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Intermolecular Hydrogen Bonds of 5-Benzylidene-2,4-thiazolidinedione Derivatives and Related Compounds in Crystalline State

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From the viewpoint of noncentrosymmetric molecular arrangement design in crystalline state, which is indispensable to second order nonlinear optical materials, intermolecular hydrogen bond formation of eight 5-benzylidene-2,4-thiazolidinedione derivatives and related compounds were investigated by X-ray crystallography. 5-Benzylidene-2,4-thiazolidinedione (**1**) itself forms centrosymmetric head-to-head (or tail-to-tail) intermolecular hydrogen bonds and takes a centrosymmetric molecular arrangement in crystalline state. Introduction of 4-methoxy group into the phenyl moiety of **1** was the only useful means for head-to-tail type intermolecular hydrogen bond formation. 5-(4-Methoxybenzylidene)-2,4-thiazolidinedione shows head-to-tail type intermolecular hydrogen bonds and noncentrosymmetric molecular arrangement in crystalline state. Similarities in both hydrogen bond formation and molecular arrangement in crystalline state are obtained by conversion of 2,4-thiazolidinedione to 2-thioxo-4-oxazolidinone, but in the case of conversion to 2,4-oxazolidinedione only hydrogen bond formation is shown in a similar manner. In the case of conversion to rhodanine, no similarity in either hydrogen bond formation or molecular arrangement in crystalline state was shown. Such behaviors were considered from viewpoints of pK_a and hydrogen bond energy.

5-Benzylidene-2,4-thiazolidinedione derivatives are expected to be useful as second order nonlinear optical materials because of their fairly large molecular hyperpolarizability (β) values.[1] For second order nonlinear optical effects to occur, materials must have noncentrosymmetric molecular alignment. It is well-known that intermolecular hydrogen bonds are useful means to achieve noncentrosymmetric molecular alignment. A molecular crystal of urea is one of the typical second order nonlinear optical materials which reveals noncentrosymmetric molecular alignment by means of intermolecular hydrogen bonds.[2] 4-Nitroaniline and its derivatives, which are also typical second order nonlinear optical materials, were studied in detail from the viewpoint of intermolecular hydrogen bonds in the crystalline state.[3]

In the case of 5-benzylidene-2,4-thiazolidinedione derivatives, head-to-tail type intermolecular hydrogen bonds will make their crystals useful as second order nonlinear optical materials. In the present paper, crystal structures of 5-benzylidene-2,4-thiazolidinedione derivatives and related compounds (Fig. 1) will be mentioned from the viewpoint of intermolecular hydrogen bonds.

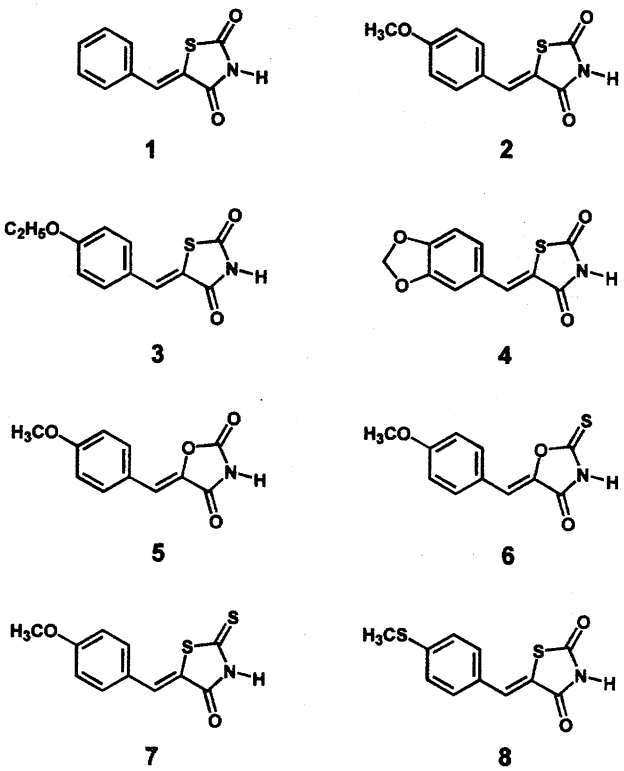


Fig. 1. Compounds used in this study.

