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REDOX PROPERTIES OF SUPEROXIDE WITH 1,2,3-TRIAZINE DERIVATIVES

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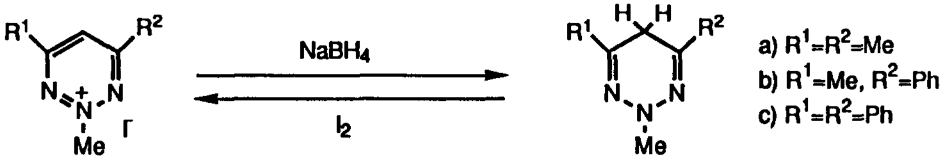
Summary: 2-Methyl-1,2,3-triazinium iodide **1** and its dihydro derivative **2** were both allowed to react with potassium superoxide to give the same products, triazine dimer **3** and 5-oxo-triazine **4**. These reactions showed the unique dual reactivities of superoxide.

Monocyclic 1,2,3-triazines[1)] are among six membered heteroaromatics, and highly π-deficient because of three nitrogen atoms in the ring system.[2)] Thus the nucleophilic reaction easily occurred mainly at C-4 position.[3)] On the contrary, electrophilic attack to the ring nitrogens was much slower than that of pyridines or pyridazines, and the long-term reaction with methyl iodide gave 2-methyl-1,2,3-triazinium iodide **1** exclusively. The compounds **1** thus obtained were readily reduced by $NaBH_4$ to afford corresponding 2-methyl-2,5-dihydro-1,2,3-triazines **2** in good yields.[4)] Moreover, dihydro derivatives **2** were transformed to **1** by the oxidation with I_2, which revealed the redox reversibility between **1** and **2** (scheme 1).



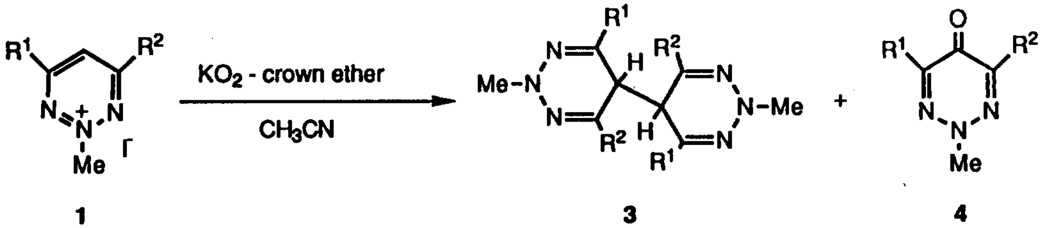
1 **2**

a) $R^1=R^2=Me$
b) $R^1=Me$, $R^2=Ph$
c) $R^1=R^2=Ph$

scheme 1

The above reaction stimulates the interest also from the viewpoint of the analogy with $NAD^+ \rightleftarrows NADH$ reversibility. Thus we have attempted to study the redox behavior of **1** and **2**, and in this paper we report the reaction with potassium superoxide.

Superoxide is known to have a variety of reactivities[5)] including one electron reduction,[6)] nucleophilic substitution,[7)] hydrogen abstraction[8)] and so on, and is biologically one of the most important radical species.[9)] Especially, we are interested in the fact that superoxide acts as both reductant and oxidant depending upon the nature of substrates. When **1** were reacted with 1.2 eq. of potassium superoxide under argon or oxygen atmosphere, one electron reduction of **1** occurred readily to form 5,5'-bis(2-methyl-2,5-dihydrotriazinyl) **3** accompanied by small amounts of 2-methyl-5-oxo-2,5-dihydrotriazines **4** (scheme 2 and Table 1). No influence of oxygen atmosphere suggested that the reaction solvent was saturated with oxygen which was derived from one electron release of superoxide even under argon.



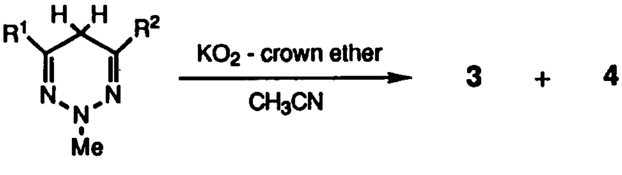
scheme 2

Table 1 Reaction of 2-Methyl-1,2,3-triazinium Iodide 1 with Potassium Superoxide

substrate	conditions	yield of 3 (%)	yield of 4 (%)
1a	10min under Ar	52	12
1b		54	6
1c		57	13
1a	10min under O_2	58	7
1b		61	11
1c		65	12

In the typical experiment, 0.2 mmol of **1a** was dissolved in 10 ml of abs.CH_3CN, and KO_2 (0.24 mmol) and 0.03 mmol of 18-crown-6-ether were added under argon or oxygen atmosphere at -10°C. The reaction was continued for 10 min until the red color of **1a** was disappeared. Then the reaction mixture was filtered in order to remove insoluble salt, and the residual solution was evaporated to leave the residue which was chromatographed on alumina to give **3a** and **4a**.

Next, 2-methyl-2,5-dihydrotriazines **2** were allowed to react with KO_2 in CH_3CN under argon or oxygen atmosphere. The consumption of **2** was much slower than that of **1**, and the oxygen addition promoted the reaction to change the products distribution (scheme 3 and Table 2).



