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Reversible 1,4-cycloaddition of singlet oxygen to *N*-substituted 2-pyridones: 1,4-endoperoxide as a versatile chemical source of singlet oxygen†

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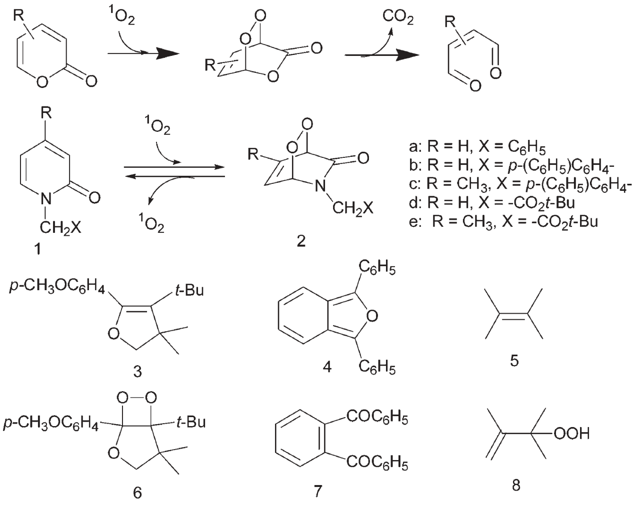
***N*-substituted pyridones (1) easily undergo singlet oxygenation to give exclusively the corresponding endoperoxides (2), which decompose to give pyridones again while liberating $^1O_2$ in high yield.**

α-Pyranones are known to undergo 1,4-cycloaddition with singlet oxygen ($^1O_2$),[1–3] to afford 1,4-endoperoxides, which decompose thermally into 1,2-diacylethylenes while extruding CO_2 (Scheme 1). We report here that a) $^1O_2$ adds also to nitrogen-analogues of α-pyranone, namely, *N*-substituted pyridones (**1**) to give 1,4-endoperoxides (**2**) exclusively, b) the thus-obtained peroxides (**2**) liberate $^1O_2$ in high yield, differing from the case of 1,4-endoperoxides of α-pyranones, and c) the peroxides (**2**) are a promising chemical $^1O_2$ source with characteristics different from those of 1,4-endoperoxides of substituted polynuclear aromatics.

Commercially available 2-hydroxypyridine and its 4-methyl-analogue were easily alkylated with benzyl bromide, 4-bromomethylbiphenyl, and *t*-butyl bromoacetate to give the corresponding *N*-substituted 2-pyridones (**1a–1e**) in high yields. When a solution of *N*-benzyl-2-pyridone (**1a**) (250 mg) in dichloromethane (10 mL) was irradiated with a Na-lamp (940 W) together with a catalytic amount of tetraphenylporphine (TPP) under an oxygen atmosphere at −78 °C for 2 h, 1,4-endoperoxide (**2a**) was produced exclusively. Chromatographic purification (silica gel/hexane–dichloromethane) was attained easily to give peroxide (**2a**) as colorless leaflets (mp 67.0–68.0 °C, dec.), the structure of which was determined by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectral analysis.‡ The other pyridones (**1b–1e**) gave also exclusively the corresponding 1,4-endoperoxides (**2b–2e**) on similar singlet oxygenation.



Scheme 1

All endoperoxides (**2a–2e**) synthesized here were stable enough for handling at room temperature and storing for > 1 year in a freezer though they decomposed into the corresponding pyridones (**1a–1e**) exclusively in a solvent such as $CDCl_3$ at 40 °C with half-life of 2–6 h. When the thermolysis of **2a–2e** was carried out in the presence of typical substrates, namely, dihydrofuran (**3**) for 1,2-addition of $^1O_2$,[4] isobenzofuran (**4**) for 1,4-addition of $^1O_2$,[5] and 2,3-dimethylbut-2-ene (**5**) for "ene" reaction of $^1O_2$,[6] dioxetane (**6**),§ diketone (**7**), and hydroperoxide (**8**) were produced, respectively. These results showed that the retro-1,4-cycloaddition proceeded to liberate $^1O_2$.

Thus, we attempted to estimate the efficiency of $^1O_2$ generation by means of a trapping experiment of $^1O_2$ with an olefin (**5**) for the thermolysis of endoperoxides (**2a–2e**). First of all, we examined whether the re-combination of $^1O_2$ with pyridones, formed during the thermolysis of **2a**, could be prevented substantially by the use of a highly reactive olefin (**5**). Sensitized photooxygenation of a mixture of **1a** (1.5×10^{-2} M) and an equimolar amount of **5** in $CDCl_3$ at 30–40 °C was confirmed to give exclusively a hydroperoxide (**8**) without formation of **2a** even after *ca.* 40% conversion of **5**.