Results and Discussion

Formation of Intermolecular Hydrogen Bonds of 5-Benzylidene-2,4-thiazolidinedione Derivatives in Crystalline State. X-Ray crystallography of unsubstituted 5-benzylidene-2,4-thiazolidinedione (**1**) showed that one molecule is face to face with another molecule in their respective 2,4-thiazolidinedione moieties and that the distances between a pair of imino hydrogen and carbonyl (4-position) oxygen are shorter than sum of the van der Waals radii of hydrogen and oxygen. So it can be recognized that the compound forms bifurcated hydrogen bonds between imino hydrogen and carbonyl (4-position) oxygen of the respective two 2,4-thiazolidinedione moieties. (Fig. 2: The intermolec-

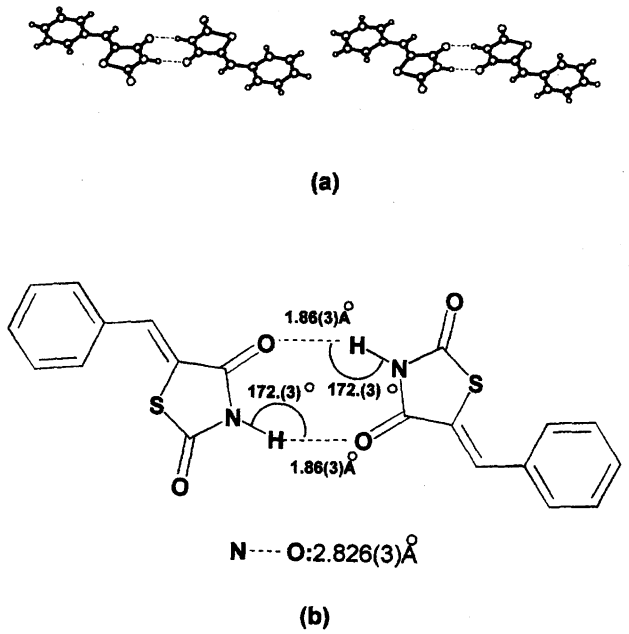


Fig. 2. Intermolecular hydrogen bond of **1**. (a) Crystal structure, (b) Illustration.

ular hydrogen bonds of this type is called type I hereafter.) The type I hydrogen bonds produce centrosymmetry of the crystal and consequent lack of the second order nonlinear optical activity (for example second harmonic generation (SHG)) in crystalline state.[4] If head-to-tail type intermolecular hydrogen bonds of 5-benzylidene-2,4-thiazolidinedione derivatives are formed, the compounds will show the second order nonlinear optical activity.[4] It is expected that introduction of a substituent, which has some ability of hydrogen bond formation, for example oxygen or nitrogen including moieties, into the phenyl moiety of **1** will bring about formation of the head-to-tail type intermolecular hydrogen bond between the oxygen or nitrogen atom and the hydrogen atom of the 2,4-thiazolidinedione moiety.

Introduction of electron donating groups into the phenyl moiety of **1** causes enhancement of molecular hyperpolarizability (β).[1] Introduction of an alkoxy group into para position of the phenyl moiety is a good step for coexistence of large β and high blue-light transparency, which is an important factor for blue-light SHG material.[1] In addition, the head-to-tail type intermolecular hydrogen bond formation between the oxygen atom of the alkoxy group and the hydrogen atom of the 2,4-thiazolidinedione moiety will be expected. From this viewpoint, the crystal structure of 5-(4-methoxybenzylidene)-2,4-thiazolidinedione (**2**) was examined by X-ray crystallography.

The crystallographic study proved that the expected head-to-tail type intermolecular hydrogen bond was formed in crystalline state of **2**, because the distance between the imino hydrogen and the methoxy oxygen is shown to be shorter than sum of van der Waals radii of hydrogen and oxygen. (Fig. 3: The intermolecular hydrogen bonds of this type is called as type II hereafter.) But the substitution of the alkoxy group on 4-position of the phenyl group does not always bring about type II hydrogen bond. Both 4-ethoxy **3** and 3,4-methylenedioxy **4** derivatives formed type I instead of type II. Consequently, we consider that the 4-methoxy derivative may be a special case in the hydrogen bond formation.

