Improvement of chemical stability of conjugated dienes by chlorine substitution

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Graphical Abstract

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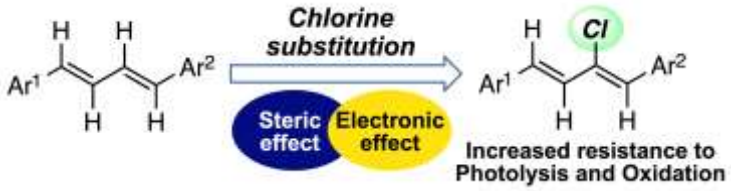

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ABSTRACT

Conjugated systems have versatile utilities in various fields including organic synthesis, pharmaceutical development, and material science. Such systems take advantage of their properties, which include their unique reactivity, relatively rigid structures, and low HOMO-LUMO gap energies. Their utility and the handling of conjugated systems however are both limited by excessively high photosensitivity and reactivity. We now report a novel molecular approach to the improvement of the chemical stability of the acyclic conjugated system against the photolysis and oxidation reactions simply by introduction of a chlorine atom into the conjugated system. Systematic studies of substrates with various substituents reveals that the improved chemical stability is based on the additive effects of the steric and electronic properties of the chlorine atom substituent.

1. Introduction

Conjugated systems are frequently structural components of synthetic intermediates,[1] chelating ligands,[2] and bioactive compounds[3] including natural products and pharmaceuticals, and optically functional materials. This is a consequence of their unique reactivities, relatively rigid and stable structures, and the decreased molecular energy difference between the HOMO and LUMO forms (the HOMO-LUMO gap) that can allow absorbance of light of longer wavelengths. Despite the importance of these compounds, their higher reactivity and photosensitivity has reduced their utility in the development of novel functional molecules. This is a problem particularly for pharmaceuticals containing acyclic conjugated systems, whose physical and chemical properties can be changed by their exposure to light, potentially resulting in reduced efficacy or unexpected toxicity.[4,5] There are some methods with which to improve the photostability of compounds with conjugated system(s),[6] but essentially the only method to preserve them is through storage in nontransparent containers to protect them from light. Because of this, development of novel structure-based strategies to increase the chemical stability of photosensitive pharmaceuticals is necessary.

As part of our research program aimed at exploring the potentials of haloalkenes in drug discovery,[7] we speculated that the halogen substitution of conjugated systems should increase the chemical stability of conjugated compounds as a result of the steric and electronic effects of the halogen atom.

In this paper, we describe an investigation of the effect of substituents on the chemical stability of substituted alkene-conjugated compounds against photolysis and oxidation reactions (Figure 1). Our study has revealed that the chemical stability of the chloroalkene-conjugated acyclic compounds against photolysis and oxidation reactions is >10-fold greater than that of the corresponding unsubstituted compounds. To the best of our knowledge, the potential ability of the chloroalkene moiety to increase the chemical stability of conjugated systems has not been reported previously.

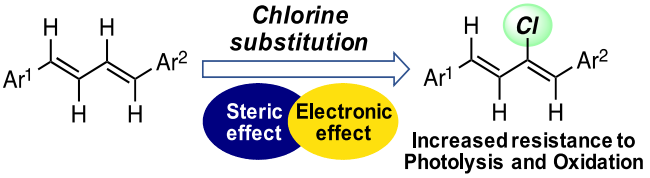
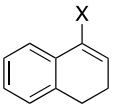


Figure 1. Chlorine substitution strategy for increased chemical stability.

2. Results and Discussion

In order to optimize the substituent on the alkene moiety, 4-substituted 1,2-dihydronaphthalene was selected as a model substrate with a relatively simple structure. Since oxygen takes an active part in the photodegradation process,[6e,8] the oxidation potentials (E_{Ox}) of 1,2-dihydronaphthalene were investigated on a platinum electrode in DMF (Table 1). As expected, the oxidation potential of 1,2-dihydronaphthalene (**1a**) was affected by the electronic properties of the 4-substituents.[9] The oxidation potential of 4-methyl-1,2-dihydronaphthalene (**1b**)[10] with the electron-donating methyl group was +1.80 V, which was lower than that of 1,2-dihydronaphthalene (**1a**) (+1.88 V). On the other hand, the oxidation potentials of 1,2-dihydronaphthalene derivatives (**1c**),[11] (**1d**)[12] and (**1e**)[13] with electron-withdrawing groups that can reduce the electron density range from +2.27 to +2.49 V, which is higher than the oxidation potential of **1a**, indicating that introduction of an electron-withdrawing group can render the compound less susceptible to oxidizable. The oxidation potential of 4-chloro-1,2-dihydronaphthalene (**1d**) is higher than that of 4-trifluoromethyl-1,2-dihydronaphthalene (**1e**), in spite of the lower electron-withdrawing ability of the trifluoromethyl group, suggesting that the increased oxidation potentials are not critically dependent on the electron-withdrawing ability of the substituents is not critically important to the increased oxidation potentials. It also suggests that the introduction of a chlorine substituent to a conjugated compound could improve the compound's stability with respect to oxidation. Thus, the oxidative stability of the 1,2-dihydronaphthalenes (**1a, 1c** and **1d**) was assessed by examining their reaction with excess 3-chloroperoxybenzoic acid (*m*-CPBA) in MeCN.[14] The oxidation reaction of **1a** follows a single-exponential decay as a trendline with the time to reach 50% conversion (t_{50}) for oxidation of **1a** of 3.0 min. As expected, introduction of the fluorine and chlorine atoms resulted in the increase of the stability to oxidation. In particular, the value of t_{50} for oxidation of **1d** is 30.1 min, more than 10 times longer than that of **1a**. Thus, the introduction of a chlorine to the conjugated compound appears to provide a protective effect against the oxidative degradation of the conjugated compound.

