Theoretical Study on the Position of Protonation of Benzodixanthene Endoperoxide and its Analogs

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Colorless endoperoxide (**1a**) of benzo[1,2,3-*kl*:4,5,6-*k'l'*]dixanthene (**2a**) changes into colored **2a** in the presence of acid at room temperature. Interaction between **1a** and acid was estimated using the AM1 molecular orbital calculation. The calculation shows that **1a** reacts with a proton more easily at an endo oxygen atom than at a xanthene oxygen atom, and that the protonated species goes through a carbocation (**4a**) to give colored **2a**. In order to propose novel functional dyes, which change their color more sensitively by the addition of acid, we studied the interaction between protons and the endoperoxides containing nitrogen (**1b**) or sulfur (**1c**) instead of oxygen. Nitrogen analog **1b** is a hypothetical molecule. The calculated proton affinity of **1b** or **1c** at peripheral heteroatoms was about 34 kcal mol⁻¹ greater than that of **1a**. The deoxygenation of endoperoxide (**1**) to give **2** is expected to be accelerated by replacement of the peripheral heteroatoms. Replacement of the peripheral heteroatom from oxygen to nitrogen also showed larger proton affinity in case the protonation would take place at the endo oxygen. Such replacement of the peripheral atoms would be effective modification for the acceleration of color forming reaction because of their greater proton affinity.

Key Words: Molecular orbital calculation, AM1 method, Benzodixanthene, Endoperoxide, Proton affinity, Protonation, Functional dye, Color former, Deoxygenation

Introduction

Photooxidation of benzo[1,2,3-*kl*:4,5,6-*k'l'*]dixanthene (**2a**) using visible light produces colorless endoperoxide (**1a**), and **1a**

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returns to colored **2a** by refluxing in toluene[1,2]. Various derivatives of **2a** have been synthesized[3]. Recently, we found that **1a** changes to colored **2a** at room temperature in the presence of acid (Scheme 1)[4].

Scheme 1

The investigation of the functional dyes, which change their color sensitively by the addition of acid, would be notable because they can be utilized as an indicator, for example, as a γ ray detecting system[4]. We used the molecular orbital method to calculate the interaction between endoperoxide and acid, and designed the sensitive endoperoxide analogs containing nitrogen (**1b**) or sulfur (**1c**)[5] instead of oxygen. Nitrogen analog **1b** is a hypothetical molecule only used for calculation.

The possible reactions from **1** to **2** in the presence of acid are summarized in Scheme 2.

Method

The initial structures of **1a-c** were built using the MM2 calculation[6,7] in the Chem 3D software[8]. Initial

Scheme 2 (a: X = O, b: X = NH, c: X = S)

geometry of protonated species such as **3** or **5** was assumed to have O-H bond length of 1.1 Å, H-O-C bond angle of 109.48° and H-O-C-C dihedral angle of 120°. The structure was optimized using the AM1[9] method in the Win-MOPAC 97[10] on a personal computer. The structural optimization of the protonated species was carried out with the key words, EF, Precise, and charge = +1 or +2.

Results and Discussion

Protonation to 1a

In order to confirm the reaction route, we have compared the heat of formation of protonated species **3a** with that of **5a**. To build up the geometry of **3a** or **5a** under the conditions where the H-O-C bond angle is fixed to 109.48°, two isomers were considered. These are **3a-1** and **3a-2**, or **5a-1** and **5a-2**, respectively, as shown in Scheme 3. For **3a-1** and **3a-2**, the configuration of the chirality center at the protonated oxygen is R for **3a-1** and S for **3a-2**. For **5a-1** and **5a-2**, the configuration of the chirality center at the protonated oxygen is R for **5a-1** and S for **5a-2**.

The protonated species at the peripheral position, **5a-1** and **5a-2** showed only a small geometrical change after the geometrical optimization. On the other hand, the protonated species at endo position, **3a-1** and **3a-2** showed a drastic change in its geometry to give carbocation **4a** as shown in Scheme 4.

In the course of geometrical optimization of **3a-1** and **3a-2**, the bond between the protonated oxygen atom and the bridgehead carbon was cleaved. The geometry of **4a**, which was obtained from geometrical optimization of

3a-1, is shown in Figure 1. *Ab initio* calculation (HF/3-21G) gave a carbocation structure similar to that from AM1 calculations. The structures with a hydroperoxy moiety have been obtained in the ene-reaction with singlet oxygen[11] or in the oxidations of endoperoxide in water[12].

Figure 1. Optimized geometry of **4a**

The calculated heat of formation of **4a** was much smaller than that of **5a** (Table 1). Thus, **1a** would be protonated at an endo oxygen more easily than at a peripheral oxygen, and the compound **4a** may be favored at this stage.

Table 1. Heats of formation, ΔH_f (kcal mol⁻¹) of **1a** and its protonated species, **4a** and **5a**, calculated using AM1 MO method.

