Table I. Rate Constants[a] for Reductions of Cobalt(III) and Chromium(III) Thiocyanate and Isothiocyanate Complexes

Reaction	M^{2+}: Cr^{2+}	M^{2+}: Fe^{2+}	Ref
$(NH_3)_5CoSCN^{2+} + M^{2+} \rightarrow [(NH_3)_5CoSCNM^{4+}]^{\ddagger}$	1.9×10^5	1.2×10^{-1}	*b*, *c*
$(NH_3)_5CoSCN^{2+} + M^{2+} \rightarrow [(NH_3)_5CoSM^{4+}]^{\ddagger}$ (C, N)	0.8×10^5		*b*
$(NH_3)_5CoNCS^{2+} + M^{2+} \rightarrow [(NH_3)_5CoNCSM^{4+}]^{\ddagger}$	1.9×10^1	$<3 \times 10^{-6}$	*d*, *e*
$(H_2O)_5CrSCN^{2+} + M^{2+} \rightarrow [(H_2O)_5CrSCNM^{4+}]^{\ddagger}$	40		*f*
$(H_2O)_5CrNCS^{2+} + M^{2+} \rightarrow [(H_2O)_5CrNCSM^{4+}]^{\ddagger}$	1.4×10^{-4}		*g*

[a] At 25° and $\mu = 1.0$ *M*. [b] This work. [c] Reference 13. [d] Reference 12. [e] J. H. Espenson, *Inorg. Chem.*, **4**, 121 (1965). [f] Reference 6. [g] D. L. Ball and E. L. King, *J. Amer. Chem. Soc.*, **80**, 1091 (1958).

Although the $Co(NH_3)_5NCS^{2+}$–Cr^{2+} reaction has been examined previously both stoichiometrically[11] and kinetically,[12] there is no direct evidence on the question of adjacent or remote attack. We have reexamined this system in order to determine the yields of $CrSCN^{2+}$ and $CrNCS^{2+}$. The measurements were carried out in the rapid-flow apparatus at 262 nm with chromium(II) in excess. At this wavelength the absorbance first increases (disappearance of $Co(NH_3)_5NCS^{2+}$, ϵ 512, appearance of $CrSCN^{2+}$, ϵ 8.0×10^3), goes through a maximum, and then decreases (Cr^{2+}-catalyzed isomerization of $CrSCN^{2+}$ to $CrNCS^{2+}$, ϵ 2.7×10^3). The time, t_{max}, for maximum absorbance is

$$t_{max} = \frac{1}{[Cr(II)](k_1 - k_2)} \ln\left[\frac{(k_2 - k_1)(\epsilon_1 - \epsilon_2)}{f_s k_2(\epsilon_3 - \epsilon_2)} + \frac{k_1}{k_2}\right]$$

where f_s is the fraction of reaction that proceeds *via* attack at S (remote), k_1 and k_2 are the second-order rate constants for the $Co(NH_3)_5NCS^{2+}$–Cr^{2+} and $CrSCN^{2+}$–Cr^{2+} reactions,[6,12] respectively, and ϵ_1, ϵ_2, and ϵ_3 are the extinction coefficients of $Co(NH_3)_5NCS^{2+}$, $CrNCS^{2+}$, and $CrSCN^{2+}$, respectively. At 25°, $[H^+] = 1.0$ *M*, $[Cr^{2+}] = 8.47 \times 10^{-3}$ *M*, and $[Co(NH_3)_5NCS^{2+}] = 3.61 \times 10^{-4}$ *M*; t_{max} was 9.5 ± 0.3 sec. Under the same conditions but with $[Cr^{2+}] = 1.7 \times 10^{-2}$ *M*, t_{max} was 4.0 ± 0.3 sec. The values of f_s calculated from these t_{max} values are 0.97 ± 0.03 and 1.04 ± 0.09, respectively, and we conclude that the $Co(NH_3)_5NCS^{2+}$–Cr^{2+} reaction proceeds quantitatively by the remote-attack mechanism.

$$Co(NH_3)_5NCS^{2+} + Cr^{2+} \longrightarrow [(NH_3)_5CoNCS\ Cr^{4+}]^{\ddagger} \longrightarrow CrSCN^{2+}$$