Table 1. 4-Substituent effects of 1,2-dihydronaphthalenes (**1a-e**) on oxidation potentials and oxidation stability.



Compound	X	σ [a]	E_{Ox} (V) [b]	t_{50} (min) [c]
1a	H	0	1.88	3.0
1b	CH_3	-0.17	1.80	n.d. [d]
1c	F	0.06	2.27	5.7
1d	Cl	0.23	2.49	30.1
1e	CF_3	0.54	2.30	n.d. [d]

[a] σ = Hammet constant of the substituent on a benzoic acid derivative.
[b] The working electrode and the reference electrode were platinum. Dihydronaphthalene derivatives were dissolved in DMF and further diluted in supporting electrolyte, consisting of a tetrabutylammonium hexafluorophosphate (substrate: 1.0 mM, supporting electrolyte: 0.5 M).
[c] Time to reach 50% conversion for oxidation reaction by an excess amount of *m*-CPBA in MeCN.
[d] n.d. = not determined.

Table 2. Substituent effects on optical properties of 1,2-dihydronaphthalenes (**1a-e**).

Compound	Substituent	λ_{max} (nm) [a]	ε_{max} ($M^{-1}cm^{-1}$) [b]
1a	H	260	9,500
1b	CH_3	260	8,600
1c	F	258	9,500
1d	Cl	262	6,400
1e	CF_3	258	9,000

[a] Absorption maxima wavelength in EtOH (0.1% DMSO).
[b] Molar extinction coefficient at the absorption maxima.

The optical properties of 4-substituted 1,2-dihydronaphthalenes (**1b-e**) were compared with those of 1,2-dihydronaphthalene (**1a**). Amongst the five compounds, no significant difference was observed in the absorption maximum wavelength (λ_{max}). On the other hand, a difference was observed in the molar extinction coefficient (ε_{max}), *i.e.* how strongly a substance absorbs light. While the values of the ε_{max} for **1b**, **1c**, and **1e** were almost equal to that of **1a**, the ε_{max} of **1d** is reduced to about 70% of that of **1a**. These results suggested that in addition to increasing its stability to oxidation, introduction of a chlorine can diminish the photosensitivity of a compound.

Having recognized the promising potentials of chlorine atom substitution, we selected the chloroalkene moiety for further study of the chemical stability of acyclic conjugated systems. The acyclic conjugated system chosen for the study is the related structure of PBB3, which was developed for tau imaging and has a high binding affinity with the aggregates of hyperphosphorylated tau proteins.[15] One of the shortcomings of a

Scheme 1. Synthetic route to acyclic conjugated compounds **4a-d**.

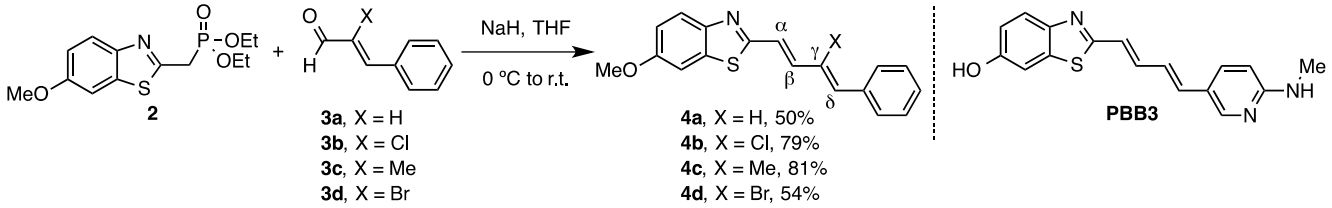
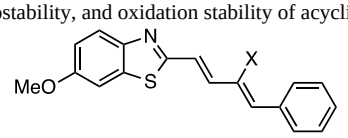


Table 3. Substituent effects on optical properties, photostability, and oxidation stability of acyclic conjugated compounds **4a-d**.



