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Preferred Conformations of *cis*-4-Hydroxy-2-chromancarboxylates and Related Compounds. Molecular Force Field Interpretation

Minoru HIROTA,* Kazuhisa ABE, Masamichi SHIBATA, Hiroko SUEZAWA, Kaoru HANAYA,*,†
Takashi MURAMATSU,† and Yusaku IKEGAMI††

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240

†*Research Institute for Science Education, Miyagi University of Education, Aramaki, Aoba Sendai 980*

††*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Katahira, Sendai 980*

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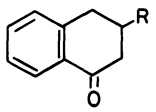
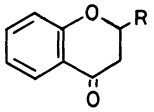
In contrast to *cis*-4-hydroxy-2-tetralincarboxylates, *cis*-4-hydroxy-2-chromancarboxylates take diaxial conformation having 4-pseudoaxial-OH and 2-axial-COOR groups preferably. The preferred conformations of these compounds were rationalized by molecular force field (MM1/MMP1) calculations on the corresponding 2-tetralin- and 2-chromancarbaldehydes as model compounds.

In connection with a series of investigations concerning the stereochemistry of catalytic hydrogenations of 4-chromanones by one of the authors (K. H.), the configuration and conformations of 4-chromanols produced by the reduction has been investigated.[1-3] The cyclohexene-like half-chair conformation has been generally accepted for the ring conformation of 3,4-dihydro-2*H*-1-benzopyrans. However, Philbin and Wheeler[4] proposed a "sofa" conformation in which all but one of the endocyclic atoms are planar. They assumed that the barrier between the sofa and the half-chair conformations is significantly low in these compounds. Contrary to this conclusion, Bolger and co-workers[5] deduced from the vicinal coupling constants of the ring protons that the dihydropyran rings of 4-benzoyloxyflavans take half-chair conformations in solution.

Hanaya and co-workers[1,6-8] found a noteworthy difference in the cis-trans ratios of the alcohols produced by the catalytic hydrogenation of 3-substituted 1-tetralones (**1**) and 2-substituted 4-chromanones (**2**) from those produced by the aluminum isopropoxide reduction of the same ketones. Thus, the *cis*-tetralols

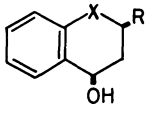


(**1**) R=CH_3, C_6H_5

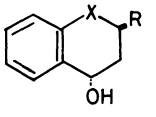


(**2**) R=CH_3, C_6H_5

(**3a**) and *cis*-chromanols (**4a**) were produced almost exclusively when the ketones (**1**) and (**2**) were hydrogenated over a Pd on charcoal or a Raney Ni catalyst, while the *trans*-alcohols (**3b**) predominated when the tetralones (**1**) were reduced by aluminum isopro-



(**3a**) X=CH_2
(**4a**) Y=O



(**3b**) X=CH_2
(**4b**) X=O

R=CH_3, C_6H_5

poxide (the Meerwein-Ponndorf reduction). The catalytic hydrogenation of ethyl 1-tetralone-3-carboxylate gave similarly ethyl *cis*-4-hydroxy-2-tetralincarboxylate, which is revealed to be the less stable epimer by equilibration carried out in the presence of aluminium isopropoxide. The configurations and conformations of these alcohols were discussed on the basis of their infrared spectra in the OH stretching region.[3,9]

On the other hand, ^{1}H NMR vicinal coupling constants are also very powerful in assigning the conformations of different torsional angles about a single bond.[10] Conformations of some 4-substituted flavans were discussed by the complete analysis of their ^{1}H NMR spectra.[5] In this investigation, the conformations of alkyl 4-hydroxy-2-chromancarboxylates and related compounds deduced from the infrared and ^{1}H NMR spectroscopic evidence are shown to be reproduced by molecular force field calculations on 4-hydroxy-2-tetralin- and 4-hydroxy-2-chromancarboxaldehydes as the model compounds.

Experimental

Preparation of the materials by reducing the corresponding ketones has previously been reported.[7,11] ^{1}H NMR spectra were measured with a Hitachi R-20 and a JEOL C-60H spectrometers.

Molecular force field calculations were carried out at the computer center of the Institute for Molecular Science and at the computer center of the University of Tokyo by use of MM1/MMP1 program originally written by Allinger and co-workers[12] and modified by Osawa.

Results and Discussion

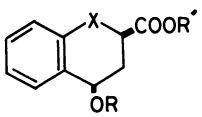
In order to determine the preferred conformations, ^{1}H NMR spectra of *cis*- and *trans*-4-hydroxy-2-tetralincarboxylates (**5a** and **5b**), *cis*-4-hydroxy-2-chromancarboxylate (**6a**), and their acetyl derivatives (**7a**, **7b**, and **8a**) were measured in chloroform-*d* at room temperature. In addition, the spectra of the alcohols in dimethyl-d_6 sulfoxide were also measured so as to assure the assignment of H on C(4) which is geminal to the hydroxyl group. The signal of H(4) was complicated by additional spin-spin interaction with hydroxyl proton in DMSO-d_6. The results of ^{1}H NMR measurement are summarized in Table 1.

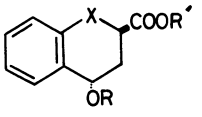
Vicinal coupling constants have been shown to be

Table 1. Chemical shifts ($\delta_{H(4)}$) and vicinal spin-spin coupling constants ($J_{3,4}$) of ethyl *cis*-4-hydroxy-2-chromancarboxylate and related compounds in chloroform-*d* at room temperature

	$\delta_{H(4)}$/ppm	$J_{3,4}$/Hz[a]
Alcohols		
5a	5.28	5.9, 9.5 dd
5b	4.80	3.6 broad t
6a	4.81	5.0 t
3a[b]	5.21	6.0, 11.0 dd
3b[b]	5.13	3.0 t
Acetates		
7a	6.05	5.8, 8.0 dd
7b	6.09	3.4 t
8a	5.96	4.5 t

a) dd: doublet of doublets, t: triplet. b) The corresponding values of *cis*- and *trans*-3-phenyl-1-tetralols (**3a** and **3b**, respectively) are given for reference.