A solution of endoperoxide (**2a**) (1.5×10^{-2} M) and an olefin (**5**) (7.5×10^{-2} M) in $CDCl_3$ was heated, and the time-course of the formation of **8** and **1a** and of the decrease of **2a** was followed by means of ^{1}H-NMR at 30, 40, and 50 °C.¶ Similar kinetic experiments were carried out for thermolysis of the other endoperoxides (**2b–2e**). All endoperoxides (**2a–2e**) were found to decompose into the corresponding 2-pyridones (**1a–1e**) by first-order kinetics and to afford $^1O_2$ in high yields even at high conversion (~80%). These results are summarized in Table 1 together with activation parameters for the thermolysis, which were estimated from the Arrhenius plots.

Reversible 1,4-cycloaddition of $^1O_2$ to a conjugate system has been recognized as one rather characteristic feature for polynuclear aromatic hydrocarbons.[7] In fact, endoperoxides of 9,10-diphenylanthracenes and 1,4-dialkylnaphthalenes are well known to generate $^1O_2$ in yields from 30 to 95% on heating.[8,9] Turro and his co-workers have found for the thermolysis of these endoperoxides that a) $\Delta S^\ddagger$ values range from positive to slightly negative,

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b414845b/
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Table 1 Activation parameters and efficiency of $^1O_2$ generation for thermolysis of *N*-substituted 2-pyridone endoperoxides (**2a–2e**) in $CDCl_3$

	$\Delta G^‡$/ kcal mol^{-1}	$\Delta H^‡$/ kcal mol^{-1}	$\Delta S^‡$/ cal K^{-1} mol^{-1}	$^1O_2$/%	
				A[a]	B[b]
2a	24.3	22.8	−5.3	96 ± 1	81 ± 1
2b	24.1	23.0	−3.7	96 ± 1	73 ± 1
2c	24.7	23.2	−5.0	97 ± 1	84 ± 4
2d	24.6	24.1	−1.4	89 ± 2	74 ± 6
2e	25.2	25.2	0.1	84 ± 1	82 ± 1

[a] Mean of $^1O_2$ yields for < 20% conversion of **2** at 40 °C. [b] Mean of $^1O_2$ yields at 30, 40, and 50 °C. $^1O_2$ yield at each temperature was estimated from the data at five points for 30–80% conversion of **2**.

and 2) positive $\Delta S^‡$ values correlate with the relatively low yields of $^1O_2$, and slightly negative or near zero $\Delta S^‡$ values correlate with the high yields of $^1O_2$.[8,9] They have also suggested that these tendencies can be interpreted in terms of a diradical mechanism which leads to a low yield of $^1O_2$ and a concerted mechanism which leads to high yields of $^1O_2$, respectively.

$\Delta S^‡$ values ranged from slightly positive to negative for endoperoxides of pyridones (**2a–2e**). Furthermore, column A in Table 1 shows that the liberation of $^1O_2$ occurred nearly quantitatively for most cases of thermolysis of **2** at low conversion of **2** (< 20%). These relationships between the yield of $^1O_2$ and the $\Delta S^‡$ value are illustrated in Fig. 1. One would realize from Fig. 1 that endoperoxides of pyridones (**2**) (squares) belong to the same class which includes endoperoxides of polynuclear aromatics for the mechanism of $^1O_2$ liberation. On the other hand, the efficiency of $^1O_2$ generation decreased considerably at high conversion of **2** except **2e** (~80%), though the absolute yields of $^1O_2$ stayed at a high level. When the thermolysis of **2a** was carried out in the presence of an equimolar amount of 2-pyridone (**1a**), $^1O_2$ yield decreased to *ca.* 80% at low conversion of **2a**. Thus, the decrease of $^1O_2$ yields is likely to be attributable to the fact that 2-pyridone (**1**) produced during the thermolysis of **2** quenches $^1O_2$ physically, though detailed experiments would be required to confirm such a conclusion.

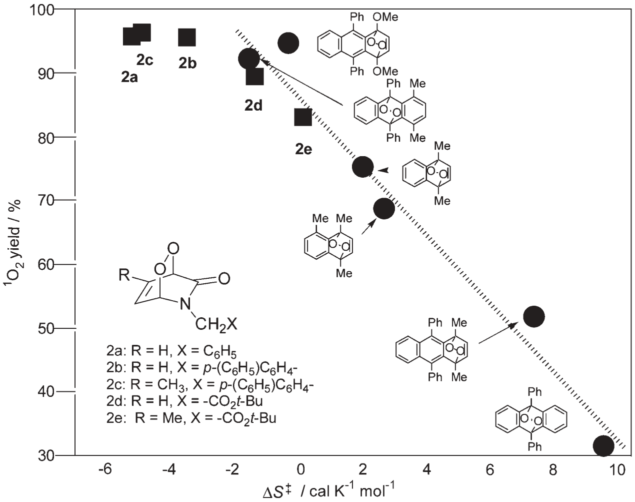
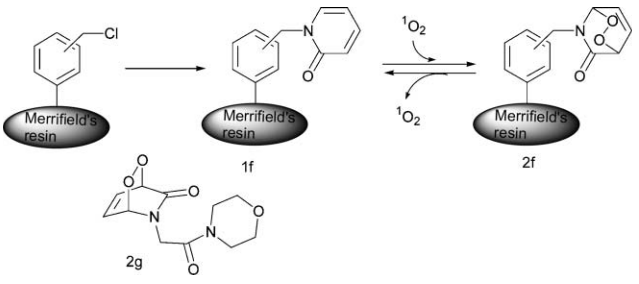