Compound	X	E_s [a]	λ_{max} (nm) [b]	ε_{max} ($M^{-1}cm^{-1}$) [c]	Photostability	Oxidation stability
					t_{50} (sec) [d]	t_{50} (min) [e]
4a	H	0.00	367	52,400	36	25.7
4b	Cl	-0.97	339	22,200	438	347
4c	CH_3	-1.24	357	37,900	244	n.d. [f]
4d	Br	-1.16	363	34,200	28	n.d. [f]

[a] E_s = Taft steric parameter[18]
[b] Long wavelength absorption maxima in EtOH (0.1% DMSO).
[c] Molar extinction coefficient at the absorption maxima.
[d] Time to reach 50% conversion for photolysis reaction at 350 nm irradiation in MeCN/H_2O (v:v = 1:1).
[e] Time to reach 50% conversion for oxidation reaction by an excess amount of *m*-CPBA in MeCN.
[f] n.d. = not determined.

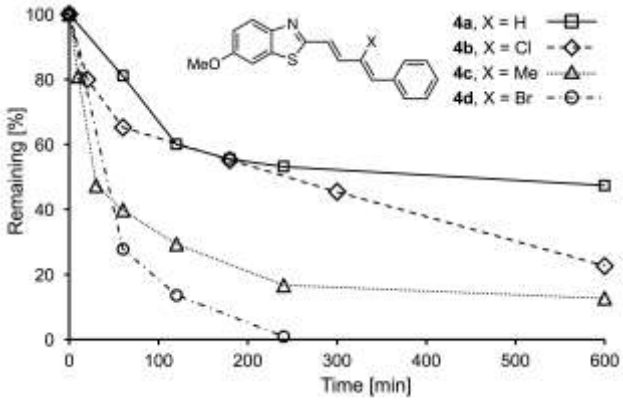


Figure 2. Time courses of the photolysis reaction of **4a-d.**

PBB3-derived ^{11}C-radioligand is its high photosensitivity: the radiochemical purity of ^{11}C-PBB3 decreased to about 77% after exposure to fluorescent light for only 1 min.[15b] The tested conjugated compounds (**4a-d**) with a phenyl group in place of the pyridine ring in PBB3 were prepared from the phosphonate (**2**)[16] (Scheme 1). Treatment of **2** with NaH and *trans*-cinnamaldehydes (**3a**, **3b**[17]) gave the corresponding conjugated compounds (**4a**, **4b**) in 50% and 79 % yields, respectively. In order to determine the effect of the chlorine atom substitution, compounds **4c** and **4d**, with a methyl group or a bromine atom both similarly bulky as a chlorine atom, were synthesized in 81% and 54% yields, respectively.

The optical properties and the stability against photolysis and oxidation of **4a-d** were examined (Table 3). In contrast to the results from the 4-substituted 1,2-dihydronaphthalenes, introduction of a γ-substituent into a conjugated diene system results in a blue shift of the absorption maxima (λ_{max}), implying a somewhat non-planar structure of the conjugated systems. The absorption maxima (λ_{max}) of **4b** with a chlorine substituent shifted from 366 nm for **4a** to 339 nm for **4b**. Interestingly, the γ-chloro substitution effect on the molar extinction coefficient (ε_{max}) at the maximum wavelength was more significant than that in the 4-substituted 1,2-dihydronaphthalene (**1d**). The ε_{max} of **4b** is 22,200 $M^{-1}cm^{-1}$, which is much smaller than that of the methyl-substituted compound **4c** (ε_{max} = 37,900 $M^{-1}cm^{-1}$) or the bromine-substituted compound **4d** (ε_{max} = 34,200 $M^{-1}cm^{-1}$) and corresponds to approximately 40% of that of the unsubstituted compound **4a** (ε_{max} = 52,400 $M^{-1}cm^{-1}$). These findings strongly suggest that a chlorine atom, when compared with a methyl group or a bromine atom, is more effective at reducing the photosensitivity of the conjugated compounds.

