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Novel asymmetric photodimerization reaction of coumarin derivatives bearing a chiral 2-oxazolidinone auxiliary†

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A novel asymmetric photodimerization reaction of coumarin derivatives bearing the (S)-4-benzyl-2-oxazolidinone auxiliary provides only the *syn*-head-to-tail (*syn*-HT) dimer with moderate diastereoselectivity (up to 75 : 25). The mechanism of complete *syn*-HT selectivity and moderate diastereoselectivity is proposed based on the result of density functional theory (DFT) calculation. The benzyl group of the (S)-4-benzyl-2-oxazolidinone auxiliary in combination with a Lewis acid exerts effective diastereofacial shielding of the reaction site.

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The photodimerization reactions of coumarin derivatives have been recognized as attractive photochemical transformation reactions in terms of their photophysical properties as well as their photochemical properties, from the theoretical point of view.¹ Recently, photodimerization reactions of coumarins have become increasingly important in several progressive research areas, *e.g.*, drug delivery by the use of coumarin-modified mesoporous silica MCM-41^{2a} and the use of coumarin-modified polymeric nanoparticles,^{2b,2c} chemical biology,^{2d} 3D cell culture,^{2e} photopatterning of ion gels,^{2f} reversible two-photon optical data storage,^{2g} nanolithography,^{2h} polyoxometalate-containing materials,²ⁱ single-chain nanoparticles,^{2j} gelators,^{2k} and optically active polymers.^{2l} Although [2 + 2] photodimerization reactions of coumarin derivatives are useful photochemical reactions, difficulties in controlling head-

to-head (HH)/head-to-tail (HT), *syn/anti*, enantio- and diastereoselectivity of the reactions in solution have prevented further improvement of the usefulness and understanding of the reaction. To overcome these issues, several methodologies for *syn/anti* and HH/HT selective [2 + 2] photodimerization reactions of coumarins in solution have been developed, *e.g.*, Lewis acid catalysis,³ supramolecular photocatalysis accomplished by the use of cyclodextrins,^{4a} hydrazine derivatives,^{4b} bisurea macrocycles,^{4c} cucurbit[8]uril,^{4d} taco-type host-guest complexes^{4e} and self-assembled monolayers of coumarin derivatives on gold.^{4f} For an enantioselective reaction, Tanaka and Fujiwara reported outstanding results of an asymmetric photodimerization of simple coumarin by the use of TADDOL derivatives which gave an *anti*-HT dimer with excellent enantiomeric excess (up to 96% ee).⁵ However, to the best of our knowledge, the methodology to synthesis a *syn*-HT dimer in a diastereoselective manner has yet to be demonstrated.⁶ Herein, we report a novel asymmetric [2 + 2] photodimerization of chiral coumarin-3-carboxamide which gives only *syn*-HT dimers along with moderate diastereoselectivity.

We initially conducted [2 + 2] photodimerization reactions of (S)-4-phenyl-3-(2-oxo-2H-chromene-3-carbonyl)-2-oxazolidinone (**1A**) in acetone, resulting in recovery of **1A** without any desired dimers, which could be caused by the incredibly poor solubility of **1A** (Table 1). Next, we tried to use (S)-4-isopropyl-3-(2-oxo-2H-chromene-3-carbonyl)-2-oxazolidinone (**1B**), which gave **2BE** and **2BF** as an inseparable mixture with good yield and the ratio of **2BE** to **2BF** as 55 : 45. X-ray crystallographic analysis provided a structure of 50 : 50 diastereomeric mixture of **2BE** and **2BF**, which revealed that the reaction had progressed in a *syn*- and HT-selective manner (Fig. 1). We also used (S)-4-benzyl-3-(2-oxo-2H-chromene-3-carbonyl)-2-oxazolidinone (**1C**) (entry 3) instead of **1B**.