Effect of Modification of the 2,4-Thiazolidinedione Ring on Intermolecular Hydrogen Bonds of 4-Methoxybenzylidene Derivatives in Crystalline State. 4-Methoxybenzylidene derivatives in which the 2,4-thiazolidinedione ring was converted to 2,4-oxazolidinedione **5**, 2-thioxo-4-oxazolidinone **6** or rhodanine **7** were examined from the viewpoint of intermolecular hydrogen bond formation by X-ray crystallography. The crystallographic data (Table 1) indicated that both compounds **5** and **6** formed type

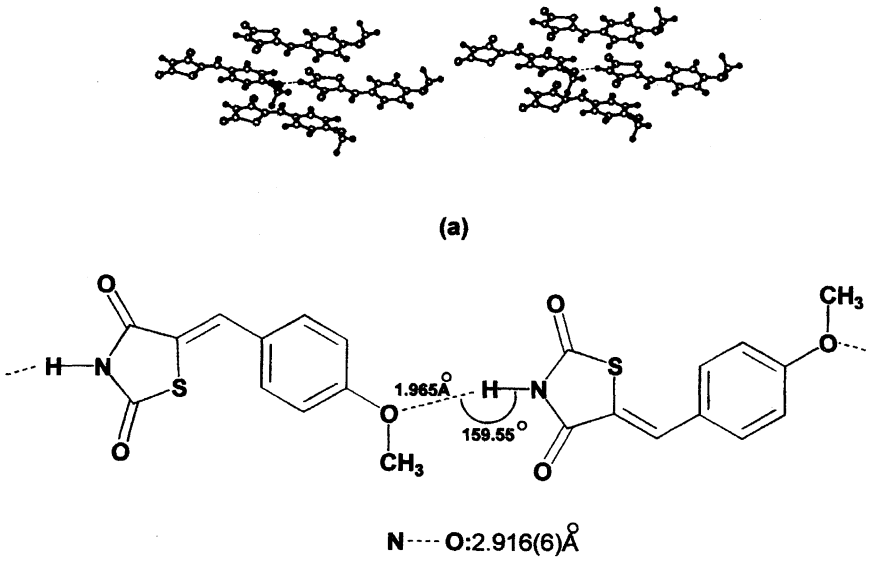


Fig. 3. Intermolecular hydrogen bond of **2**. (a) Crystal structure, (b) Illustration.

Table 1. Crystallographic Data of **1** to **8**

Compound	Crystal system	Space group	Unit cell				Z	R factor (Refs.)	Density (D_c)
1	Monoclinic	$P2_1/a$	$a=8.237$, $b=11.700$, $c=9.515$ Å	$\beta=96.16°$	$V=911.7$ Å^3		4	0.050 (1288)	1.495
2	Orthorhombic	$Pna2_1$	$a=13.151$, $b=12.213$, $c=6.468$ Å		$V=1038.8$ Å^3		4	0.034 (700)	1.504
3	Monoclinic	$P2_1/c$	$a=9.099$, $b=7.686$, $c=17.430$ Å	$\beta=104.04°$	$V=1182.5$ Å^3		4	0.037 (928)	1.400
4	Monoclinic	$P2_1/n$	$a=14.106$, $b=3.866$, $c=19.330$ Å	$\beta=104.11°$	$V=1022.3$ Å^3		4	0.044 (1561)	1.619
5	Monoclinic	$P2_1/n$	$a=5.592$, $b=13.672$, $c=13.220$ Å	$\beta=93.41°$	$V=1009.0$ Å^3		4	0.056 (1378)	1.443
6	Orthorhombic	$Pna2_1$	$a=13.877$, $b=11.941$, $c=6.433$ Å		$V=1065.9$ Å^3		4	0.037 (895)	1.466
7	Monoclinic	$P2_1/c$	$a=5.181$, $b=10.513$, $c=20.729$ Å	$\beta=92.52°$	$V=1128.0$ Å^3		4	0.035 (1217)	1.480
8	Monoclinic	$P2_1/c$	$a=6.571$, $b=9.835$, $c=18.051$ Å	$\beta=100.43°$	$V=1147.4$ Å^3		4	0.062 (1471)	1.455