The photosensitivity of compounds **4a-d** under photolysis in a 1:1 mixture of MeCN and H_2O at 350 nm was evaluated. Figure 2 shows the time course of photolysis of **4a-d** in terms of the consumption of the starting materials and reveals that rapid

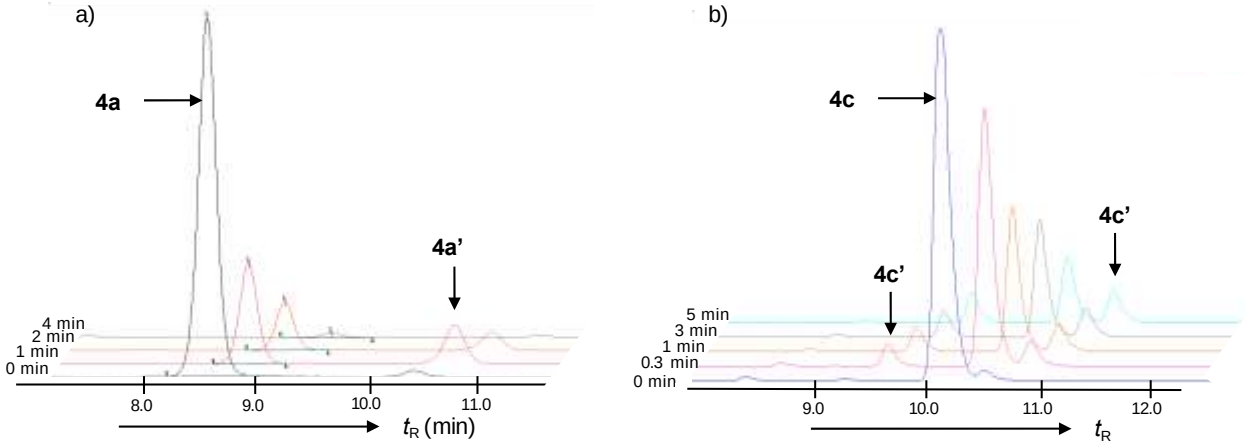


Figure 3. (a) HPLC analysis for the photolysis reaction of **4a** (X = H) in MeCN/H_2O (v:v = 1:1). (b) HPLC analysis of the photolysis reaction of **4c** (X = Me) in MeCN/H_2O (v:v = 1:1).

photolysis of **4a**, **4c** and **4d** occurred in 50 seconds and was followed by slow photolysis. On the other hand, photolysis of **4b** with a chlorine substituent proceeded more slowly than that of other compounds, and the consumption of **4b** became much slower still after 120 seconds. The time to reach 50% conversion (t_{50}) for photolysis of **4b** is 438 seconds, which is much longer than that of other tested compounds - t_{50} = 36 s for **4a**, 244 s for **4c**, and 28 s for **4d**.[19] Thus, the photochemical stability of **4b** is >10-fold higher than that of the reference compound (**4a**). In addition, improvement of the photochemical stability of compound **4c** with an electron-donating methyl substituent was also observed: the stability of **4c** is about 7-fold higher than that of **4a**, but 1.8-fold lower than that of **4b**. On the other hand, a rapid photolysis reaction was observed with compound **4d** which has a bromine substituent on the conjugated diene; the stability of **4d** is about 1.3-fold lower than the reference compound **4a**. Overall, chlorine atom substitution on the conjugated system resulted in a notable increase of the photochemical stability of **4b**.

The oxidation stability of **4b** with *m*-CPBA was also investigated under the conditions similar to those used with the 1,2-dihydronaphthalenes. The value of t_{50} for oxidation of **4b** is 347 min, which is >13-fold longer than t_{50} for **4a** (t_{50} = 25.7 min), showing that chlorine atom substitution on the conjugated system can also increase the stability of **4b** to oxidation. This is consistent with the results from the 1,2-dihydronaphthalenes (Table 1), indicating that the electronic properties of the chlorine atom are involved in the improved chemical stability of **4b**.

The order of photochemical stability found in the photolysis reaction is: compound **4b** (X = Cl) is most stable, followed by **4c** (X = CH_3), **4a** (X = H), and **4d** (X = Br). The improved stability of **4c** resulting from its methyl substituent can be explained by steric effects which indicate that the conjugated structure of **4c** would be non-planar around the methyl substituent by the steric effects. The steric bulk of the chlorine atom (E_s = **–**0.97) is similar to that of the methyl group (E_s = **–**1.24), suggesting that the steric effects of the chlorine atom substituent in **4b** could be responsible for the improved photochemical stability. In terms of the electronic properties, the methyl group is an electron-donating group (σ = –0.17) and the chlorine atom is electron-withdrawing group (σ = 0.23). This electron-withdrawing ability of the chlorine atom should further improve the photochemical stability. Taken together, these considerations show that both steric and electronic effects of the chlorine substituent on the conjugated system can contribute to the significantly improved photochemical stability of **4b**.

