EXPLANATION FOR STEREOSELECTIVITY OF THE *CIS*-DIHYDROXYLATION OF *CIS*-3,5-DISUBSTITUTED CYCLOPENTENES[1)]

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Stereoselectivity of the *cis*-dihydroxylation of *cis*-3,5-disubstituted cyclopentenes has been found to depend on the conformation of cyclopentenes and has been explained by both steric and Cieplak effects.

KEYWORDS carbocyclic nucleoside; *cis*-dihydroxylation; *cis*-3,5-disubstituted cyclopentene; stereoselectivity; steric effect; Cieplak effect

cis-Dihydroxylation of *cis*-3,5-disubstituted cyclopentenes is one of the most important manipulations in the synthesis of carbocyclic nucleosides such as aristeromycin and related compounds.[2)] Although there are many reports concerning *cis*-dihydroxylation by using potassium permanganate or osmium tetroxide, rationalization for the stereoselectivity has not been reported so far.[3)]

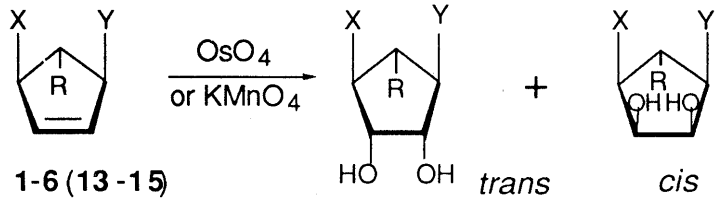
We propose here a rational explanation for the stereoselectivity of *cis*-dihydroxylation by a combination of steric and Cieplak effects.

It was reported that the dihydroxylation of *cis*-3-acetamino-5-acetoxymethylcyclopentene (**1**) with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide gave a mixture of *trans*- (**7***trans*) and *cis*-products (**7***cis*) with the ratio of 1:2[4)] whereas the reaction of (+)-methyl 4-*cis*-acetamidocyclopent-2-ene 1-carboxylate (**2**), under the same conditions, produced the *trans*-product (**8**) exclusively.[5)] It was also reported that *O*-monoacetyl- (**3**)[6)] and *O*-diacetyl (**4**)[7)] derivatives of cyclopentene-3,5-diol were dihydroxylated to give selectively the corresponding *trans* products (**9** and **10**).

In order to obtain a deeper insight into this problem, we carried out the dihydroxylation of *cis*-3,5-bisacetoxymethyl- (**5**)[8)] and *cis*-3-acetoxy-5-methylcyclopentene (**6**)[9)] using osmium tetroxide in the presence of *N*-methylmorpholine oxide. The dihydroxylation of **5** gave a mixture of *trans*- (**11***trans*) and *cis*-products (**11***cis*) in respective yields of 40% and 56%, whereas that of **6** produced exclusively the *trans*-product (**12**).[10)]

It is obvious that all *cis*-3,5-disubstituted cyclopentenes bearing one or two acetoxy groups produce

Table I. *cis*-Dihydroxylation of *cis*-3,5-Disubstituted Cyclopentenes



1-6 (13-15)

Compd	R	X	Y	Product	Yield (%)	*trans*	*cis*
1	H	AcOCH2	NHAc	**7**[4)]	90[a)]	1	2
2	H	AcNH	CO2Me	**8**[5)]	40[b)]	alone	-----
3	H	HO	OAc	**9**[6)]	94	alone	-----
4	H	AcO	OAc	**10**[7)]	89[c)]	alone	-----
5	H	AcOCH2	CH2OAc	**11**	95	1	1.4
6	H	Me	OAc	**12**	74	alone	-----
13	H	HO	adenin-9-yl	**16**[16)]	----[d)]	alone	-----
14	H	HOCH2	adenin-9-yl	**17**[16)]	88	2.4	1
15	CH2OH	HOCH2	adenin-9-yl	**18**	75	1	1.5

a) isolated as their hydrolyzed products, b) isolated as the corresponding amino alcohol, c) isolated as its acetonide, d) not described.