II hydrogen bonds, but compound **7** formed type I hydrogen bonds. The crystal structure of **6** is very similar to that of **2** (Fig. 4: Direction of *C*-axes are opposite with each other), and both **2** and **6** showed SHG activity (at 1064 nm by Kurtz's method;[5] Table 2) coincident with the indication of each space group (Table 1). On the contrary, the crystal structure of **5** possessed centrosymmetry. In consequence of that, the crystal of **5** was inactive in SHG in spite of forming the type II hydrogen bond. In this case, direction of adjacent row of head-to-tail hydrogen bond chains are opposite with each other. Type I hydrogen bond forming compounds were inactive in SHG because of the centrosymmetric crystal structures which were due to centrosymmetric bimolecular hydrogen bond formation.

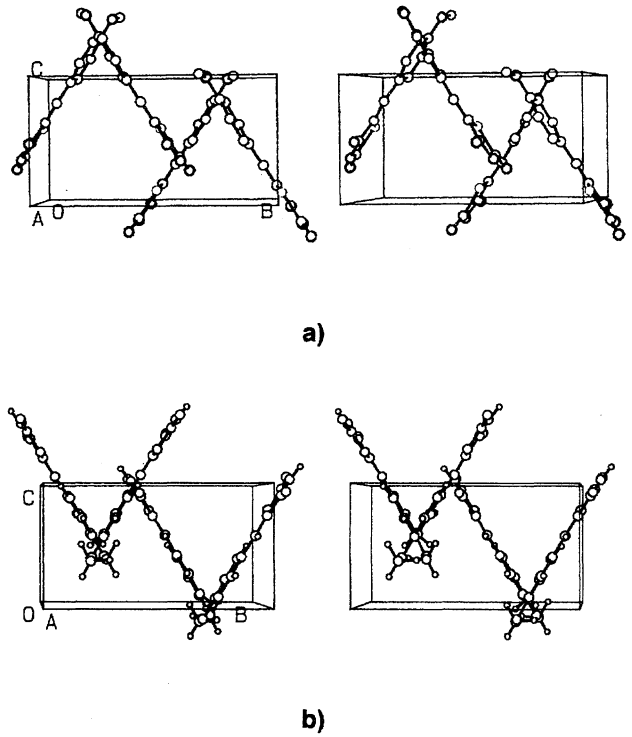


Fig. 4. Stereoscopic view of crystal structure viewed down the *A* axis. (a) Compound **2**, (b) Compound **6**.

Table 2. The SHG Activity of **1** to **8**

Compound	SHG activity[a)]	Type
1	0	I
2	12	II
3	0	I
4	0	I
5	0	II
6	20	II
7	0	I
8	0	I

a) Relative activity vs. urea at 1064 nm.

Consideration of Structural Effect on Hydrogen Bond Formation. Structural effects which might affect hydrogen bond formation of 5-benzylidene-2,4-thiazolidinedione derivatives and related compounds were studied from viewpoints of pK_a of proton of 3-position of the 2,4-thiazolidinedione or the related moiety and hydrogen bond energy.

1) The viewpoint of pK_a of proton of 3-position of the 2,4-thiazolidinedione or the related moiety.

The hydrogen atom of 3-position of the 2,4-thiazolidinedione or the related moiety is the hydrogen itself which contributes to formation of both type I and type II hydrogen bonds. A value of pK_a of a proton is one of the typical indices of the hydrogen atom's property. From this reason, pK_a values of the proton of 3-position of the 2,4-thiazolidinedione or the related moiety of compounds **1** to **8** were estimated. The experiments were carried out in 60% aqueous tetrahydrofuran(THF) solution because of the solubility of the compounds. Results obtained are not genuine pK_a values, but are apparent values which are expressed as pK'_a hereafter. These pK'_a values are shown in Table 3. No characteristic feature was observed concerning the difference between type I and

Table 3. The Energy of Hydrogen Bond Formation and pK'_a of **1** to **8**

Compound	Energy/kJ mol^{-1}			pK'_a	Type
2	−22.34[a)]	−44.68[b)]	−56.48[c)]	7.17	II
5	−24.89[a)]	−49.78[b)]	−43.86[c)]	6.68	II
6	−23.43[a)]	−46.86[b)]	−51.47[c)]	5.95	II
1	−52.38[a)]			6.71	I
3	−44.18[a)]			7.19	I
4	−33.43[a)]			6.94	I
7	−37.91[a)]			6.86	I
8	−41.55[a)]			6.97	I

a) Calculated values for dimmeric state. b) Doubled values of a) under assumption of infinite hydrogen bond chain. c) Calculated values for non-observed type I hydrogen bond.

type II hydrogen bond. These results allow us to conclude that pK_a values of protons of 3-position of the 2,4-thiazolidinedione or related moiety do not concern hydrogen bond type.