Next, we became interested in the degradation pathways of **4a-d**. Figures 3 and 4 show the HPLC chart of the photolysis reactions of compounds **4a-d**. HPLC analyses from the photolysis reaction of the unsubstituted compound **4a** showed that the peak corresponding to **4a**, with a retention time of 8.7 min disappeared with increasing irradiation time and a new peak, with a retention time of 10.3 min was generated simultaneously. LC-MS analysis revealed that the mass number of the peak with a retention time of 10.3 min was same with that of **4a**, suggesting the generation of the stereoisomer of **4a** (Figure 3a). When the irradiation time was further increased, the new peak corresponding to the stereoisomer of **4a** disappeared. Other byproducts were not detected under these HPLC conditions. These results indicate that the photolytic degradation of **4a** proceeds through photoisomerization of the conjugated diene. A similar result was obtained with the photolysis of **4c** with a methyl substituent on the conjugated system (Figure 3b). On the other hand, HPLC analysis of the photolysis reaction of compound **4b** with a chlorine substituent however, showed that the peak corresponding to **4b** with a retention time of 9.8 min decreased with increasing irradiation time, two new peaks being generated at the same time (Figure 4a). The peak generated with a retention time of 9.2 min corresponds to the structural isomer of **4b**. Interestingly, it was found that the peak generated with an approximate retention time of 8.5 min was the conjugated enyne product (**5**), which was isolated by preparative HPLC and whose structure was verified by NMR analysis, and IR spectroscopy and electrospray ionization-high resolution mass spectrometry.[20] A significant decrease in the reaction rate of **4b** after 120 seconds of irradiation suggests that the photoisomerization of the chloroalkene moiety of **4b** is reversible. Formation of the conjugated enyne product (**5**) was slower than that of **4b'**, indicating that the photolysis degradation of **4b** proceeds through the photoisomerization of the conjugated diene and is followed by oxidative dehydrochlorination to form the conjugated enyne system **5** (Figure 4c). A similar result was obtained from the photolysis of **4d** with a bromine substituent, and the photolysis reaction of **4d** was found to proceed more efficiently than that of

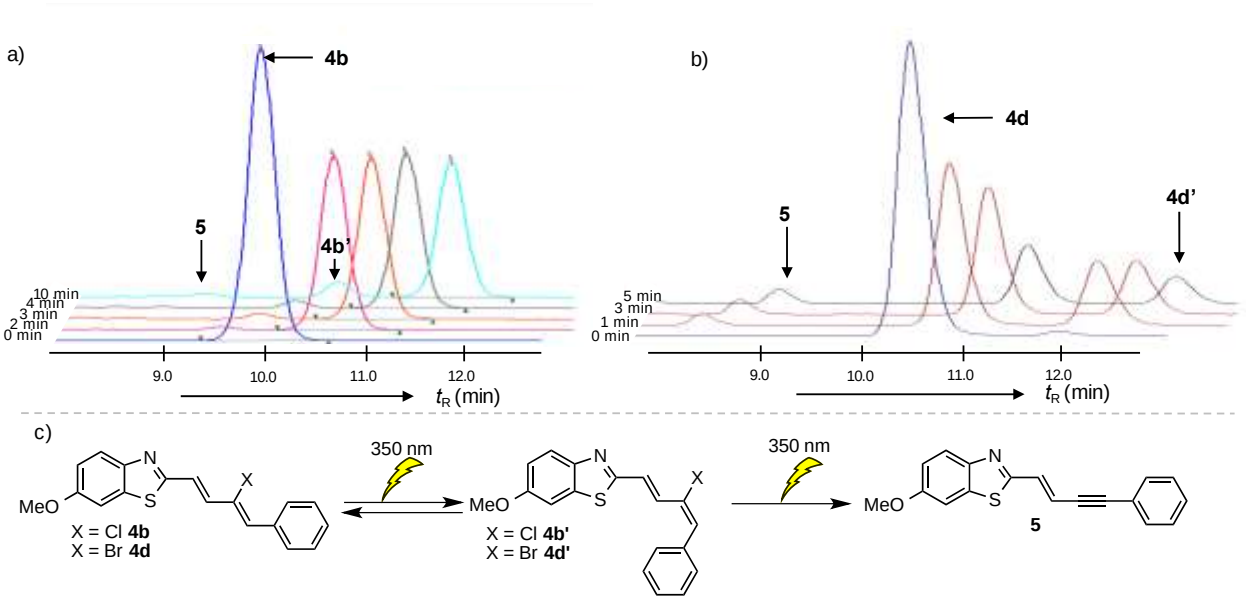


Figure 4. (a) HPLC analysis for the photolysis reaction of **4b** (X = Cl) in MeCN/H_2O (v:v = 1:1). (b) HPLC analysis of the photolysis reaction of **4d** (X = Br) in MeCN/H_2O (v:v = 1:1). (c) Possible mechanism of the photolysis reaction of **4b** and **4d**.

