Crystal Structure and Conformation of β-Substituted (*Z*)- and (*E*)-6-Styrylpurines as Conformer Models

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Crystal structures of conformationally restricted (*Z*)- and (*E*)-6-styrylpurines with the β-substituents involving hydrogen, chlorine, and bromine atoms as well as a methylthio group were studied as conformer models of N^6-adenines in relation to active conformation of cytokinins. X-ray crystallographic analyses confirmed that all of the *trans*-isomers exist in an *anti* conformation, whereas the *cis*-isomers except the (*E*)-methylthio derivative adopt a *syn* conformation. The derivative with a bulky β-substituent was found to be in an *anti* conformation in contrast to the other *cis*-isomers. The preferred *anti* conformation and potent cytokinin activity of the *trans*-isomers supports the *anti-transoid* form as the most plausible active conformation of N^6-adenines. In addition, it is likely that the *syn-cisoid* form of N^6-adenines is also involved in receptor binding, by considering both the preferred *syn* conformation of the *cis*-isomers and their moderate activity, although it does not play a major role compared to the *anti-transoid* form.

Keywords: *Cytokinin; 6-styrylpurine; crystal structure; conformation−activity relationship; tobacco callus bioassay*

INTRODUCTION

Cytokinins including N^6-adenines are plant growth regulators that regulate the development and cell division of plants. Many studies on structure−activity relationships of cytokinins (Iwamura et al., 1980; Matsubara, 1990; Shudo, 1994), revealed some structural requirements necessary for high cytokinin activity. The requirements found should allow one to design new cytokinin analogues not only for isolating cytokinin binding protein (Fujimoto et al., 1998) but also for solving fundamental problems such as active conformation as well as the functions of the nitrogen atoms in the cytokinin−receptor interaction (Nishikawa et al., 1996). Conformations of N^6-furfurylaminopurine (Soriano-Garcia and Parthasarathy, 1975), N^6-benzyladenine (Raghunathan et al., 1983), N^6-isopentenyladenine (McMullan and Sundaralingam, 1971; Leonard et al., 1981) were determined crystallographically, and it was proposed that the conformation, which the N^6-adenines adopted in common in the crystal were relevant to active conformation. Furthermore, a stereochemical model for cytokinin activity was postulated on the basis of these N^6-adenines, in support of the proposal (Korszun et al., 1989). Another study using quantum mechanical method (Kaneti and Karanov, 1983) showed that there was an approximate relation between cytokinin activity and the flexibility of the side chain of N^6-adenines and the related N^6-deazaadenines. Although the distal conformation of N^6-adenines is believed to be a plausible active conformation, there remains a controversy with respect to the details of the conformation, that is, the folding of the side chain. For example, N^6-benzyladenine has three single bonds in the side chain about which, in principle, rotation occurs with, more or less, an energy barrier and should be in *cisoid-transoid* and *syn-anti* conformation equilibrium (Figure 1). X-ray crystallography of *N*-phenyl-*N*′-pyridylureas, which behave as N^6-adenines in exerting cytokinin activity was carried out in comparison with the conformation of N^6-adenines, and it was concluded that *trans* extended planar conformation is responsible for the activity (Yamaguchi and Shudo, 1991).

In carbon-substituted purines including β-substituted (*Z*)- and (*E*)-6-styrylpurines, their rotational freedom is restricted by a double bond in the side chains. For these compounds, we can expect an additional effect that bulky β-substituents further constrain their conformation by electronic or steric repulsion. Therefore, the carbon-substituted derivatives with potent cytokinin activity are appropriate conformer models of N^6-adenines and give useful information about the active conformation more straightforwardly. Similarly, there exits a simple *syn-anti* equilibrium in solution or in isolated state for the conformer models (Figure 2). However, the involvement of the *cisoid* conformation in cytokinin activity has rarely been discussed on the basis of experimental evidence. Because most of the β-substituted 6-*cis*-isomers show a moderate cytokinin activity distinctly, their relation to active conformation is of