2) Estimation of hydrogen bond energy.

Hydrogen bond energy of compounds **1** to **8** were estimated by ab initio molecular orbital calculation. The estimation was carried out under following conditions.

a) The hydrogen bond was formed between isolated two molecules in both cases of type I and type II.

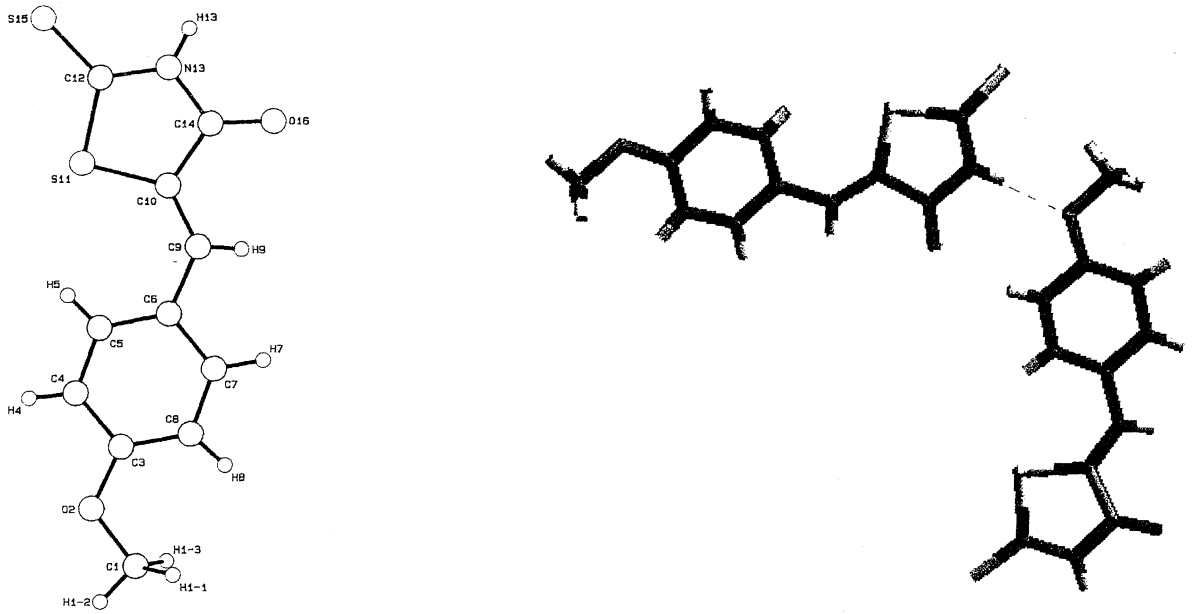
b) Used values of molecular geometry were obtained by X-ray crystallography.

The results are shown in Table 3. The values of type II with notation b) were doubled because one hydrogen bond would be formed for every one molecule under infinite head-to-tail hydrogen bond formation condition. The results indicate that there is no significant difference between hydrogen bond formation energy of type I and type II. The difference of averaged hydrogen bond formation energy between type I and type II (doubled) is only 5.23 kJ mol^{-1}. The choice of type I and type II may be decided by subtle factors. For the type II compounds, the calculation was carried out for unobserved type I hydrogen bond, in which the molecular structure of the monomolecular state used the data observed in the type II structures. The results are shown in Table 3. Only the compound **5** reveals any advantage of hydrogen bond energy in type II. For the type I compounds, the type II structures were not obtained by the calculation using observed monomolecular state structure, but bend structures were obtained as in the case of compound **7** shown in Fig. 5(a) because of the direction of the alkyl moiety in the alkoxy group (Fig. 5(b)). It is doubtful that the direction of the alkyl moiety is the determining factor for hydrogen bond type because the relationship between the crystal structure and the molecular structure may be considered as "a which-came-first-the-chicken-or-the-egg question" relationship.

