

Conformational Analysis of Fungicidal MOA Compounds: *Ab initio* and Semi-empirical Studies on the Relationship between Activity and Torsional Energy[†]

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The antifungal metabolite strobilurin A (**1**) was first isolated from the fungus *Strobilurus tenacellus*.^{1,2} The following efforts by major industrial R & D groups to develop more active synthetic analogs have led to a new class of fungicides containing methyl β -methoxyacrylate (MOA) group, which has a novel mode of action and good broad-spectrum activity. Azoxystrobin by Zeneca Agrochemicals³ and Kresoxim-methyl by BASF⁴ are the first two MOA compounds recently introduced to the market (Figure 1). MOA fungicides act on a new biochemical target site in fungi: they inhibit electron transport at the bc₁-complex in mitochondria.⁵ Research of Zeneca scientists involved synthesis and biological test of quite a wide range of synthetic analogs of **1**.^{5,6} The most salient structural feature observed in the conformational analysis of **1** is the orthogonal geometry of two planar moieties: the phenylpentadienyl group and methyl β -methoxyacrylate function.⁵

We are interested in examining the geometry of two moieties in **1** and its synthetic analogs **2–4** in Figure 2. The stilbene analog **2**, like strobilurin A (**1**) (Respiration I₅₀ = 0.11 μ M) is a strong inhibitor of mitochondrial respiration (Respiration I₅₀ = 0.04 μ M) and highly active against a range of plant pathogenic fungi, while its regioisomers, **3** and **4**, are far less active.⁵

To examine the orthogonality of two planar moieties: the lipophilic backbone (the stilbene moiety of **2–4**) and methyl β -methoxyacrylate moieties, we carried out conformational search for the lowest energy conformations. All calculations were carried out using GAUSSIAN-98 programs.⁷ The optimizations of energies and geometries were conducted using a Hartree-Fock method (HF/6-31G*) and a DFT method (B3LYP/6-31G*)⁸ as well as a semi-empirical method (AM1) without restricting any symmetry.

Our studies have been initiated by searching the minimized energy conformations of strobilurin A (**1**) and its stilbene analog **2**. Two types of minimum conformations are shown

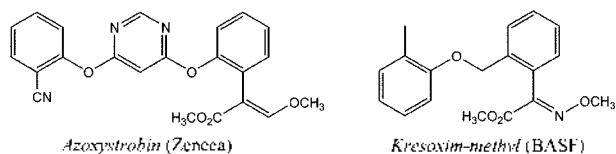


Figure 1. Azoxystrobin and Kresoxim-methyl.

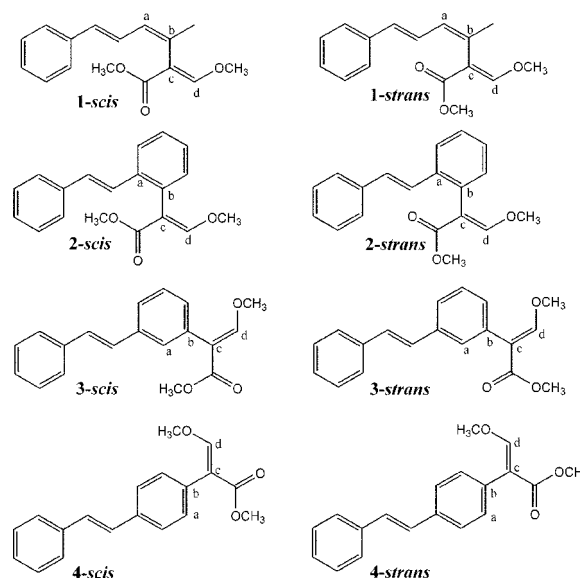


Figure 2. Strobilurin A (**1**) and its synthetic derivatives, **2–4**.

as *s-cis* and *s-trans* for methyl β -methoxyacrylate moiety of compound **1** and **2**. Their optimized geometries and relative energies are illustrated in Figure 3. Both isomers show almost the same stability (~ 0.1 kcal/mol) by AM1 calculation. The *s-cis* conformer of **1** is slightly more stable than the *s-trans* conformer by 1.02 and 0.85 kcal/mol in HF/6-31G* and B3LYP/6-31G*, respectively. The two isomers should be readily interconvertible. According to the optimized geometry in **1-*s-cis***, the phenylpentadienyl and methyl β -methoxyacrylate moiety are each planar but almost orthogonal to one another. The optimized torsional angles ($C_a-C_b-C_c-C_d$) of **1-*s-cis*** are shown by 77.2°, 78.1°, and 68.6° in AM1, HF/6-31G* and B3LYP/6-31G*, respectively. Although a planar conformation may be favored in this molecule by an electron-delocalization effect, the steric effect between the phenylpentadienyl and β -methoxyacrylate moiety seems to prevent its complete planar geometry. **1-*s-trans*** as well as the stilbene analog **2** shows similar features.

Our methods are expanded to compare the structural features of the active compounds (**1** and **2**) and the less active compounds (**3** and **4**). We investigated relative energies of **1–4** varying torsional angle between two moieties (phenylpentadiene/ β -methoxyacrylate for **1**, stilbene/ β -methoxyacrylate for **2–4**). Figure 4 shows the torsional potentials obtained from AM1 calculation for *s-cis* and *s-trans* conformers of **1–4**.

[†]This paper is dedicated to the late Professor Sang Chul Shim, a teacher and scientist.