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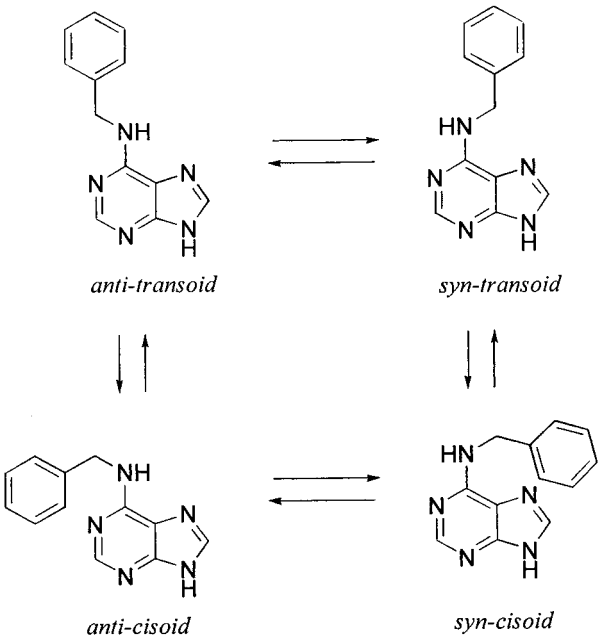


Figure 1. Conformation equilibrium of N^6-benzyladenine.

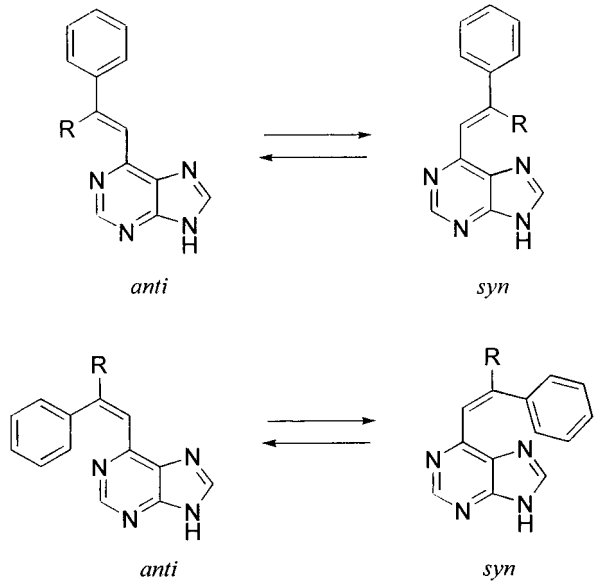


Figure 2. Conformation equilibrium of β-substituted *trans*- and *cis*-6-styrylpurines.

interest. Therefore, more studies on conformation−activity relationships are required for identifying active conformation of cytokinins.

This paper describes the structures and the preferred conformation in the crystal of some pairs of (*Z*)- and (*E*)-6-styrylpurines. Also, the effects of the β-substituents on the planarity of the purine and phenyl rings are compared, and the involvement of *anti-transiod* as well as *syn-cisoid* forms in cytokinin activity are discussed.

MATERIALS AND METHODS

(*Z*)- and (*E*)-6-styrylpurines **1**−**8** were prepared as previously (Nishikawa et al., 1994). The compounds except **1** and **4** were recrystallized from ethyl acetate or a mixture of ethyl acetate and methanol. The latter two compounds, which afforded very thin needles by the conventional crystallization, were crystallized by sublimation in vacuo at ~170 °C with shielding from light.

Table 1. Bond Lengths (Å) of β-Substituted 6-Styrylpurines

compd	C(6)−C(10)	C(10)−C(11)	C(11)−C(12)
1	1.522 (8)[a]	1.298 (8)	1.444 (8)
2	1.452 (6)	1.321 (7)	1.467 (6)
3	1.455 (4)	1.335 (4)	1.480 (4)
4 (1)	1.451 (6)	1.338 (6)	1.489 (6)
4 (2)	1.442 (6)	1.333 (6)	1.501 (6)
5 (1)	1.491 (6)	1.333 (6)	1.456 (6)
5 (2)	1.488 (6)	1.323 (6)	1.464 (6)
6	1.482 (8)	1.307 (8)	1.498 (8)
7	1.485 (11)	1.315 (12)	1.492 (12)
8	1.426 (8)	1.350 (8)	1.486 (8)

[a] Estimated standard deviations are shown in parentheses.

X-ray analysis was carried out with a Rigaku AFC-5R automated four-circle diffractometer equipped with Cu Kα radiation ($\lambda = 1.5418$ Å) at 20 °C. Independent reflections ($2\theta < 122°$, the $\theta - 2\theta$ scan technique) were collected [$|F_0| > 3\sigma(F_0)$]. For compound **3**, X-ray analysis was carried out with a Rigaku AFC-7R automated four-circle diffractometer equipped with Mo Kα radiation ($\lambda = 0.71069$ Å) at −50 °C. Independent reflections ($2\theta < 55°$, the $\omega - 2\theta$ scan technique) were collected [$|F_0| > 3\sigma(F_0)$]. The structures were solved by the program MULTAN 84 (Main et al., 1984), refined as usual. Crystal structure models were depicted by ORTEP (Johnson, 1976). Details of crystal properties as well as data collection and structure refinement of **1**−**8** are deposited as Supporting Information.