These considerations will be better confirmed if both type I and type II crystals are obtainable from one compound. Unfortunately we have not found such a compound yet.

Conclusion

Introduction of methoxy group into 4-position of phenyl moiety of 5-benzylidene-2,4-thiazolidinedione caused the compound to alter the type of hydrogen bond from type I to type II. The type II hydrogen bond, which belongs to head-to-tail type, brings about a noncentrosymmetric molecular arrangement in crystalline state to the methoxy derivative and endows the crystal with SHG activity. Among methoxy derivatives, 2,4-oxazolidinedione and 2-thioxo-4-oxazolidinone derivatives except rhodanine form type II hydrogen bonds. The calculated value of hydrogen bond formation energy difference between type I and type II was as small as 5.23 kJ mol^{-1} in average. A conformation difference of the alkoxy moiety was observed between type I and type II compounds in the monomolecular state. This is, however, not concluded to be the cause of the type selection of the hydrogen bond, because the conformation difference may be recognized as only the result of formation of type I hydrogen



(a) Molecular structure **(b) Calculated head-to-tail hydrogen bond**

Fig. 5. Molecular structure and calculated head-to-tail hydrogen bond of compound **7**. (a) Molecular structure, (b) Calculated head-to-tail hydrogen bond.

Table 4. Data of Melting Point, UV-vis Spectra and ^{1}H NMR of the Compounds

Compound	mp / °C	λ_{max} / nm (ε) in methanol	^{1}H NMR (δ / ppm in DMSO-d_6)
1	243—244	322 (2.87×10^4)	7.40—7.65 (m,5H), 7.80 (s,1H), 12.70 (bs,1H)
3	198	346 (2.64×10^4)	1.37 (t,3H), 4.10 (q,2H), 7.09 (d,2H), 7.54 (d,2H), 7.74 (s,1H), 12.50 (bs,1H)
4	254—255	356 (3.33×10^4)	6.13 (s,2H), 7.11 (d,1H), 7.15 (s,1H), 7.18 (d,1H), 7.72 (s,1H), 12.55 (bs,1H)
6	210	364 (3.61×10^4)	3.84 (s,3H), 6.80 (s,1H), 7.13 (d,2H), 7.84 (d,2H), 13.80 (bs,1H)
7	262	391 (3.47×10^4)	3.85 (s,3H), 7.12 (d,2H), 7.60 (d,2H), 7.65 (s,1H), 13.80 (bs,1H)
8	214.5—255	357 (4.71×10^4)	2.51 (s,3H), 7.41 (d,2H), 7.55 (d,2H), 7.86 (s,1H), 12.70 (bs,1H)

bond.

Experimental

Syntheses of Compounds. All of the compounds except 5-(4-methoxybenzylidene)-2,4-oxazolidinedione (**5**) were synthesized by using the Knoevenagel reaction.[6] As typical examples, synthetic methods for 5-(4-methoxybenzylidene)-2,4-thiazolidinedione (**2**) and **5** are shown.

1) Synthesis of 5-(4-Methoxybenzylidene)-2,4-thiazolidinedione (2). In a 300 ml flask equipped with a reflux condenser, 23.2 g (0.17 mol) of anisaldehyde, 20.0 g (0.17 mol) of 2,4-thiazolidinedione, 10.2 g (0.17 mol) of acetic acid, 6.6 g (0.085 mol) of ammonium acetate and 200 ml of acetonitrile were placed and the solution was refluxed for 30 min. The resulting reaction mixture was left to stand until its temperature fell to room temperature. The precipitated crystals were gathered by filtration. The crystals were dissolved by 100 ml of *N*,*N*-dimethylformamide (DMF) and the solution were stirred for 5 min under 100 °C with activated carbon powder. By adding water to the filtrate of the solution, crystals were precipitated and gathered by filtration. The crystals were washed by water, then with acetonitrile. By drying, 22 g (55%) of **2**, mp = 219 °C, was obtained.