The results of the investigations on the present and related systems are summarized in Table I. It will be seen that the thiocyanate complexes are reduced at a much faster rate than the isothiocyanate complexes. Since all the metal centers involved in the redox reactions under consideration display a preference for nitrogen over sulfur, the reactivity order $SCN^- \gg NCS^-$ for reaction *via* remote attack is expected on the basis of free energy considerations.[13]

However, the high reactivity of $Co(NH_3)_5SCN^{2+}$ for reaction with Cr^{2+} *via* adjacent attack is, in our opinion, a most remarkable finding. On the basis of thermodynamic considerations,[13] the Cr–S bond being 3×10^5 less stable than the Cr–N bond, adjacent attack would be expected to proceed at a rate ~500 times slower than remote attack. Moreover, on the basis of steric effects we would expect the adjacent S to be less available than the remote N for precursor binuclear complex formation. Based on these considerations, a value of 10^3 for the ratio of remote to adjacent attack by Cr^{2+} on $Co(NH_3)_5SCN^{2+}$ would appear to be a reasonable (and perhaps conservative) estimate. The observed ratio of 2.4 is substantially smaller than the estimated value, and therefore an additional factor must be invoked to explain the unusually high reactivity of $Co(NH_3)_5SCN^{2+}$ for reaction with Cr^{2+} *via* adjacent attack. As noted previously,[6] this factor may be the high electron-mediating ability of the sulfur bound to the oxidizing center for reaction *via* an inner-sphere mechanism. Additional work with other reducing agents and with other sulfur-containing ligands is planned.[14]

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(14) Note Added in Proof. Work in progress indicates that the reaction of $Co(NH_3)_5SCN^{2+}$ with $Co(CN)_5^{3-}$ proceeds with a rate constant larger than 10^6 M^{-1} sec^{-1} (25°, ionic strength 0.10 *M*) and produces $Co(CN)_5SCN^{3-}$ in *ca.* 100% yield.

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A Stereoselective Synthesis of *cis*-Zeatin

Sir:

Zeatin, the highly active stimulant of cell division in plant tissue cultures, which was first isolated from *Zea mays*, has the structure 6-(4-hydroxy-3-methyl-*trans*-2-butenylamino)purine (**1**).[1-5] Although this trans isomer has been synthesized,[6-9] previous attempts to obtain the corresponding cis isomer have been unsuccessful mainly because of cis–trans isomerization encountered with the types of intermediates employed. Interest in the synthesis of *cis*-zeatin (**2**) stems from the isolation of a cytokinin assigned the structure ribosyl-*cis*-zeatin (9-ribosyl-**2**) from the tRNA of certain plant tissue, *e.g.*, peas, spinach, corn,[10-12] and from the finding that cy-

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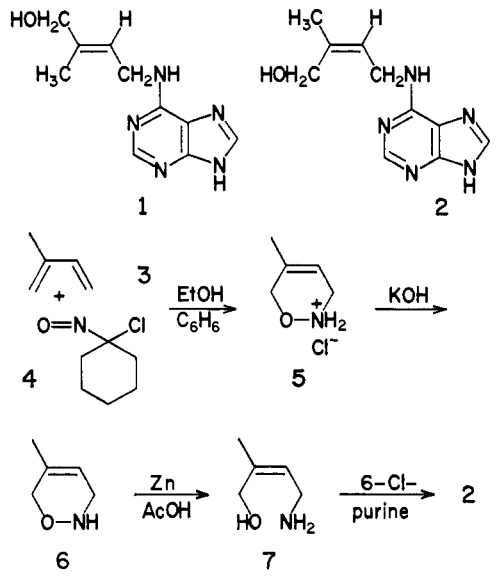
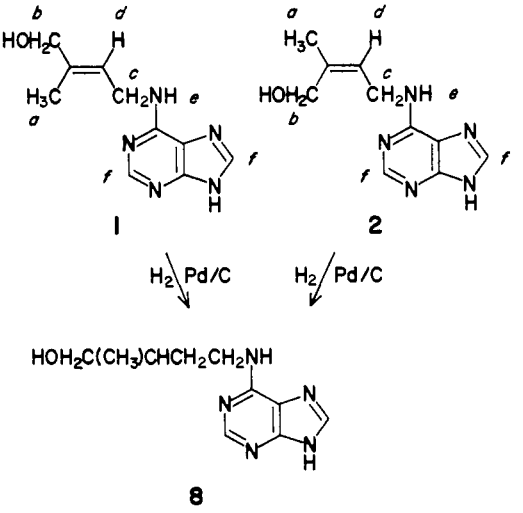


tokinin activity is influenced by spatial factors including side-chain geometry.[13]