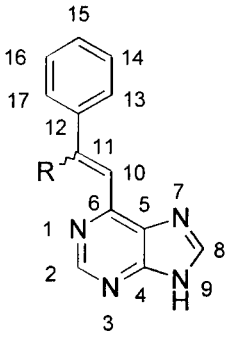
RESULTS AND DISCUSSION

Conformationally restricted molecules are useful in identifying conformations responsible for their biological activity. When they retain high biological activity, we can safely draw a conclusion that the conformation they adopt is the same as the active conformation in receptor binding (Hart and Rich, 1996). Therefore, we studied the conformation in the crystal of *trans*- and *cis*-styrylpurines, which are constrained conformer models of N^6-adenines.

The structures with numbering and cytokinin activities of the β-substituted *trans*-**1**−**4** and *cis*-isomers **5**−**8** and their crystal structures drawn by ORTEP are shown in Figure 3 and Figures 4 and 5, respectively. Crystal structures of **2** and **6**, previously reported (Nishikawa et al., 1994), are included for comparison among the isomers. The crystals of the (*Z*)-methylthio derivative **4** and (*Z*)-6-styrylpurine (**5**) contain two different molecules in the asymmetrical unit, whereas the other derivatives have a single molecule. For the protonation on nitrogen, all of the *trans*- and *cis*-isomers except for **4** and **5** exist in the N(9)*H* form, similar to N^6-adenines; the latter adopt the N(7)*H* form.

The unsubstituted *trans*-isomer **1** has typical values of the bond lengths of the side chains, as expected for a single and a double bond consisting of sp^2 hybridized carbon atoms: the values of C(6)−C(10), C(11)−C(12), and C(10)−C(11) are 1.522, 1.441, and 1.298 Å, respectively (Table 1). The bond distances of C(6)−C(10) of the β-substituted *trans*-isomers **2**−**4** are considerably shorter than those of **1**. Accordingly, substitution of the β-hydrogen atom with bulky substituents involving halogen atoms or a methylthio group results in the decrease in the bond length. The bond length of C(11)−C(12) of the methylthio derivative **4** is moderately elongated among the *trans*-isomers. Also, the replacement leads to a small increase of the C(10)−C(11) bond of **4**.

The *cis*-isomers **6** and **7** undergo only a minute change in the bond distances of C(6)−C(10) and C(10)−C(11)



Compound	R	Config.	Cytokinin activity[#]
1	H	(*E*)	1.8×10^{-8}
2	Cl	(*Z*)	2.8×10^{-10}
3	Br	(*Z*)	3.2×10^{-10}
4	SMe	(*Z*)	6.0×10^{-8}
5	H	(*Z*)	1.5×10^{-8}
6	Cl	(*E*)	1.9×10^{-8}
7	Br	(*E*)	1.1×10^{-8}
8	SMe	(*E*)	N.d.

[#] Cytokinin activity in a tobacco callus bioassay is expressed as a concentration at which each sample gives the same amount of fresh callus as the half maximum yield induced by kinetin. N.d. not determined (Nishikawa et al., 1994).

Figure 3. Structures of (*Z*)- and (*E*)-6-styrylpurines with numbering.