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† Electronic supplementary information (ESI) available: Materials, experimental details, and characterization data. CCDC 1552472 (**1C**), 1885142 (**2BE** + **2BF**), 1484443 (**2CE**) and 1552473 (**2CF**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra00822e



As a result, solubility of the chiral coumarin and the diastereomeric ratio of dimers were improved to give **2CE** and **2CF** with the ratio of 63 : 37 in 99% yield. Photodimer **2CE** and **2CF** were separable. *syn*-HT structures of **2CE** and **2CF** were also successfully determined by X-ray crystallographic analyses. When the reaction was carried out in toluene (entry 4), *syn*-HT **2CE** and *syn*-HT **2CF** were obtained in excellent yield with the same diastereomeric ratio as the reaction in acetone (entry 3 *versus* entry 4). The yield of *syn*-HT **2CE** and *syn*-HT **2CF** was decreased by the use of α,α,α -trifluorotoluene ($\text{CF}_3\text{C}_6\text{H}_5$) as a reaction solvent, which was probably due to low solubility of **1C** in $\text{CF}_3\text{C}_6\text{H}_5$ (entry 5). Solubility enhancement of **1C** had a good impact on increasing the reaction rate by the use of CH_2Cl_2 , CHCl_3 and CH_3CN as reaction solvents, but decreased the diastereoselectivity as compared to the reaction in toluene (entries 6–8 *versus* entries 3 and 4). As far as we know, there is only one example of a non-photochemical reaction, which is the highly diastereoselective 1,3-dipolar cycloaddition reaction, by the use of a chiral oxazolidinone-functionalized substrate in the absence of Lewis acid as reported by Sibi and co-workers.⁷ We were intrigued by induction of moderate diastereoselectivity in the absence of a chelating agent Lewis acid. Therefore, we tried to add Lewis acid in an effort to improve diastereoselectivity by utilizing a chelation control agent.⁸ Regarding a role for the Lewis acid in [2 + 2] photodimerization reactions, Lewis and co-workers reported the [2 + 2] photodimerization reaction of

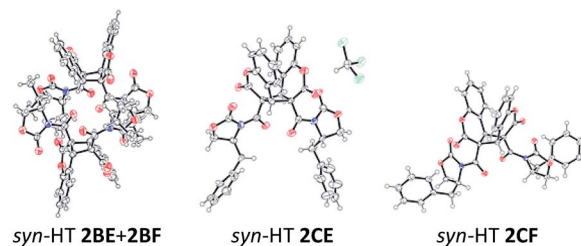
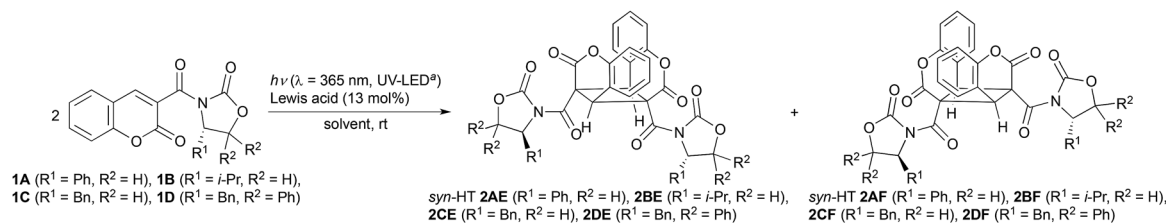


Fig. 1 ORTEP drawing of photodimers: the inclusion of chloroform was observed in *syn*-HT **2CE**.

achiral coumarin in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give the *syn*-HT dimer as a single product.³ In the search for a good chelating Lewis acid for 3-acyl-2-oxazolidinone derivatives, we tested $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ for the reaction of **1B** (entry 9).⁹ A non-coordination solvent toluene was used for the reaction. As a result, the reaction of **1B** was inhibited by the addition of Zn(II) salt to give **2BE** and **2BF** with recovery of **1B** (entry 9).