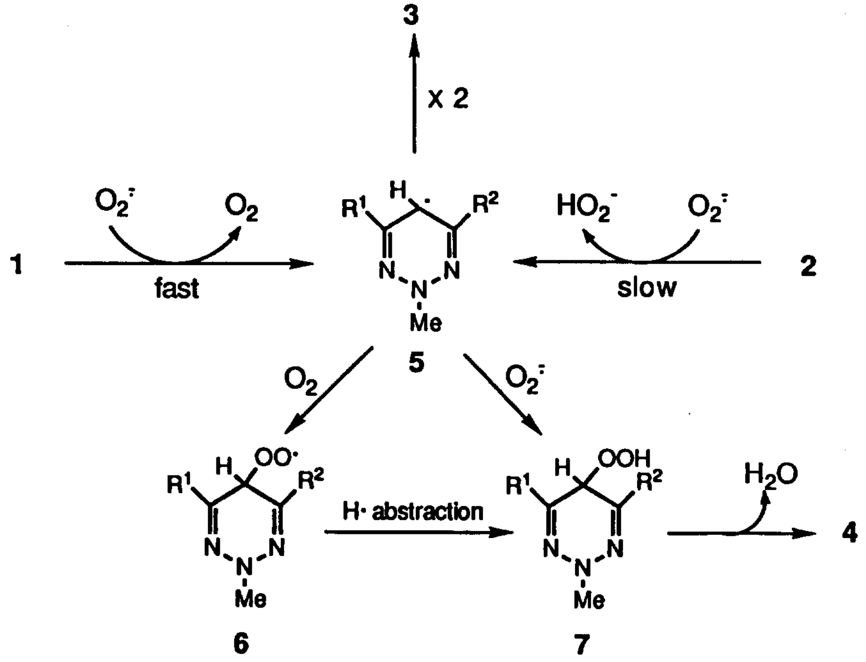
scheme 3

Table 2 Reaction of 2-Methyl-2,5-dihydrotriazine **2** with Potassium Superoxide

substrate	conditions	yield of 3 (%)	yield of 4 (%)
2a	24 hr under Ar	14	64
2b		73	10
2c		69	15
2a	2 hr under O_2	4	73
2b		16	55
2c		3	85

Consumption of the starting material **2** was followed with TLC, and the same work-up procedure was adopted as the reaction of **1**.

When **2** were allowed to react with electrogenerated superoxide under oxygen, it was revealed that the electric current less than one equivalent was enough to complete the reaction (0.5 F/mol for **2a**). The fact suggested that the radical chain reaction was partly comprised in the formation of **4**. Therefore the total reaction mechanism is regarded as shown in scheme 4. Superoxide is suggested to act as one electron reductant for **1**, and as hydrogen abstractor for **2** to generate a common radical intermediate **5**. The reduction of **1** occurred rapidly to form **5** in high concentration, which caused the preferential dimerization of **5**. The hydrogen abstraction from **2** is considered to be relatively slow because of its electron deficiency, thus under oxygen atmosphere the reaction of **5** with triplet oxygen prevailed over the dimerization to afford a peroxy radical **6**, and **6** abstracted hydrogen to give a peroxide **7**. When the hydrogen source was **2**, radical **5** was regenerated to cause the chain reaction. The other hydrogen source is supposed to be solvent, CH_3CN. The compounds **4** were formed in every case, particularly in the case of **2a**, **4a** was mainly obtained even in the absence of oxygen, therefore there seemed to be another pathway to **7**, which may be the reaction of **5** with superoxide. Peroxide **7** thus formed was dehydrated to give 5-oxo derivative **4**.



scheme 4

The successful formation of **3** (and **4**) from both **1** and **2** is thought to be attributable to the electron deficiency of 1,2,3-triazine ring. Sawyer et al. reported the reaction of *N*-benzyl-1,4-dihydronicotinamide (BNAH) with superoxide.[10] BNAH is known to be one of the most popular NADH model compounds. It was shown that superoxide oxidized BNAH by a one-hydrogen-atom process to give

BNA·, which is highly reactive to make the reaction complicated. While dihydrotriazine **2** is more electron deficient than BNAH[11], thus the reaction with superoxide was considered to be much slower. However the radical **5** thus abtained was more stable than BNA· because of its electron deficiency, so the dimer **3** was obtained in a moderate yield. On the contrary, triazinium salt **1** is reduced more readily than BNA$^+$,[12] therfore the stable radical **5** was formed in high concentration, which caused the formation of **3** even in the presence of oxygen.

In this paper we described that one of the redox couples of six-membered heteroaromatics showed the dual reactivities with superoxide. It was suggested that the reactions of these kinds would be of use for precise research for the reactivity of superoxide. The application of these reactions to other heteroaromatics is now under investigation.

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References and Notes

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11. BNAH in DMF has an irreversible oxidation wave at $E_{1/2}$= + 0.70 V, whereas those of **2** were + 1.20 V (**2a**), + 0.90 V (**2b**), and + 1.16 V (**2c**) vs. SCE.
12. BNA$^+$ in CH_3CN has the first irreversible reduction wave at $E_{1/2}$= - 1.11 V , while those of **1** were - 0.42 V (**1a**), - 0.30 V (**1b**), and - 0.32 V (**1c**) vs. SCE.

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