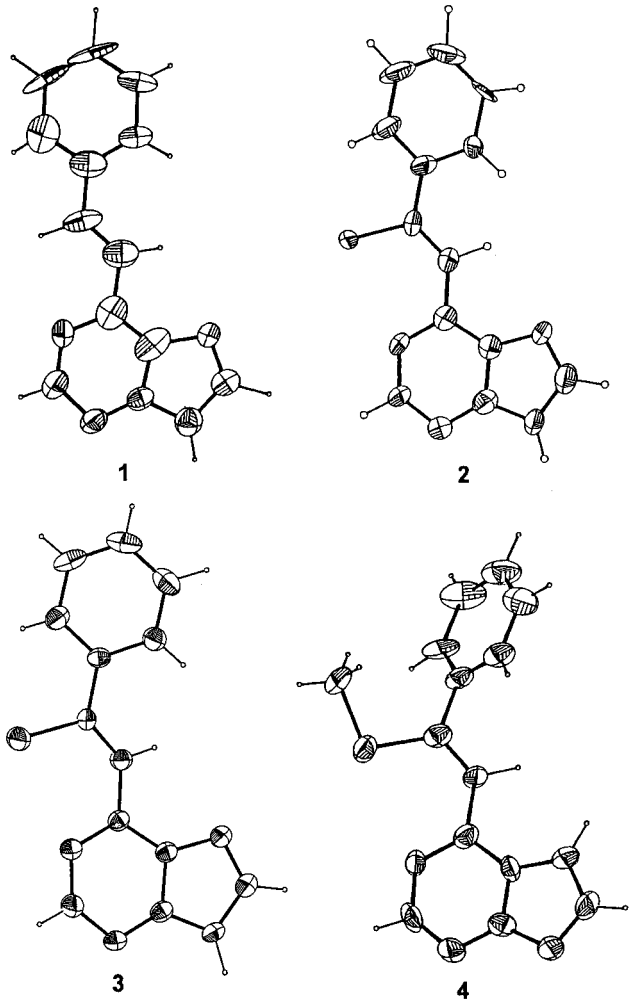


Figure 4. Crystal structures of *trans*-6-styrylpurines drawn by ORTEP.

in the substitution, but their bond lengths of C(11)−C(12) are slightly longer than that of the unsubstituted **5**. Among the *cis*-isomers, the methylthio derivative **8** is an exception; the bond lengths of C(6)−C(10) and C(10)−C(11) are shorter and slightly longer, respectively, than those of **5**. This may come from its conformation being different from those of the other *cis*-isomers described later.

Some bond angles of the carbon atoms of C(6), C(10), and C(11), which constitute the ethenyl linkage in the side chain, are summarized (Table 2). The bond angles except for C(10)−C(11)−C(12) of the unsubstituted **1** are very close to 120° , showing typical values of an sp^2 carbon atom. On the other hand, the *cis*-unsubstituted **5** affords bond angles of C(6)−C(10)−C(11) and C(10)−C(11)−C(12) that deviate moderately (by 7−10°) from the typical value. The most striking is the change in the bond angle of C(6)−C(10)−C(11) of the *trans*-isomers **2** and **3** upon substitution with halogens. The introduction of chlorine and bromine atoms into the β-position leads to a significant increase in the bond angle by 10−11° compared to that of **1**. This diminishes the steric or electronic repulsion between the N^1 atom and the β-halogens. In addition, although there is a slightly lower increase (by 7−8°) in the bond angle of C(6)−C(10)−C(11) of the *trans* methylthio derivative **4**, a moderate decrease in the bond angle of C(10)−C(11)−C(12) occurs, due to a similar repulsion together with the folding of the methylthio group onto the phenyl ring. The changes in the other bond angles of the β-substituted *trans*- and *cis*-isomers are small and fall within a range of ±2° compared to the corresponding unsubstitued **1** and **5**. Again, the methylthio derivative **8** differs from the other *cis*-isomers **5**−**7** with respect to the bond angles.

Tortion angles, ϕ_1 and ϕ_2, are defined as N(1)−C(6)−C(10)−C(11) and C(10)−C(11)−C(12)−C(17), respectively (Table 3). All of the *trans*-isomers exist in an *anti* form as shown by their ϕ_1 values close to 0°. The change in the torsion angles ϕ_1 seems to be dependent on the bulkiness of the β-substituent (H < Cl < Br < SMe). On the other hand, the values of ϕ_1 of the *cis*-isomers **5**−**7** are near 180°, indicating that they adopt a *syn* conformation. The only exception is the *cis*-methylthio derivative **8**, which prefers an *anti* conformation to a