Compound	Heat of formation (ΔH_f)	$\Delta\Delta H_f$
1a	92.28	
4a	229.27	
5a-1, 5a-2	284.16, 284.23	0.07

Two values of heat of formation shown in the column of Table 1 for **5a** correspond to the isomers, **5a-1** and **5a-2**, respectively. The difference in the heat of formation between the two isomers of **5a** ($\Delta\Delta H_f$) was 0.07 kcal mol⁻¹. Thus, the difference in heat of formation was so small that we dealt with only one of the isomers in this paper.

Equation(1) shows that the protonated **4a** reacts with chloride anion when **1a** reacts with hydrochloric acid. The reaction would easily produce the colored compound **2a** and oxygen exothermally.

However, the coloring reaction of compound **1a** with small amount of acid proceeds so slowly that novel endoperoxides, which are more sensitive to acid, have been needed for the γ -rays dosimeter.

In order to promote the coloration to be more rapid, we designed the replacement of the xanthene oxygen atoms of **1a** with nitrogen or sulfur atoms with the expectation of easier protonation to the endo oxygen or the peripheral position of the endoperoxides to facilitate the easy deoxygenation. We investigated the proton affinities[13] of compounds **1b** and **1c** in Scheme 3 using the AM1 method.

Effect of replacement of peripheral heteroatoms

As the heats of formation cannot be directly compared among molecules constructed from different components, the effect of the replacement of the heteroatoms was compared using proton affinity. Proton affinity of fundamental molecules has been calculated using various MO methods [13]. The proton affinity of a compound X which gives XH^+ by protonation, ($\text{PA}(\text{X} \rightarrow \text{XH}^+)$), was estimated by the equation (2) using the heat of formation calculated by semi-empirical MO method such as AM1,

$$\text{PA}(\text{X} \rightarrow \text{XH}^+) = -\Delta H_f(\text{XH}^+) + \Delta H_f(\text{H}^+) + \Delta H_f(\text{X}) \quad (2)$$

where $\Delta H_f(\text{X})$ and $\Delta H_f(\text{XH}^+)$ are heats of formation of compound X and its protonated species XH^+ , respectively. Heat of formation of a proton, $\Delta H_f(\text{H}^+)$ is the electronic energy of 1s orbital, 313.51 kcal mol⁻¹. The results calculated using this equation (2) are shown in Table 2.

Table 2. Proton affinities, PA (kcal mol⁻¹) of **1a** - **c** to give **4a** - **c** or **5a** - **c** calculated using AM1 MO method.

	PA (1 -> 4)	PA (1 -> 5)
a (X = O)	178.7	121.6
b (X = NH)	189.5	156.3
c (X = S)	178.5	155.8

The calculated proton affinities of **1b** or **1c** at peripheral heteroatoms to give **5b** or **5c** were about 35 kcal mol⁻¹ larger than that of **1a** to give **5a** due to the replacement of the peripheral heteroatoms from oxygen atoms to nitrogen or sulfur atoms. On the other hand, the proton affinities of **1b** to give **4b** showed the 11 kcal

mol⁻¹ larger values than those of **1a** or **1c** to give **4a** or **4c**.

We compared the hypothetical protonated species **3a-c** and **5'a-c** to consider to which heteroatoms proton would approach. The optimization of **3a-c** and **5'a-c** are carried out only around the additional proton atom. They might correspond to the early stage in protonation before optimized structures **4a-c** and **5a-c**, respectively. The input data for AM1 calculations of **3a-c** and **5'a-c** were prepared from a free proton and the optimized structure of **1a-c** which have been fixed through the SCF calculations. The results are shown in Table 3.

Table 3. Proton affinities^{a)} (kcal mol⁻¹) of **1a** - **c** to give **3a** - **c** and **5'a** - **c** calculated using AM1 MO method.

	PA(1 -> 3)	PA(1 -> 5')	$\Delta\text{PA}[(\mathbf{1} \rightarrow \mathbf{3}) - (\mathbf{1} \rightarrow \mathbf{5'})]$
a	133.6	115.8	17.8
b	140.3	149.6	-9.3
c	134.2	155.1	-20.9

a) the geometry of the endoperoxide moiety was fixed.

The calculation indicated that the benzodioxanthene endoperoxide **1a** would have the selectivity in proton addition to give **3a** as the positive value was obtained in ΔPA . But **1b** and **1c** showed easier protonation at peripheral heteroatoms to give **5b** and **5c** than **3b** and **3c** as the negative values were obtained in ΔPA . Deoxygenation of **5** to give the dye **2** must take place more easily than in case of **4**. To make sure that the deoxygenation of **5b** would take place more easily than that of **1b**, the transition states of deoxygenating process were calculated. The results are shown in Tables 4 and 5.

Table 4. Energies in transition state TS and $\Delta E(\mathbf{1} \rightarrow \text{TS})$ values(kcal mol⁻¹) of the deoxygenating reaction of **1** to give **2** and O₂.

	1	TS	2 + O ₂	$\Delta E(\mathbf{1} \rightarrow \text{TS})$
a	92.3	116.6	79.5	24.3
b	151.4	175.2	139.6	23.8
c	149.0	175.2	140.8	26.2

Table 5. Energies in transition state TS and $\Delta E(\mathbf{5} \rightarrow \text{TS})$ values(kcal mol⁻¹) of the deoxygenating reaction of **5** to give **8** and O₂.