only the corresponding *trans* products. Knowing that *cis*-3,5-disubstituted cyclopentenes take the 4-endo envelope conformation regardless of the kind of substituent,[11] stereochemical results of the osmylation should be related to two possible conformations with the two substituents in either a quasi axial (**A**) or a quasi equatorial (**B**) position (Chart 1). The conformations of the substrates can be readily determined by their ^{1}H-NMR spectrum in which the coupling constant of 4a-H between 3-H or 5-H in the conformation **A** is less than 5 Hz, whereas that in the conformation **B** is more than 5.5 Hz.[12] Conformational analysis using this method has revealed that all compounds (**2-4, 6**) giving the *trans* products take conformation **A** and both compounds (**1, 5**) giving mixtures of the *cis* and *trans* products take conformation **B**.[13]

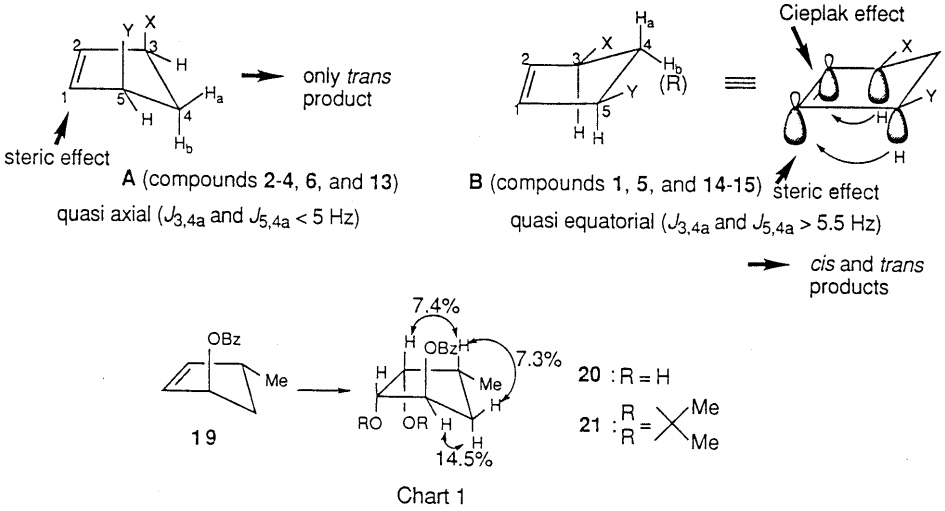


Chart 1

Hence, in conformation **A**, the *cis*-dihydroxylation would occur at the less hindered *trans* side (even though it has a concave face) relative to two substituents to give only the *trans* products.

Stereoselectivity of the *cis*-hydroxylation to conformation **B** seems to be rationalized in terms of the Cieplak theory.[14] Thus, the stabilization of the more hindered transition state (*cis*-side attack) can occur by electron donation from two anti periplanar C-H bonds to the antibonding orbitals of the incipient bonds ($\sigma^*‡$ orbitals, the low-lying vacant orbitals of the forming bonds). Therefore, though the less hindered side (*trans*-side) attack still survives,[15] the dihydroxylation at the *cis*-side is accelerated appreciably. Such hyper-conjugation of the C-H bonds to the $\sigma^*‡$ orbitals decreases in conformation **A** (the C-H bonds at 3,5-position are not anti periplanar to the incipient bonds), and, hence, only the less hindered side attack occurs.

During the course of the synthesis of aristeromycin, Trost and his coworkers[16] reported that 9-(*cis*-4-hydroxycyclopent-2-en-1-yl)-9*H*-adenine (**13**) was dihydroxylated to give the *trans* product (**16**) as a sole product, whereas the dihydroxylation of 9-(*cis*-4-hydroxymethylcyclopent-2-en-1-yl)-9*H*-adenine (**14**) resulted in the formation of aristeromycin (**17***trans*) and its lyxo isomer (**17***cis*) with the ratio of 2.4:1.