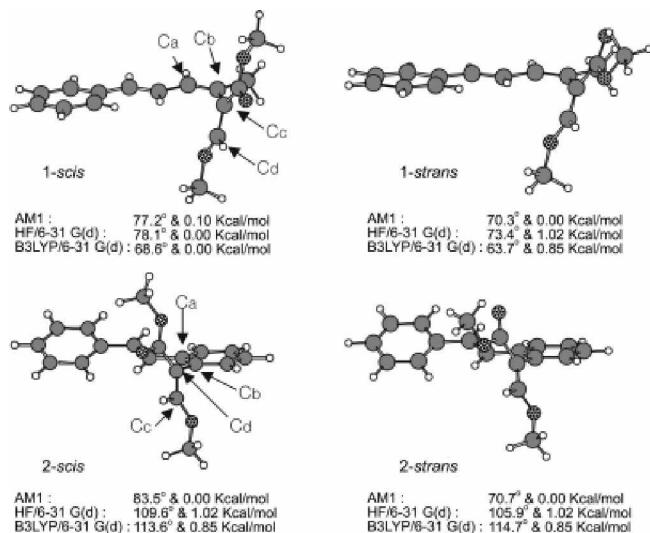


Figure 3. The optimized structures for the lowest energy conformations of **1-scis**, **1-strans**, **2-scis** and **2-strans** at the B3LYP/6-31G(d) levels. The AM1 and HF/6-31G(d) optimized structures are almost identical. The values are torsional angles ($C_a-C_b-C_c-C_d$, degree) and relative energy differences (kcal/mol) between *scis* and *strans* isomers.

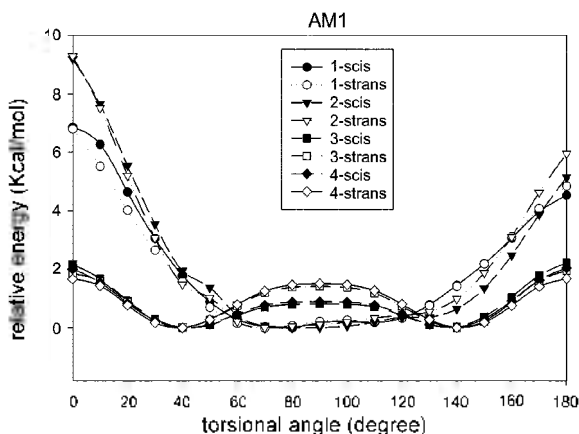


Figure 4. Energy profile to torsional angles ($C_a-C_b-C_c-C_d$, degree) for **1-scis**, **1-strans**, **2-scis**, **2-strans**, **3-scis**, **3-strans**, **4-scis** and **4-strans** at the AM1 method. The relative energies (kcal/mol) are obtained from the lowest energy of the corresponding compound.

And the energy profiles obtained from B3LYP/6-31G* method for *scis* conformers of **1-4** are given in Figure 5.

As shown in Figure 4 and 5, all these calculation methods result in similar energy profiles: **1** and **2** have a 'U' shape profile, while **3** and **4** have a 'W' shape. The torsional energies at 0° for **1** and **2** are predicted to be 7-10 kcal/mol by AM1 method. The calculated energies obtained from B3LYP/6-31G* method are 10-12 kcal/mol.⁹ Therefore, the rotation of two planar moieties in **1** or **2** should be quite restricted due to a high rotational barrier, and each of these compounds likely exists as two enantiomeric rotamers. However, two planar moieties in **3** or **4** are expected to rotate quite freely (the torsional energies are less than 2-3 kcal/mol at 0° calculated by AM1 and B3LYP/6-31G*). The energy curves between 60° and 120° in **1** or **2** are almost flat and torsional energies are near to zero. The torsional energy of **1-scis** at

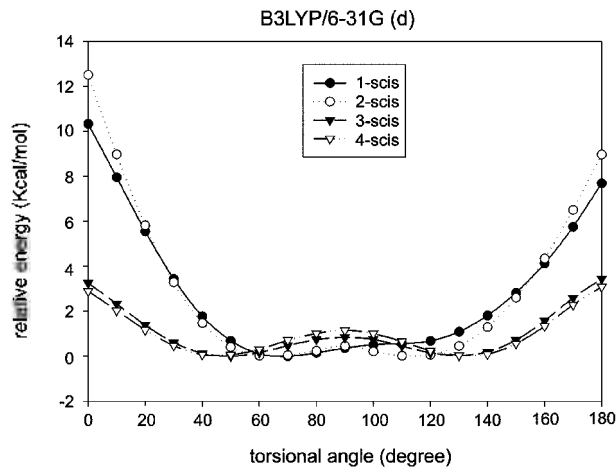


Figure 5. Energy profile to torsional angles ($C_a-C_b-C_c-C_d$, degree) for **1-scis**, **2-scis**, **3-scis** and **4-scis** at the B3LYP/6-31G(d) levels. The relative energies (kcal/mol) are obtained from the lowest energy of the corresponding compound.

90° , for an example, is predicted to be ~ 0.3 kcal/mol by B3LYP/6-31G* method. However, **3** and **4** show two energy minima at $\sim 50^\circ$ and $\sim 130^\circ$ for dihedral angle $C_a-C_b-C_c-C_d$, and apparent rotational barriers between two minima. The torsional energy of **4-scis** at 90° , for an example, is predicted to be ~ 1.2 kcal/mol by B3LYP/6-31G* method. Therefore, **3** and **4** are less prone to maintain the optimum structure required for high activity and show very weak fungicidal effect.

To our knowledge, our results in this study are the first quantitative analysis concerning the structure-activity relationship in fungicidal β -methoxyacrylate molecules. We are currently extending our studies to other analogs, and these results will be presented in due course.

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- The torsional energies at 0° for **1** and **2** are predicted to be 13-18 kcal/mol by HF/6-31G*, and their energy profiles are shown by similar shapes with AM1 and B3LYP/6-31G* methods.