	5	TS	8 + O ₂	$\Delta E(\mathbf{5} \rightarrow \text{TS})$
a	284.2	306.5	264.1	22.3
b	308.6	330.2	290.7	21.6
c	306.9	330.2	290.8	23.3

Table 4 shows the transition energies (ΔE) of **1** to give **2** and O_2 , and Table 5 shows those of **5** to give **8** and O_2 , respectively. The transition energies (ΔE) show similar values in spite of the difference in X. The ΔE (**5** $\rightarrow$ TS) were 1 - 3 kcal mol⁻¹ smaller than ΔE (**1** $\rightarrow$ TS). The difference is rather small. It suggests that the coloring reaction to give dyes would not be accelerated so much by the protonation at peripheral heteroatom X, as the coloring reaction of **1a** at 100 °C would become to take place at room temperature by the protonation.

Protonation to 5

The further protonation at peripheral or endo position of **5a-c** produces **6a-c**, **9a-c** or **10a-c**. Proton affinities of **5a-c** to give **6a-c**, **9a-c** or **10a-c** were calculated by the same manner with **1a-c**. **9a-c** and **10a-c** also showed the drastic geometrical change to **11a-c** and **12a-c**, respectively (Scheme 5).

The calculated results are shown in Table 6. The proton affinities of **5a-c** at a peripheral heteroatom to give **6a-c** were 47 – 55 kcal mol⁻¹ smaller than those of **1a-c** to give **5a-c**. The proton affinities of **5a-c** at an endo oxygen to give **12a-c** were 60 – 62 kcal mol⁻¹ smaller than those of **1a-c** to give **4a-c**. So, the protonation at a peripheral heteroatom would take place easier than those at an endo oxygen in **5a-c** compared with **1a-c**.

Table 6. Proton affinities (kcal mol⁻¹) of mono-protonated species (**5a-c**) to give **6**, **11** and **12** calculated using AM1 MO method.

	PA (5 $\rightarrow$ 6)	PA (5 $\rightarrow$ 11)	PA (5 $\rightarrow$ 12)
a	68.1	93.4	115.6
b	109.6	96.3	126.5
c	102.6	93.8	118.3

Conclusion

Benzodioxanthene endoperoxide **1a** was shown to react with proton at endo oxygen more easily than at xanthene oxygen from the calculation of proton affinity using the AM1 method. We have designed the nitrogen analog **1b** and sulfur analog **1c**. The proton affinities of **1b** and **1c** at peripheral heteroatoms became about 34 – 39 kcal mol⁻¹ larger than that of **1a**. The proton affinity of **1b** at the endo oxygen showed larger value than that of **1a** or **1c**. The transition energies ΔE (**5a-c** $\rightarrow$ TS) were 1 - 3 kcal mol⁻¹ smaller than ΔE (**1a-c** $\rightarrow$ TS). The coloring reaction to give dyes by the protonation at the endo oxygen of **1b** would be accelerated by the replacement of the peripheral heteroatoms to nitrogen. The proton affinity would be important to accelerate the deoxygenation to give **2**.

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ベンゾ[1,2,3-*kl*:4,5,6-*k'l'*]ジキサンテンエンドペルオキシド 類縁体のプロトン化物に関する理論化学的研究

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酸を添加することによりエンド酸素が脱離し着色するベンゾ[1,2,3-*kl*:4,5,6-*k'l'*]ジキサンテンエンドペルオキシド(1a)とその窒素類縁体(1b)またはイオウ類縁体(1c)について, AM1分子軌道法計算によりプロトンとの反応性, および, 色素骨格の周辺部に位置するヘテロ原子の違いが脱酸素反応に与える影響について検討した. まず, 酸素類縁体(1a)については, エンド酸素のプロトン親和性が色素部位の酸素のプロトンの親和性に比べて大きく, エンド酸素へのプロトン化によって生成する中間体 4a を経て色素体に分解することが推定された. しかし, その反応が実験的に遅いことから, 色素部位のヘテロ原子を硫黄や窒素に換えることによる効果をシミュレートした. 色素部位のプロトン親和性は大きくなり, また, そのヘテロ原子にプロトンが付くことにより, 酸素の脱離反応の活性化エネルギーが軽減され, 酸素の脱離がおこり易くなることが計算により示唆された. 一方, 特に窒素のとき, 4 を経由するエンド酸素へのプロトン化反応が有利であった. これらのことにより周辺部のヘテロ原子を酸素から窒素や硫黄に変換することにより, エンドペルオキシドの酸との着色反応を促進できると期待できる. 酸をトリガーとする新しい機能性色素を見出す指導原理になると考えられる.

キーワード: 半経験的分子軌道法計算, AM1法, ベンゾジキサンテン, エンドペルオキシド, プロトン親和性, プロトン化物, 機能性色素, カラーフォーマー, 脱酸素反応

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