Interestingly, the reaction of **1C** in the presence of $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in toluene proceeded to achieve an improvement of yields and diastereomeric ratio of *syn*-HT dimers (**2CE** : **2CF** = 75 : 25, entry 10). The use of acetone as a reaction solvent and $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ as a Lewis acid diminished the yield of *syn*-HT **2CE** and *syn*-HT **2CF** (entry 11). The reaction of **1C** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in toluene showed a slightly improved diastereomeric ratio in comparison with the reaction

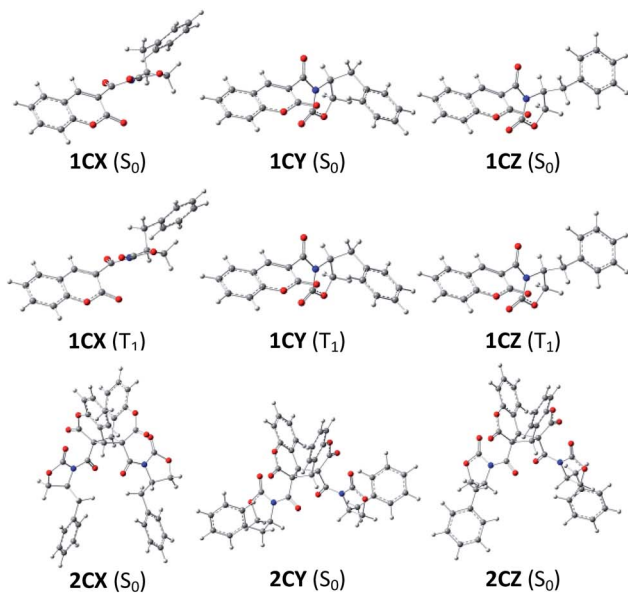
Table 1 [2 + 2] Photodimerization reactions of chiral coumarin-3-carboxamides



Entry	Coumarin	Solvent	Additive	Time/h	Yield ^b /%	Diastereomeric ratio ^c
1	1A	Acetone	No	48	0	— (2AE) : — (2AF)
2	1B	Acetone	No	48	83	55 (2BE) : 45 (2BF)
3	1C	Acetone	No	48	99	63 (2CE) : 37 (2CF)
4	1C	Toluene	No	48	90	63 (2CE) : 7 (2CF)
5	1C	$\text{CF}_3\text{C}_6\text{H}_5$	No	48	56	59 (2CE) : 41 (2CF)
6	1C	CH_2Cl_2	No	24	95	61 (2CE) : 39 (2CF)
7	1C	CHCl_3	No	24	96	58 (2CE) : 42 (2CF)
8	1C	CH_3CN	No	24	92	53 (2CE) : 47 (2CF)
9	1B	Toluene	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	96	24 ^d	70 (2BE) : 30 (2BF)
10	1C	Toluene	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	48	92	75 (2CE) : 25 (2CF)
11	1C	Acetone	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	48	72	75 (2CE) : 25 (2CF)
12	1C	Toluene	$\text{BF}_3 \cdot \text{OEt}_2$	48	90	70 (2CE) : 30 (2CF)
13	1C	Toluene	$\text{Mg}(\text{ClO}_4)_2$	48	72	69 (2CE) : 31 (2CF)
14	1C	Toluene	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	48	75	67 (2CE) : 33 (2CF)
15	1C	Toluene	$\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	48	51	70 (2CE) : 30 (2CF)
16	1C	Toluene	$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	48	42	71 (2CE) : 29 (2CF)
17	1C	Toluene	$\text{Fe}(\text{ClO}_4)_2 \cdot x\text{H}_2\text{O}$	48	77	72 (2CE) : 28 (2CF)
18	1D	Toluene	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	96	0	— (2DE) : — (2CF)

^a The external irradiation was directed toward the Pyrex test tube with a working distance of 1 cm. All reactions were degassed by argon bubbling for 15 min prior to irradiation. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Recovery of **1B** in 52%.