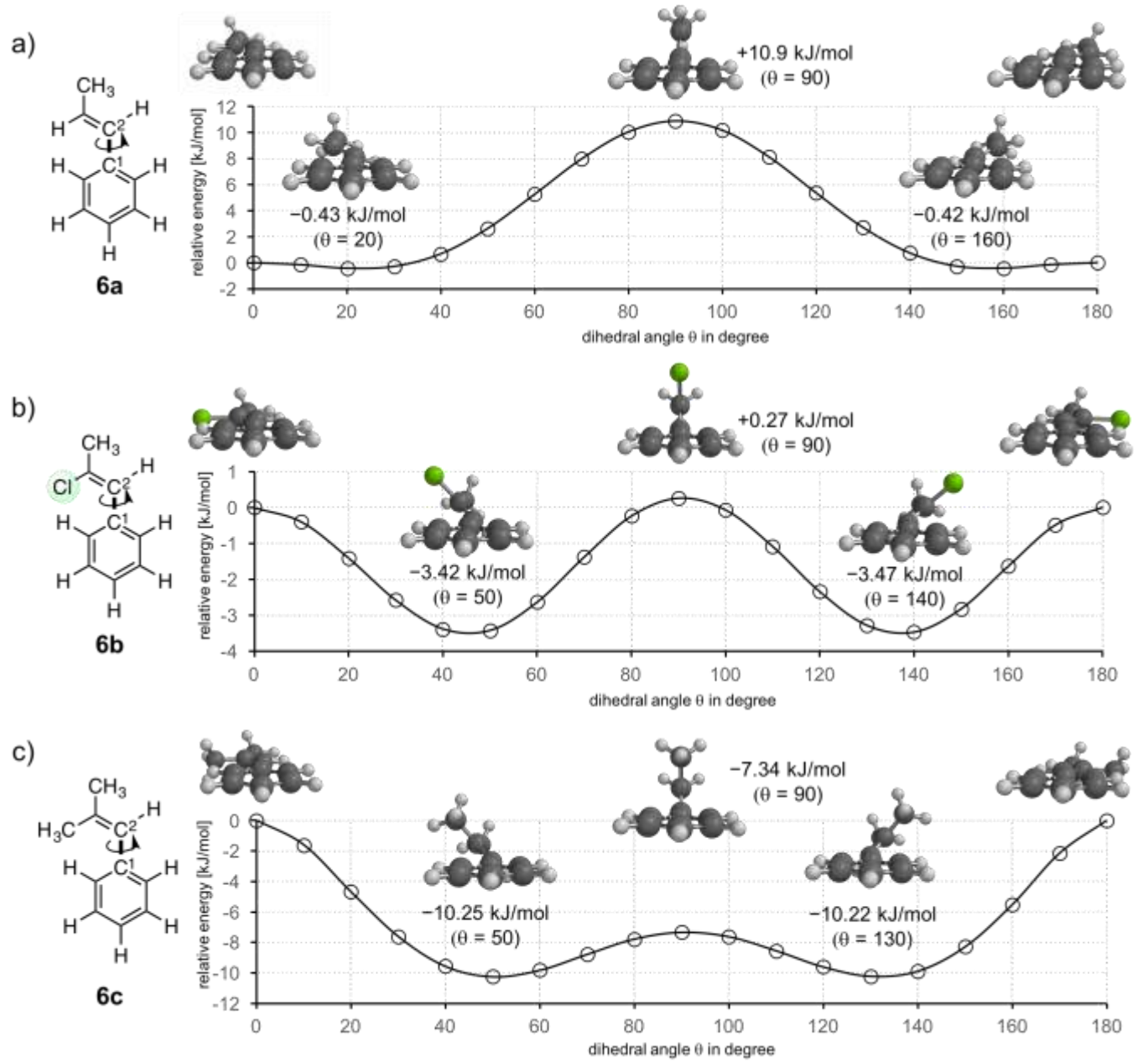


Figure 5. Energy level diagram of the C1-C2 bond. (a) (*E*)-β-methylstyrene **6a**. (b) (*Z*)-β-chloro-β-methyl-styrene **6b**. (c) β,β-dimethylstyrene **6c**. Energy profiles of **6a-c** were calculated by Spartan'10 program [HF/6-31* in vacuum].

the reference compound **4a** (Figure 4b). This is probably due to the bromine-derived heavy atom effect which promotes the rate of intersystem crossing, suggesting that the photolysis degradation of those compounds could occur *via* the triplet state.[21]