Fig. 1 Relationship between $^1O_2$ yield and activation entropy for thermolysis of endoperoxides of polynuclear aromatics and pyridone endoperoxides (**2**).



Scheme 2

Chemical $^1O_2$ sources which are less complicated mechanistically are quite useful for $^1O_2$ reactions of biological substrates, mechanistic investigations of $^1O_2$ reactions with organic substrates, and as an essential chemical species for COIL (chemical oxygen–iodine laser).[10] As described earlier, the present endoperoxides (**2**) would be useful as a new chemical source of $^1O_2$. Comparing **2** with 1,4-endoperoxides of alkylnaphthalene derivatives[11,12] as chemical $^1O_2$ sources, one advantageous feature of **2** probably lies in the easy preparation and modification of their precursors, namely, *N*-substituted 2-pyridones (**1**), since the synthesis of most substituted naphthalenes is unexpectedly burdensome. A good example is the preparation of a polymer-supported $^1O_2$ generator.

Functionalized polymer represented by Merrifield's resin is often used in a wide variety of reactions in the solid phase. 2-Pyridone was easily joined to Merrifield's resin|| to give **1f** by means of nucleophilic substitution similar to the synthesis of **1a–1e**. The thus-prepared pyridone supported on polymer (**1f**) was also easily converted into the corresponding endoperoxide (**2f**) by sensitized photooxygenation similar to the case of **1a–1e** except that a suspension of the substrate was used (Scheme 2).** When endoperoxide supported on Merrifield's resin (**2f**) was heated with olefin (**5**) at 40 °C for 1 h, $^1O_2$ was estimated to be liberated in 85% yield based on produced hydroperoxide (**8**) and the consumed endoperoxide.

In conclusion, we have shown here that *N*-substituted pyridones (**1**) easily undergo singlet oxygenation to give exclusively the corresponding endoperoxides (**2**), which decompose to give pyridones again while liberating $^1O_2$ in high yields. Endoperoxides (**2**) have been shown to be a new type of chemical $^1O_2$ source, preparation and structural modification of which are very easy and the efficiency of $^1O_2$ liberation from which is high. Finally, it should be noted that a water-soluble and neutral $^1O_2$ generator, such as an amide derivative (**2g**), was also obtained.

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Notes and references

‡ Selected data for **2a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 4.42 (d, *J* = 15.3 Hz, 1H), 4.87 (d, *J* = 15.3 Hz, 1H), 5.08 (ddd, *J* = 5.8, 2.1, 0.6 Hz, 1H), 5.53 (ddd, *J* = 5.2, 2.1, 0.6 Hz, 1H), 6.71 (ddd, *J* = 7.8, 5.2, 2.1 Hz, 1H), 6.76 (ddd, *J* = 7.8, 5.8, 2.1 Hz, 1H), 7.19–7.24 (m, 2H), 7.28–7.39 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 46.9, 78.0, 83.2, 127.8, 127.9, 128.6, 128.8, 134.2, 135.1, 167.9 ppm; IR (KBr): 3089, 3031, 2932, 1691, 1426, 1350, 1158 cm^{-1}; Mass (EI, %): 217 (M^+, 25), 201 (70), 185 (76), 184 (34), 106 (34), 91 (100), 65 (20).

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§ When an endoperoxide (**2**) (1.5×10^{-2} M) and a dihydrofuran (**3**) (3.0×10^{-3} M) were heated in $CDCl_3$ for 2 h, a dioxetane (**6**) was produced in 12–56% yield.

¶ The reaction was carried out in an NMR sample tube without stirring.

|| As Merrifield's resin, 1% cross-linked polystyrene (200–400 mesh, 1.2 mmol Cl^-/g) was used. The 2-pyridone unit was estimated to be supported nearly quantitatively on the polymer from the difference between the pyridone used initially and that recovered.

** Completion of singlet oxygenation was checked by monitoring the increase of the C=O peak (1710 cm^{-1}) due to endoperoxide of pyridone and disappearance of the C=O peak (1661 cm^{-1}) due to *N*-substituted 2-pyridone for the IR spectrum.

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