Compounds	ΔE (kcal/mol)
1CX (S_0)	0
1CY (S_0)	1.45
1CZ (S_0)	0.54
1CX (T_1)	0
1CY (T_1)	1.44
1CZ (T_1)	0.36
2CX (S_0)	0.14
2CY (S_0)	1.30
2CZ (S_0)	0

Scheme 1 Optimized structures of **1C** (S_0 and T_1) and **2C** (S_0).

in the absence of $\text{BF}_3 \cdot \text{OEt}_2$ (**2CE** : **2CF** = 70 : 30, entry 12). Other metal perchlorates such as Mg, Ni, Co, Cu and Fe slightly improved the **2CE** : **2CF** ratio (entries 13–17). To improve

solubility of the chiral coumarin, we prepared **1D** having three hydrophobic phenyl groups and used this compound for the photodimerization reaction. However, undesired photodecomposition of **1D** occurred (entry 18). Interestingly, no reaction was induced when the reaction of **1C** was performed in the presence of a stoichiometric amount of $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ as well as $\text{BF}_3 \cdot \text{OEt}_2$. This phenomenon might suggest that the ratio of the metal complex of **1C** and metal-free **1C** in solution is important for the reaction to progress.^{3,10}

To gain insight into the mechanism of complete *syn*-HT selectivity and moderate diastereoselectivity, we optimized the structure of **1C** in toluene using DFT calculations (Scheme 1).¹¹ All calculations were performed using the B3LYP hybrid functional and a basis set (6-311G**) level of theory with Gaussian 16. The solvent effect of toluene was modeled *via* the polarizable continuum model using the integral equation formalism variant (IEFPCM). Three conformers **1CX**, **1CY** and **1CZ** were generated which are energetically closed.¹² We revealed that the order of the change in energy among three conformers was **1CX** (S_0) < **1CZ** (S_0) < **1CY** (S_0). The crystal structure of **1C** was similar to **1CZ**, which indicates that the major conformer involved in the [2 + 2] photodimerization would be changed between the solution and the crystalline states.¹³

Energies of photodimers *syn*-HH, *anti*-HH and *anti*-HT in toluene were also optimized by DFT calculation (B3LYP/6-311G**) to explain the exclusive formation of *syn*-HT dimer, which would be induced predominantly by accommodating the (*S*)-4-benzyl-2-oxazolidinone auxiliary in a favorable direction with a special allowance in the TS (Fig. 2).¹⁴ Structures of **2CX** and **2CY** were found to correspond to the structures of the cycloadducts *syn*-HT **2CE** and *syn*-HT **2CF**, respectively. It must be noted that **2CZ** is the major diastereomer with a different conformation from that of **2CY**. Thus, the order of the change in energy for photodimers was **2CZ** < **2CX** < **2CY**. There was not much difference in energy between **2CX** and **2CZ**. Time-dependent DFT (TD-DFT) calculations showed that HOMO \rightarrow

