 10^{-6}$ |
| Id | $C_2H_5$ | $C_6H_4OH$-4 | $9{,}8 \cdot 10^4$ | $1{,}1 \cdot 10^{-5}$ |
| Ie | $C_2H_5$ | $C_6H_2(OCH_3)_3$-3,4,5 | $1{,}3 \cdot 10^5$ | $5{,}1 \cdot 10^{-6}$ |
| If | $C_2H_5$ | $CH{=}CHC_6H_5$ | $8{,}9 \cdot 10^4$ | $7{,}5 \cdot 10^{-6}$ |
| IIa | $C_{10}H_{19}$ (menthyl-3′) | $\beta$-Py | — | $4{,}4 \cdot 10^{-5}$ |
| IIb | $C_2H_5$ | $\beta$-Py | — | $2{,}9 \cdot 10^{-5}$ |
| IIc | $C_2H_5$ | $C_6H_5$ | — | $4{,}5 \cdot 10^{-5}$ |
| 1,4-diazabicyclo[2,2,2]octane | | | $2.2 \cdot 10^7$ | — |

mined nature [4]. Comparison of the changes in $k_q$ and $k_{ox}$ shows the contribution of chemical quenching to $k_q$ to be about the same, in good agreement with the literature data for NAD-H and NADP-H [3]. Thus, for compounds Ia-e, $k_q$ and $k_{ox}$ vary symbatically. However, the increased degree of conjugation in If ($R^4 = CH{=}CH{-}C_6H_5$) compared to Ic ($R^4 = C_6H_5$) causes an almost twofold increase in $k_q$ while $k_{ox}$ is practically unchanged, indicating an increased contribution from the physical quenching mechanism. It is also of interest to note that compound Ia, which has a large $k_q$, is used in cosmetics as a shield against UV radiation (in the composition of the antisunburn cream Brig), and in medicine as a protective agent against radiation.

## EXPERIMENTAL

The $^1O_2$ quenching constants ($k_q$) were determined in a pulse apparatus [5] from oscillograms of the decay of the oxygen luminescence corresponding to the $^1\Delta_g \rightarrow \Sigma_g^-$ transition in molecular $O_2$ (1270 nm). The experiments were carried out in a $CCl_4$ (90%)/$CHCl_3$ (10%) mixture with the Pd(II) complex of the IX-diethyl ester of mesoporphyrin as a sensitizer. Having determined the dependence of the lifetime of $^1O_2$ on the concentration of 1,4-DHP by the Stern–Volmer equation, we calculated $k_q$. WE determined the rate constants of the chemical oxidation spectrophotometrically from the initial rate of the decrease in the intensity of absorption by the 1,4-DHP derivatives at the wavelength of the wavelength maximum in the photochemical generation of $^1O_2$ by red light ($\lambda > 630$ nm), using methylene blue in methanol as a sensitizer.

## REFERENCES

1. A. F. Frimer (ed.), Singlet $O_2$, CRC Press, Vol. 1-5 (1985).
2. G. D. Tirzim, I. M. Byteva, K. I. Salokhiddinov, G. P. Gurinovich, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 7, 924 (1981).
3. G. Peters and M. A. J. Rodgers, Biochim. Biophys. Acta, **637,** 43 (1981).
4. R. S. Bodaness, Biochem. Biophys. Res. Commun., **108,** 1709 (1982).
5. K. I. Salokhiddinov, I. M. Byteva, and B. M. Dzhagarov, Opt. Spektr., **47,** 881 (1979).