We applied the same reaction to BCA (**15**) (9-[*c*-4, *t*-5-bis(hydroxymethyl)cyclopent-2-en-*r*-1-yl]-9*H*-adenine), which is an anti-HIV agent recently developed in our laboratory.[17] As expected, the dihydroxylation of **15** gave a mixture of the *trans* and *cis* products (1:1.5). These reactions would be also explained well by a combination of steric (conformation **A**) and Cieplak effects (conformation **B**).[18]

All cyclopentene derivatives having an electron-withdrawing group or an oxygen functional group mentioned so far are verified to take conformation **A**.[13] The benzoyloxy group of *trans*-3-benzoyloxy-5-methylcyclopentene (**19**) also exists in a conformation having the quasi axial benzoyloxy group.[9] Expectedly, the dihydroxylation of **19** occurred exclusively at the opposite side (less hindered side) of the benzoyloxy group to give compound (**20**). The structure of **20** was determined by the NOE experiment of its acetonide (**21**) as shown in Chart 1.

In summary, stereoselectivity of the *cis*-dihydroxylation of *cis*-3,5-disubstituted cyclopentenes previously reported could be rationalized by both steric and Cieplack effects. We consider that the combination of the Cieplak and steric effects as proposed above could be widely applicable to the explanation for stereoselectivity of *cis*-dihydroxylation of substituted cyclopentenes.

ACKNOWLEDGMENT This work was supported in part by a Grant-in-Aid for Scientific Research (No. 06672230, N. K.) from the Ministry of Education, Science and Culture, Japan.

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9) Compounds (**6** and **19**) were prepared from 4-methylcyclopent-2-en-1-one by reduction with LiAlH4 followed by acetylation and benzoylation, respectively. Detailed preparation and full details of their ^{1}H-NMR spectra will be reported in a full paper.
10) The structures of **11***trans*, **11***cis*, and **12** were determined by NOE experiments. The 0.6 and 8.8 % NOE effect were observed between 1-H and 2-H of **11***trans* and **11***cis*, respectively. On the other hand, the acetonide of **12** showed the 3.5 % NOE effect between 3-H and 4-Me.
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13) Chemical shifts (δ) and coupling constants (Hz) of Ha and Hb (CDCl3): **1**: 1.29 ($J_{4a,3} = J_{4a,5}$ = 6.0), 2.57 ($J_{4b,3} = J_{4b,5}$ = 8.5), **2:** 1.88 ($J_{4a,3} = J_{4a,5}$ = 3.0), 2.46 ($J_{4b,3} = J_{4b,5}$ = 9.0), **3**: 1.66 ($J_{4a,3} = J_{4a,5}$ = 4.5), 2.81 ($J_{4b,3} = J_{4b,5}$ = 7.0), **4**: 1.57 ($J_{4a,3} = J_{4a,5}$ = 3.8), 2.73 ($J_{4b,3} = J_{4b,5}$ = 7.5), **5**: 1.27 ($J_{4a,3} = J_{4a,5}$ = 6.6), 2.25 ($J_{4b,3} = J_{4b,5}$ = 8.6), **6**: 1.35 ($J_{4a,3} = J_{4a,5}$ = 4.0), 2.49 ($J_{4b,3} = J_{4b,5}$ = 6.2): **15** (CD3OD): 2.37 ($J_{4a,3}$ = 7), 5.54 ($J_{4a,5}$ = 6).
14) a) This theory may be summarized as follows. Diastereofacial addition to substrates capable of stabilizing developing antibonding orbital in the transition state will be preferred. Hence, the new bond would be formed on the site which has an electron-rich bond (in the present case C-H*axial* bond) adjacent to it in the antiperiplanar position. A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981); A. S. Cieplak, B. D. Tait, C. R. Johnson, *J. Am. Chem. Soc.*, **111**, 8447 (1989); b) Tortional effects (1,2-interactions) of two axial protons at 3,5-positions could also be adapted for explanation of the *cis* orientated stereoselectivity. E. Vedejs, W. H. Dent, III, *J. Am. Chem. Soc.*, **111**, 6861 (1989).
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18) Since 9-(*cis*-4-hydroxymethylcyclopent-2-en-1-yl)-9*H*-guanine (carbovir) has the 5-endo conformation with the two substituents in a quasi equatorial position, compound **14** would have the same conformation (**B**). A. M. Exall, M. F. Jones, C. -L. Mo, P. L. Myers, I. L. Paternoster, H. Singh, R. Storer, G. G. Weingarten, C. Williamson, A. C. Brodie, J. Cook, D. E. Lake, C. A. Meerholz, P. J. Turnbull, R. M. Highcock, *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2467.

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