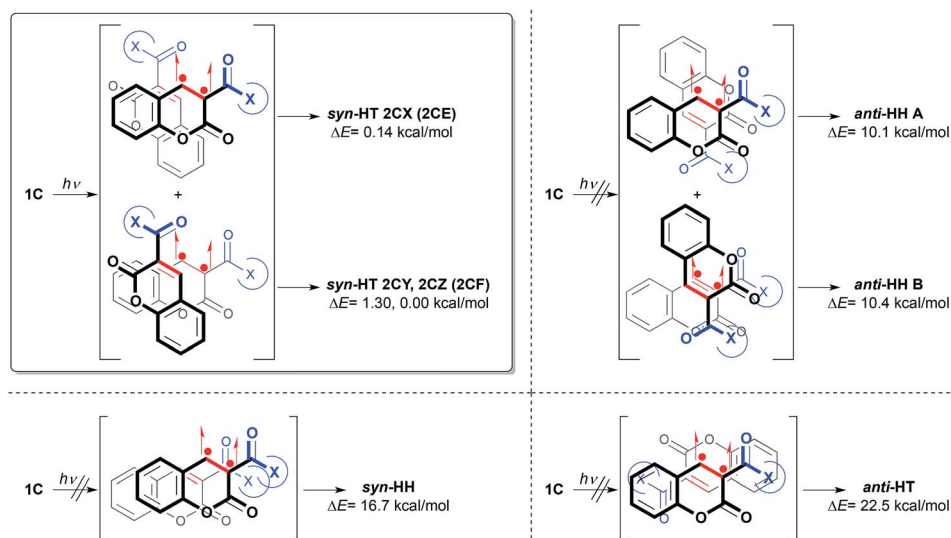
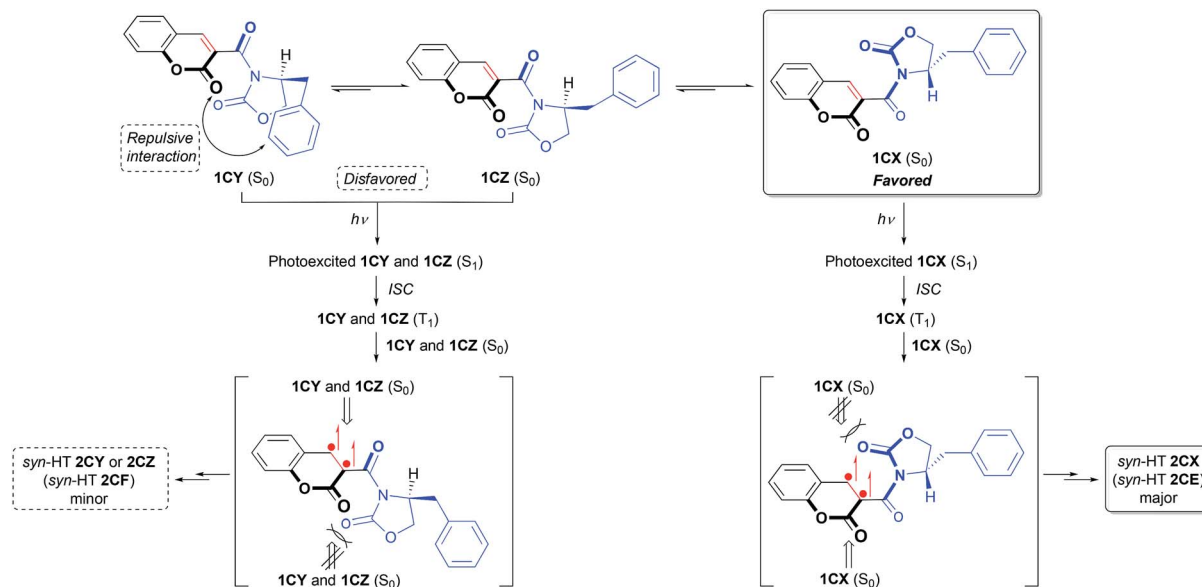


Fig. 2 Exclusive formation of *syn*-HT dimers caused by the steric hindrance between two chiral coumarins.

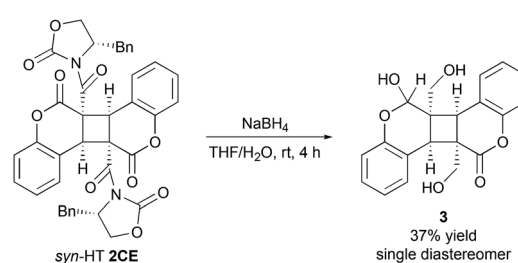




Scheme 2 Proposed mechanism for diastereofacial selectivity.