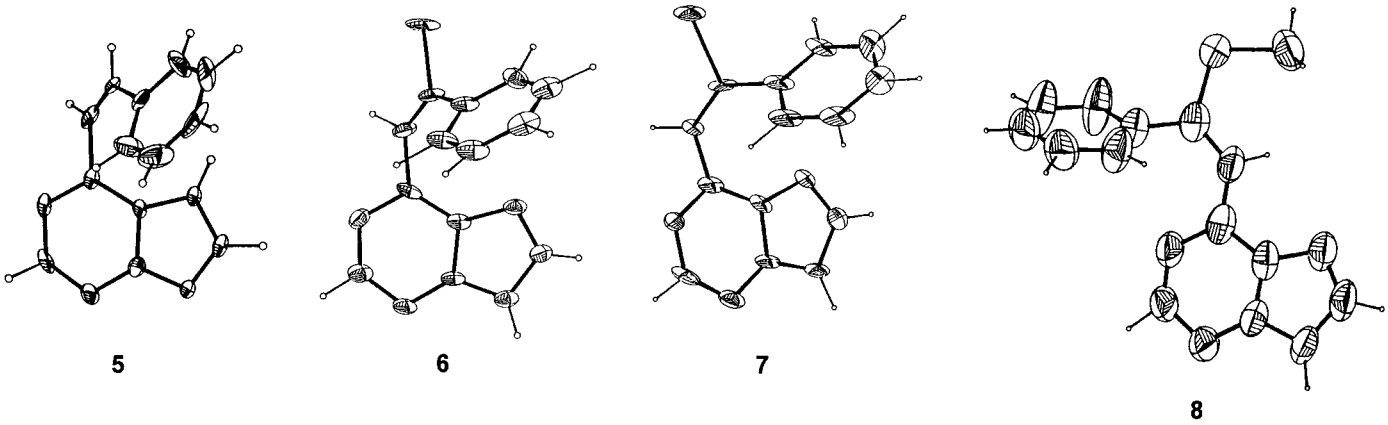


Figure 5. Crystal structures of *cis*-6-styrylpurines drawn by ORTEP.

Table 2. Bond Angles (Degrees) of *β*-Substituted 6-Styrylpurines

compd	C(5)−C(6)−C(10)	N(1)−C(6)−C(10)	C(6)−C(10)−C(11)	C(10)−C(11)−X	C(10)−C(11)−C(12)
1	120.0 (5)[a]	120.9 (5)	122.8 (5)	120.1 (30)	125.9 (6)
2	119.6 (4)	122.2 (4)	133.3 (4)	119.9 (4)	126.0 (4)
3	119.7 (3)	122.0 (3)	132.6 (3)	121.5 (2)	119.8 (3)
4 (1)	120.4 (4)	122.5 (4)	129.8 (4)	122.2 (3)	118.3 (4)
4 (2)	120.6 (4)	121.7 (4)	130.1 (4)	122.7 (4)	118.7 (4)
5 (1)	122.9 (4)	118.1 (4)	124.9 (4)	118.8 (28)	129.8 (4)
5 (2)	123.2 (4)	118.7 (4)	125.7 (4)	121.3 (27)	129.5 (4)
6	124.8 (5)	116.1 (5)	126.1 (5)	117.5 (5)	129.2 (5)
7	125.0 (7)	116.2 (7)	125.3 (8)	116.7 (7)	130.4 (8)
8	120.5 (5)	123.7 (6)	130.2 (6)	124.3 (5)	126.1 (5)

[a] Estimated standard deviations are shown in parentheses.

Table 3. Torsion Angles (ϕ_1 and ϕ_2)[a] and Angle between the Purine Ring and the Phenyl Ring (ω) of *β*-Substituted 6-Styrylpurines.

compd	ϕ_1 (deg)	ϕ_2 (deg)	ω (deg)
1	−4.7 (9)[b]	−3.8 (10)	171.4 (2)
2	−5.8 (8)	18.0 (7)	164.2 (1)
3	13.6 (5)	153.5 (3)	18.1 (1)
4 (1)	17.9 (7)	124.4 (5)	141.6 (1)
4 (2)	−12.0 (8)	−104.8 (6)	63.6 (2)
5 (1)	122.9 (5)	153.4 (5)	60.5 (1)
5 (2)	−124.0 (4)	−149.3 (5)	64.4 (1)
6	135.1 (6)	138.0 (9)	63.4 (2)
7	131.6 (9)	133.5 (10)	65.4 (3)
8	6.7 (11)	−123.6 (7)	116.6 (2)

[a] ϕ_1 and ϕ_2 are torsion angles of N(1)−C(6)−C(10)−C(11) and C(10)−C(11)−C(12)−C(17), respectively. [b] Estimated standard deviations are shown in parentheses.

syn one in the crystal. Among the *trans*-isomers, the net change of ϕ_2 from 0° or 180° (phenyl group is symmetrical) becomes larger with the increase in the bulkiness of the *β*-substituents: 3.8°, 18.0°, 26.5°, and 55.6° (or 75.2°) for H, Cl, Br, and SMe, respectively. In the *trans*-isomer **4**, the resonance between the phenyl group and the ethenyl group is substantially difficult because of a significant twist from the planarity. The inhibition of the resonance folds for all the *cis*-isomers.