With the role of the chlorine atom substitution on the conjugated systems established, we sought to further clarify the conformational effects on the rotation of the C-C single bond with respect to the chlorine substituent. Thus, the rotational energy barriers of the C1-C2 single bond in (*E*)-β-methylstyrene **6a**, (*Z*)-β-chloro-β-methyl-styrene **6b**, and β,β-dimethylstyrene **6c** were investigated by energy profile calculations using Spartan'10. With (*E*)-β-methylstyrene (**6a**), the two conformations with dihedral angles 20° and 160° represent energy minima but their relative energy is almost as the same as that of the planar conformations (θ = 0° and 180°), whereas the conformation with dihedral angle 90° in which the benzene ring and the double bond are orthogonal, has the maximum energy. The value of the rotational barrier around the C1-C2 bond in **6a** is approximately 11 kJ/mol, and is comparable to that of the C-C bond of ethane at 25 °C (12 kJ/mol),[22] indicating that the C1-C2 bond in **6a** can rotate as easily as the C-C bond in ethane. In the case of (*Z*)-β-chloro-β-methyl-styrene (**6b**), the two conformations with dihedral angles 50° and 140° in which the *o*-H and Cl repulsion is slightly relieved are energy minima, whereas the conformation with a dihedral angle of 90° is the energy maximum. Interestingly, the rotational barrier in **6b** is lower than that in the unsubstituted compound **6a** - approximately 4 kJ/mol compared to 12 kJ/mol, indicating that the C1-C2 bond in **6b** allows essentially free rotation. These results probably reflect the ability of the chlorine substituent to destabilize the planar conjugated structure. Considering the result that the rotational barrier around the C1-C2 bond in **6c** with steric interactions is comparable to that of **6b**, electronic effects derived from the chlorine substituent would appear to be the dominant force responsible for the lower rotational barrier.

3. Conclusion

In summary, we have identified a new structure-based strategy of chlorine substitution to improve the chemical stability of

conjugated systems against photolysis and oxidation reactions. The utility of chloroalkene-conjugated systems in improving the photochemical stability is thought to arise not only from steric effects, which affects the planar structure of the conjugated system, but also from electronic effects, which lead to changed optical properties of the compound, including a much smaller molar extinction coefficient. The main advantage of such chloroalkene-conjugated systems lies in their simple chemical modification, allowing the application of this strategy to various molecules with acyclic conjugated system(s). These studies provide the basis for our future work which includes the development of novel photoresistant molecules for material science and pharmaceutical chemistry development. Efforts to extend this work to the development of the PBB3 derivatives with a chloroalkene-conjugated structure for bio-imaging of aggregated Tau protein are currently in progress.

4. Experiment Section

4.1 General methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under a nitrogen atmosphere, using commercially supplied solvents and reagents unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates which were visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin. Flash column chromatography was carried out using silica gel 60 N (Kanto Chemical Co., Inc.).

4.2 Characterization data

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker Biospin AVANCE III HD. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR 6300, and are reported in wavenumbers (cm^{-1}). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics compact (ESI-MS) spectrometers in the positive and negative detection mode.

4.3 HPLC conditions

For analytical HPLC, a YMC-Triart C18 column (4.6 × 250 mm, YMC CO., LTD., Kyoto, Japan) was employed with a linear gradient of MeCN containing 0.1% (v/v) TFA at a flow rate of 1 cm^3 min^{-1} an JASCO MD-2010 plus with PDA detection (JASCO corporation, Ltd., Tokyo, Japan) and a JASCO PU-980 (JASCO corporation, Ltd., Tokyo, Japan), and eluting products were detected by UV at 365 nm.

4.4 Experimantal procedure of conjugated compounds 4a-d

4.4.1 6-Methoxy-2-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)benzo-[*d*]thiazole (**4a**): To a stirred solution of the phosphonate **2** (947 mg, 3.00 mmol) in THF (10.7 mL) was added NaH (60% dispersion in mineral oil, 101 mg, 4.20 mmol) at 0 ºC under N_2 atmosphere. After being stirred at room temperature for 30 min, *trans*-cinnamaldehyde **3a** (348 µL, 2.76 mmol) was added. The mixture was stirred at room temperature for 12 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. After being diluted with CH_2Cl_2, the reaction mixture was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (6:1) gave the title compound **4a** as a yellow solid (440 mg, 50%): IR (ATR) ν 3056, 3026, 2999, 2959, 2935, 2831, 1750, 1595, 1487, 1460, 1433, 1319, 1261, 1227, 1060, 1026, 941, 830: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.84 (d, *J* = 15.5 Hz, 1H), 6.91 (d, *J* = 15.5 Hz, 1H), 6.98 (dd, *J* = 15.5, 10.5 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.23 (dd, *J* = 15.5, 10.5 Hz, 1H), 7.26–7.32 (m, 2H), 7.31–7.40 (m, 2H), 7.44–7.51 (m, 2H), 7.85 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 104.1, 115.6, 123.4, 125.6, 126.9 (2C), 127.6, 128.5, 128.8 (2C), 135.8, 136.6, 137.0, 137.1, 148.5, 157.9, 164.5; HRMS (ESI), *m/z* calcd for $C_{18}H_{16}NOS^+$ $[M+H]^+$ 294.0947, found 294.0947.