UV-vis spectra λ_{max} (ε) = 343 nm (2.94×10^4) in methanol,

^{1}H NMR (DMSO-d_6) δ = 3.85 (s, 3H), 7.10 (d, 2H, J = 9 Hz), 7.55 (d, 2H, J = 9 Hz), 7.75 (s, 1H), 12.50 (br, 1H).

Found: C, 56.11; H, 3.86; N, 5.99%. Calcd for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86; N, 5.96%.

2) Synthesis of 5-(4-Methoxybenzylidene)-2,4-oxazolidinedione (5).

i) Synthesis of 5-(4-Methoxybenzylidene)-2-methylthio-4-oxazolinone (9). In a 200 ml three-necked flask equipped with a stirrer and a dropping funnel, 9.5 g (0.04 mol) of 5-(4-methoxybenzylidene)-2-thioxo-4-oxazolidinone (**6**), 5.5 g (0.04 mol) of potassium carbonate (anhydrous) and 100 ml of acetonitrile were placed. To this mixture, 5.7 g (0.04 mol) of methyl iodide was added dropwise under stirring at room temperature and then the entire mixture was stirred for 30 min. The reaction mixture was poured into 1 L of water. Precipitated crystals were gathered by filtration and recrystalized from 2-propanol. By drying, 10 g (quantitative) of **9** was obtained.

ii) Synthesis of 5. In a 100 ml flask equipped with a stirrer, 5 g (0.02 mol) of **9** and 75 ml of 12% aq HCl were placed and the mixture was stirred at 50 °C for 30 min. The reaction mixture was cooled to room temperature and precipitated crystals were gathered by filtration. The crystals were purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) and 2.9 g (66%) of **5**, mp = 229 °C, was obtained.

UV-vis spectra λ_{max} (ε) = 323 nm (2.64×10^4) in methanol,

^{1}H NMR (DMSO-d_6) δ = 3.80 (s, 3H), 6.70 (s, 1H), 7.05 (d, 2H, J = 10 Hz), 7.75 (d, 2H, J = 10 Hz), 12.35 (br, 1H).

Found: C, 60.23; H, 4.03; N, 6.32%. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39%.

Data of other compounds are listed in Table 4.

Crystal Structure Analysis. Crystallographic data of **1** to **8** are listed in Table 1. Crystals used for this study were prepared by the evaporation method. Names of used solvents are listed in Table 5. X-Ray reflection intensity measurement was carried out on an Enraf–Nonius CAD4 four-circle diffractometer, graphite-monochromatized Cu $K\alpha$, at room temperature. Structures were solved by direct methods using the program package TEXAN. All positions of non-H atoms were determined from E map and refined by full-matrix least square method with anisotropic thermal parameters. Almost all H atoms were found from difference syntheses and refined with isotropic thermal parameters.

Measurement of pK'_a. A solution for measurement was prepared by dissolving 5×10^{-5} mol of a compound in 30 ml of tetrahydrofuran and 20 ml of water and adding 0.25 ml of 0.2 M (1 M = 1 mol dm^{-3}) hydrochloric acid. The solution was titrated by a 0.2 M NaOH of aqueous solution. The titration was carried out on an AT-210 type automatic titration apparatus (Kyoto Denshi Co.).

Calculation of Hydrogen Bond Energy. The intermolecular hydrogen bond energies for dimers of 5-benzylidene-2,4-thiazolidinedione derivatives were calculated by the Hartree–Fock (HF) method. In the calculations, the STO-3G basis set was used and BSSE (basis set superposition error) corrections were not considered. The hydrogen bond energies were estimated according to Eq. 1.

$$\Delta E \text{ (hydrogen bond)} = E \text{ (bimolecule)} - 2 \times E \text{ (monomolecule)}. \quad (1)$$

Molecular structures and orientations in the mono- and bimolecules were taken from the crystallographic data. In the case of the non-observed orientation, i.e. type II orientation for the compounds of type I orientation in the crystal and vice versa, only the intermolecular parameters were optimized with the monomer structures from the crystallographic data.

Negative ΔE values mean stabilization and positive ΔE values mean destabilization.

Table 5. Solvents Used for Single Crystal Preparation

Compound	Solvent
1	3-Methyl-2-butanone
2	Acetonitrile
3	Methanol
4	2-Propanol
5	Methanol
6	Methanol
7	Methanol–acetonitrile
8	Acetonitrile

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