The parameter ω is the angle between the purine ring and the phenyl ring. ω values of **1**−**3** close to 0° or 180° indicate that both of the rings are almost coplanar or only slightly slanted. Compared to this, the planarity is considerably reduced in **4** (Table 3). In contrast, the ω values of the *cis*-isomers **5**−**7** are almost constant irrespective of the bulkiness of the *β*-substituents. The *cis*-isomer **8** gives a different ω value that is derived from its *anti* conformation.

The planarity of cytokinin molecules was hypothesized for potent cytokinin activity in the case of *N*-phenyl-*N*′-pyridylureas (Yamaguchi and Shudo, 1991). If such planarity is essential, the unsubstitued *trans*-derivative **1** is ideal from the viewpoint of the planarity, as shown in the small ϕ_1 and ϕ_2 values together with the ω value close to 180°. 6-(2-Phenetyl)purine, a saturated analogue of **1** or **5**, is flexible and can freely rotate about the three single bonds of the side chain. In the crystal, it adopts a conformation in which the phenyl ring is nearly parallel with the purine ring with a span of ∼1.5 Å and the side chain extrudes from the bond of C(6)−C(10) as fully extended (Leonard et al., 1981). Thus, there is a difference in conformation between them; whereas the two rings of the phenethyl derivative are almost parallel, those of **1** are practically coplanar. The former is as active as or slightly less active than the unsubstituted **1** in an tobacco callus bioassay (Henderson et al., 1975), and ∼3-fold weaker than **1** and N^6-benzyladenine in an *Amaranthus* betacyanin bioassay and a tobacco callus bioassay (Nishikawa et al., 1986). The lower activity is explained from the substituent-directing effect that cytokinins, which are organized in advance as active conformation, are stronger than flexible ones. Because the difference in the activity between the conformationally constrained **1** and the flexible phenethyl derivative is small, the planarity of the molecules appears to be more important than the substituent-directing effect. A receptor would accommodate cytokinin analogues having two flat rings not only in a coplanar conformation but also in a parallel one. The *trans*-isomers **1**−**3** resemble each other in their conformation in the first approximation, and the structural feature common to the three isomers is the planarity. If the restricted form is relevant to active conformation, high activity should appear. In fact, the *trans*-isomers **1**−**3** strongly induced betacyanin biosynthesis of *Amaranthus* and the growth of tobacco callus (Nishikawa et al., 1994); **2** and **3** exhibited an excep-

tionally potent activity in the tobacco callus bioassay (Table 1). The higher activities of **2** and **3** compared to that of **1** in the bioassay may be attributable to the enhanced restriction of the rotation about the bond of C(6)−C(10) caused by the β-halogen atoms, in addition to their increased hydrophobicity that favors the activity. The lower activity of **4** compared to **1** may reside in its inability to take a planar conformation or the hindrance of a secondary binding site of receptor by the bulky methylthio group.

The *cis*-isomers **5**−**7** take a *syn* form and their conformations are similar, but the derivative **8** exists in an *anti* form in which the methylthio group is away from the phenyl ring. The former three, which exist in similar conformations, have no planarity in contrast with the *trans*-isomers. This study showed experimentally that the *cis*-isomers of the β-substituted 6-styrylpurines exist in both *syn* and *anti* forms. Most of the *cis*-isomers prefer a *syn* conformation to an *anti* one. Conformations of the *cis*-isomers have rarely been studied until now. Besides the binding sites postulated previously in receptor mapping (Iwamura et al., 1980, 1985), an additional binding site at which the cytokinin receptor recognizes aromatic rings of their side chains should be provided, because they are cytokinin-active, although their activities are less active than those of the corresponding *trans*-isomers.

On the basis of the preferred conformation and strong activity of the *trans*-isomers, it was concluded that the most plausible active conformation of cytokinins was the *anti-transoid* form in which the planarity of the molecules is maintained. This conformation would play the utmost role in the receptor binding to induce a significant biological response. Similarly, the *syn-cisoid* form that most of the *cis*-isomers adopt could be also involved in the binding to some extent. Because the conformation in the crystal is affected by some factors such as packing force and conditions for crystallization, it is not always identical with the active form and the conformation in solution or in isolated state. Other studies of the conformer models by molecular mechanics calculation and by dynamic NMR method would give a firm basis on the active conformation proposed here. This study revealed the conformational characteristics in the crystal of the β-substituted 6-styrylpurines as conformer models. Furthermore, we showed that the use of conformationally restricted conformer models was quite effective in identifying active conformation.

Supporting Information Available: Tables listing experimental details of X-ray analysis and fractional coordinates of compounds **1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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