4.4.2 2-((1*E*,3*Z*)-3-Chloro-4-phenylbuta-1,3-dien-1-yl)-6-metho-xy-benzo[*d*]thiazole (**4b**): To a stirred solution of the phosphonate **2** (172 mg, 0.545 mmol) in THF (1.95 mL) was added NaH (60% dispersion in mineral oil, 30.6 mg, 0.765 mmol) at 0 ºC under N_2 atmosphere. After being stirred at room temperature for 30 min, *trans*-α-chlorocinnamaldehyde **3b** (83.0 mg, 0.498 mmol) was added. The mixture was stirred at room temperature for 9 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. After being diluted with CH_2Cl_2, the reaction mixture was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (5:1) gave the title compound **4b** as a yellow solid (129 mg, 79%): IR (ATR) ν 3057, 3006, 2955, 2925, 2875, 2837, 1599, 1554, 1484, 1457, 1433, 1319, 1261, 1221, 1060, 1026, 941, 827: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.97 (s, 1H), 7.10 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.33 (d, *J* = 15.2 Hz, 1H), 7.33 (d, *J* = 15.2 Hz, 1H), 7.33-7.45 (m, 4H), 7.75-7.85 (m, 2H), 7.93 (d, *J* = 9.0 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 104.1, 116.4, 123.2, 123.4, 128.5 (2C), 129.1, 129.5, 130.1 (2C), 133.6, 134.3, 135.5, 136.5, 146.9, 158.4, 164.0; HRMS (ESI), *m/z* calcd for $C_{18}H_{15}ClNOS^+$ $[M+H]^+$ 328.0557, found 328.0553.

4.4.3 6-Methoxy-2-((1*E*,3*E*)-3-methyl-4-phenylbuta-1,3-dien-1-yl)benzo[*d*]thiazole (**4c**): To a stirred solution of the phosphonate **2** (316 mg, 1.00 mmol) in THF (3.57 mL) was added NaH (60% dispersion in mineral oil, 56.0 mg, 1.40 mmol) at 0 ºC under N_2 atmosphere. After being stirred at room temperature for 30 min, *trans*-α-methylcinnamaldehyde **3c** (167 µL, 1.20 mmol) was added. The mixture was stirred at room temperature for 12 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl. After the reaction mixture was diluted with CH_2Cl_2, the mixture was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (5:1) gave the title compound **4c** as a yellow solid (249 mg, 81%): IR (ATR) ν 3054, 2993, 2925, 2851, 1760, 1723, 1602, 1487, 1457, 1437, 1319, 1258, 1225, 1053, 1022, 952, 827: ^{1}H NMR (400 MHz, CDCl3) δ 2.07 (s, 3H), 3.81 (s, 3H), 6.75 (s, 1H), 6.86 (d, *J* = 15.9 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.13–7.37 (m, 6H), 7.77 (d, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 55.8, 104.2, 115.5, 121.8, 123.3, 127.4, 128.3 (2C), 129.4 (2C), 135.0, 135.7, 136.1, 137.1, 142.2, 148.5, 157.9, 165.1; HRMS (ESI), *m/z* calcd for $C_{19}H_{18}NOS^+$ $[M+H]^+$ 308.1104, found 308.1108.

4.4.4 2-((1*E*,3*Z*)-3-Bromo-4-phenylbuta-1,3-dien-1-yl)-6-meth-oxybenzo[*d*]thiazole (**4d**): To a stirred solution of the phosphonate **2** (207 mg, 0.656 mmol) in THF (1.79 mL) was added NaH (60% dispersion in mineral oil, 30.6 mg, 0.77 mmol) at 0 ºC under N_2 atmosphere. After being stirred at room temperature for 30 min, *trans*-α-bromocinnamaldehyde **3d** (115 mg, 0.545 mmol) was added. The mixture was stirred at room temperature for 10 h The reaction was quenched with a saturated aqueous solution of NH_4Cl. After being diluted with CH_2Cl_2, the reaction mixture was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (4:1) gave the title compound **4d** as a yellow solid (100 mg, 54%): IR

(ATR) ν 2953, 2926, 2855, 1724, 1608, 1490, 1464, 1437, 1319, 1263, 1061, 1026, 941, 829: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.10 (dd, J = 9.0, 2.5 Hz, 1H), 7.27 (s, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.35 (s, 2H), 7.36–7.46 (m, 1H), 7.74–7.84 (m, 2H), 7.92 (d, J = 9.0 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 104.1, 116.5, 121.1, 123.1, 125.4, 128.4 (2C), 129.2, 130.0 (2C), 135.1, 135.4, 137.0, 138.0, 146.7, 158.4, 164.1; HRMS (ESI), *m*/*z* calcd for $C_{18}H_{15}BrNOS^{+}$ $[M+H]^{+}$ 372.0052, found 372.0044.

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Supplementary Material

This section contains the experimental details, and ^{1}H and ^{13}C NMR spectra. Supplementary data related to this article can be found at XXX.