LUMO transition for each of the three conformers **1CX**, **1CY** and **1CZ** would be best described as a triplet excited state [$^3(\pi, \pi)^*$] (T_1) for the carbon-carbon double bond of the reaction site with zero oscillator strength (Scheme 2). Therefore, it is suggested that the ground state (S_0) for each of the three conformers was excited to become a singlet state [$^1(\pi, \pi)^*$] (S_1) followed by intersystem crossing (ISC) to generate T_1 . Consequently, the order of the change in energy among T_1 of the three conformers was also calculated as $1CX (T_1) < 1CZ (T_1) < 1CY (T_1)$. From the results mentioned above, the [2 + 2] photodimerization reaction would start from excitation of the most stable conformer **1CX** (S_0) which preferentially generates **1CX** (T_1) via ISC of a singlet excited state **1CX** (S_1). The resulting triplet species **1CX** (T_1) would be subjected to react with **1CX** (S_0) in *syn*-HT fashion (discussed below) to give **2CX**. The effect of the Lewis acid is unclear at the present time. However, we postulate that the Lewis acid could stabilize **1CX** by a coordination in a bidentate fashion to prevent the conformational change to **1CY** and **1CZ**, which would be induced by a free rotation of the carbon-carbon single bond between the coumarin ring and the 2-oxazolidinone auxiliary.^{3,8,15,16} The moderate diastereoselectivity could be explained by the following process (also depicted in Scheme 2). Two carbonyl groups in the (*S*)-3-acyl-4-benzyl-2-oxazolidinone auxiliary could be oriented opposite each other to minimize the dipole moment and the electrostatic repulsion. To minimize steric repulsion caused between the benzyl group of the 2-oxazolidinone auxiliary and the carbonyl group of the coumarin ring, the conformational bias leads more favorably toward **1CX** rather than **1CY** and **1CZ**. The carbonyl group including the 2-oxazolidinone ring would serve as a shielding group to prevent approach from the top side, thus affording **2CX**, *i.e.*, *syn*-HT **2CE** (Scheme 3).

The reduction of the chiral oxazolidinone moiety was successfully proceeded to give triol **3**.¹⁷ Interestingly, the reduction of chroman-2-one moiety also concomitantly occurred with the removal of chiral auxiliary affording **3** as a single diastereomer.¹⁸



Scheme 3 Removal of the chiral auxiliary with the reduction of chroman-2-one moiety.

In conclusion, we have developed a novel asymmetric photodimerization reaction of chiral coumarin-3-carboxamide which affords *syn*-HT dimer selectively with a moderate level of diastereoselectivity. Removal of chiral auxiliary was conducted to expand the applicability of the photodimer by the reduction using NaBH_4 in $\text{THF-H}_2\text{O}$. Further studies to elucidate the reaction mechanism and for application in the area of medicinal chemistry, drug delivery, and chemical biology are ongoing.

Conflicts of interest

There are no conflicts to declare.

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- 12 It was difficult to distinguish three conformers of chiral coumarins **1CX**, **1CY** and **1CZ** in CD₃C₆D₅ and (CD₃)₂CO at room temperature by 1D ¹H NMR and 2D rotating-frame Overhauser spectroscopy (ROESY) NMR measurements. While conducting variable-temperature (VT) NMR measurements, chiral coumarin **1C** precipitated out under low temperature because of its low solubility.
- 13 See the ESI† for the crystal structure of **1A**.
- 14 See the ESI† for the experimental and the computational details and results.
- 15 A small extent of downfield-shifts for the H-4 and C-4 of the coumarin ring of **1C** was observed in the presence of BF₃·OEt₂ and Zn(ClO₄)₂·6H₂O (1 equiv.) by ¹H and ¹³C NMR spectroscopic analyses. Absorption of **1C** at 287 nm was enhanced slightly with an increasing amount of Zn(ClO₄)₂·6H₂O. See the ESI† for the spectra.
- 16 The structure of **1C** ZnCl₂ complex was optimized by DFT calculation (B3LYP/6-311G) to show bidentate complexation of Zn(II) ion between the carbonyl oxygen of coumarin ring and the acyl oxygen of (*S*)-3-acyl-4-benzyl-2-oxazolidinone auxiliary. See the ESI† for the computational results.
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- 18 The structure of **3** was assigned by means of NMR analyses (¹H, ¹³C, ¹H–¹H COSY, HSQC and HMBC). The stereochemistry of C-2 of chroman-2-ol moiety was not determined, albeit a single diastereomer. See the ESI† for the spectra.