We wish to report a successful synthetic route to *cis*-zeatin, 6-(4-hydroxy-3-methyl-*cis*-2-butenylamino)-purine (**2**), which utilizes cyclic intermediates to ensure correct stereochemistry. The concept was one of generating the CH_2OH and CH_2NH_2 groups on the same side of the double bond by a method which would not lead to isomerization at an intermediate stage. The cyclic O,N-substituted hydroxylamine derivative **6** suggested itself as a desirable precursor of the intermediate **7**, 4-hydroxy-3-methyl-*cis*-2-butenylamine, required for condensation with 6-chloropurine, since **6** should be obtainable *via* a Diels–Alder reaction. The reaction of 1-chloro-1-nitrosocyclohexane (**4**)[14,15] with isoprene (**3**) was effected in benzene–ethanol, with hydroquinone added, during 24 hr with the temperature maintained below 30°. Unlike the case with butadiene,[16] the yield of Diels–Alder product was sacrificed because of the allylic methyl of isoprene, since this was the major locus of nitroso attack.[17] However, the Diels–Alder product that did result was the desired positional isomer (see below), a feature consistent with the findings of Wichterle and Švastal with phenyl-substituted butadienes.[18] The crude 5-methyl-3,6-dihydro-1,2-oxazine hydrochloride (**5**) was obtained by evaporation of the reaction solution and washing of the residue with ether. Further purification was effected during the conversion of **5** to the free base **6** by aqueous potassium hydroxide with ether extraction. The entire sequence could be operated efficiently without the necessity of isolating pure intermediates. Reductive ring opening of 5-methyl-3,6-dihydro-1,2-oxazine (**6**) with zinc and acetic acid at room temperature yielded the desired amino alcohol, 4-hydroxy-3-methyl-*cis*-2-butenylamine (**7**), which was converted immediately to 6-(4-hydroxy-3-methyl-*cis*-2-butenylamino)purine (**2**) by reaction with 6-chloropurine in refluxing *n*-butyl alcohol (2 hr). On cooling the reaction mixture, the product which precipitated represented 25% conversion. Chromatography of the residual material in ethyl acetate–ethanol (4:1) on silica raised this figure to 42%, mp 206–208° (*Anal.* Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.97; N, 31.95. Found: C, 54.49; H, 6.05; N, 32.10). The ultraviolet spectra ($\lambda_{max}^{H_2O}$ 269 nm (ϵ 19,200), λ_{min} 230; $\lambda_{max}^{0.1\ N\ HCl}$ 274 (17,850), λ_{min} 234; $\lambda_{max}^{0.1\ N\ NaOH}$ 275 (18,450), 283 (sh), λ_{min} 241) and mass spectra of this compound and of zeatin (*trans*-zeatin) (**1**)[7,19] are practically indistinguishable. However, the nmr spectra of the two isomers, while quite similar, showed some significant differences in chemical shifts (in DMSO-d_6), as indicated in Table I. The question of

Table I. Comparative Nmr

Protons	Trans, δ	Multiplicity	Cis	Protons
a	1.7	s (3)	1.8	a
b	3.8	s (2)	4.2	b
c	4.2	m (2)	4.3	c
d	5.6	t (1)	5.5	d
e	7.7	t (1)	7.7	e
f	8.15	s (1)	8.2	f
f	8.25	s (1)	8.3	f



which positional isomer we had in hand throughout had been held in abeyance to this point, but the comparative nmr spectra were most encouraging. Since Katzenellenbogen had shown that the isomer pairs of representative isoprene alcohols can be readily and unambiguously distinguished by their nmr spectra,[20] our product and zeatin were recognized as being geometrical isomers. Furthermore, we found that the two zeatins could be separated in 9:1 chloroform–methanol by

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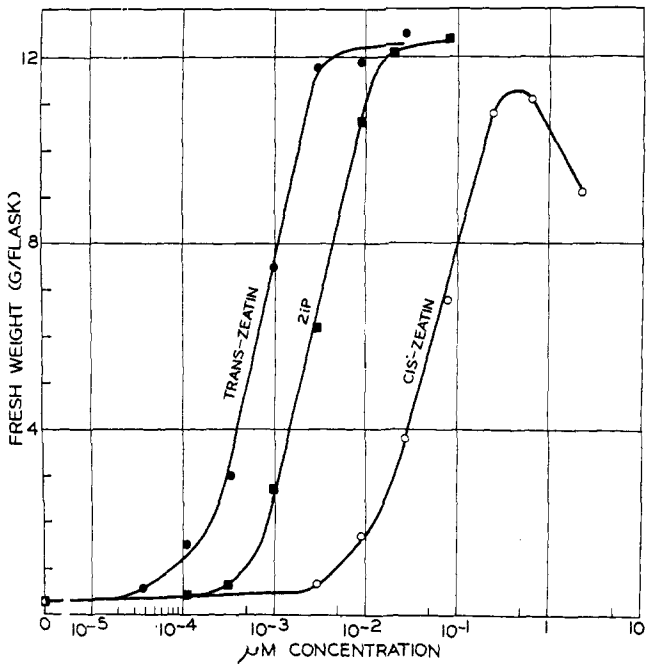

Figure 1. Comparison of cytokinin activities of *trans*- and *cis*-zeatin and of 6-(3-methyl-2-butenylamino)purine (2iP) in the tobacco bioassay. The curves represent mean values from three experiments. Growth period 35 days within the dates June 10–Sept 4, 1970.

thin-layer chromatography on silica: trans, R_f 0.25; cis, R_f 0.32. Final proof that the synthesis had been stereoselective, leading to 6-(4-hydroxy-3-methyl-*cis*-2-butenylamino)purine (**2**), was achieved by hydrogenation of the product over 5% palladium on charcoal to give (±)-dihydrozeatin (**8**),[21,22] identified by direct comparison with an authentic sample prepared by catalytic hydrogenation of zeatin (R_f, melting point, mixture melting point, nmr; picrate melting point, nmr (pyridine-d_5)).[23]

The difference in biological activity between *cis*- and *trans*-zeatin was striking. In the standard tobacco callus bioassay for cytokinin activity,[24] the trans isomer was at least 50 times more active than *cis*-zeatin (Figure 1), a finding consistent with the difference in activity of other N^6-substituted adenines and adenosines showing dependency on the geometrical configuration of the side chain.[11,13]

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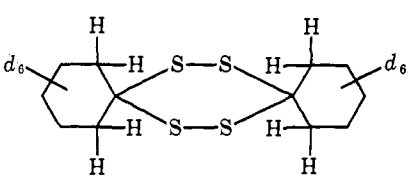
Conformational Analysis in Multisulfur Heterocycles. VI. 3,3:6,6-Bis(pentamethylene)-*s*-tetrathiane. Slow Pseudorotation in the Twist Conformer of a 6 Ring

Sir:

Since the early postulation by Sachse[1] of chair and flexible (twist) forms for cyclohexane, a wealth of experimental data indicates a general preference for the chair conformer in 6 rings both homocyclic[2] and heterocyclic.[3] Recently, we reported evidence for a low chair–twist energy difference in *s*-tetrathianes and activation parameters for the chair ⇄ twist rate process.[4]

This paper concerns evidence from dnmr spectroscopy for all three of the conformational rate processes possible in a 6 ring, *i.e.*, chair ⇄ chair, chair ⇄ twist, and twist ⇄ twist (pseudorotation[5]) interconversions, being slow on the nmr time scale at −90° in a *single* structure, the deuterated form of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane (I).



I

The ^1H nmr spectrum (100 MHz) of I in C_2Cl_4 at 80° is a singlet consistent with all protons being rendered equivalent *via* rapid exchange on the nmr time scale (Figure 1). Upon lowering the temperature, the spectrum broadens and separates into three peaks in a manner analogous to that for duplodithioacetone (3,3,6,6-tetramethyl-*s*-tetrathiane)[4] and is totally consistent with a slowing of the *s*-tetrathiane chair ⇄ twist equilibration.[4] The two smaller singlets of equal area (−6°, Figure 1) are assigned to the axial and equatorial methylene groups of the chair conformer of the *s*-tetrathiane ring (C_{2h} symmetry) in I. The lowest field singlet observed at −6° is broadened by exchange processes to be discussed. The large singlet observed at −6° (Figure 1) is assigned to the twist conformer

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