(**5a**) X=CH_2, R=H, R'=C_2H_5 (**5b**) X=CH_2, R=H, R'=$CH(CH_3)_2$

(**6a**) X=O, R=H, R'=C_2H_5

(**6a**) X=O, R=H, R'=CH_3

(**7a**) X=CH_2, R=$COCH_3$, R'=C_2H_5 (**7b**) X=CH_2, R=$COCH_3$, R'=$CH(CH_3)_2$

(**8a**) X=O, R=$COCH_3$, R'=C_2H_5

very sensitive to the dihedral angle between the two mutually interacting ^1H nuclei. The dependency of vicinal coupling constant (J_{vic}) on dihedral angle (ϕ) was formulated by Karplus equation and similar equations[10,13,14] and proved to be useful in differentiating gauche ($\phi \approx 60°$) and anti ($\phi \approx 180°$) conformers about the C–C single bond. In the trans isomer (**5b**), the conformer carrying pseudoaxial(*a'*)-4-hydroxyl and equatorial(*e*)-2-alkoxycarbonyl groups is supposed to be predominant, since the alkoxycarbonyl group has a larger conformational free energy difference than the hydroxyl group (2.9 kJ mol^{-1} for OH and 4.6 kJ mol^{-1} for $COOCH_3$).[15] In this conformer, H(4) is pseudoequatorial and located gauche to both equatorial and axial protons on C(3)(*i. e.*, *e*-H(3) and *a*-H(3)). Vicinal coupling constants between axial and equatorial (J_{ae}) and equatorial and equatorial (J_{ee}) protons fall in the range between 2 and 3.5 Hz in the series of cyclohexane derivatives, which agrees with the observed coupling constants for **3b** and **5b**.

The cis isomers, on the other hand, are expected to take a 1,3-diequatorial (*i. e.*, equatorial-2-alkoxycarbonyl and pseudoequatorial-4-hydroxyl) conformation in the usual sense. As a consequence, a doublet of doublets is expected for H(4) due to axial-axial and axial-equatorial ^1H spin-spin interaction, since H(4) should occupy a pseudoaxial position in this conformer. In the case of *cis*-tetralin derivatives (**3a**, **5a**, and **7a**), the observed spectra are in line with the above assumption. However, the J_{vic} values of the *cis*-chroman derivatives (**6a** and **8a**) cannot adequately be interpreted by the 1,3-diequatorial conformation. In turn, slightly distorted 1,3-diaxial conformation (which has axial-2-ethoxycarbonyl and pseudoaxial-4-hydroxyl groups) or an equilibrium mixture of the diaxial and the diequatorial conformers is expected to prevail in these compounds. Thus, the triplets observed with **6a** and **8a** are explained by assuming the predominant 1,3-diaxial conformer having nearly identical J_{ae} and J_{ee} values. The coupling constants (5.0 and 4.5 Hz) seemed rather large for H(eq)–H(eq) and H(ax)–H(eq) spin-spin coupling and coexistence of a small amount of the 1,3-diequatorial conformer in a fast equilibrium with the diaxial one is expected. The coupling constant is not surprisingly large even when the 1,3-diaxial conformer alone is assumed to be present, since the J_{vic} value is calculated to be 4.1 Hz from the Lemieux's parametrization[14] of the Karplus equation assuming that the dihedral angle ϕ is 60°. Lemieux's parameters were derived empirically from the J_{vic} values of oxygen-containing six-membered rings such as 1,3-dioxane and sugars and might be suitable for the estimation of the J_{vic} values of the compounds in the chroman series.

In order to rationalize the conformational preference deduced from the observed NMR spectra, molecular force field calculations were carried out on *cis*- and *trans*-4-hydroxy-2-tetralincarbaldehydes (**9a** and **9b**, respectively) and 4-hydroxy-2-chromancarbaldehydes (**10a** and **10b**, respectively). Since the force field parameters for ester group is less trustworthy even in the revised version of MM1/MMP1 program, a model calculation replacing alkoxycarbonyl by formyl group

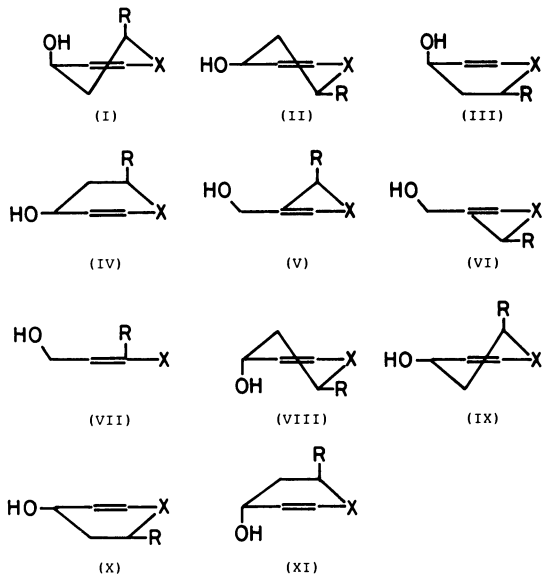


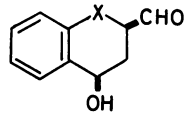
Fig. 1. Conformations selected for molecular force-field calculations. In the cases of **10a** and **10b** in Table 2 and **6a'** in Table 3, X refers to a divalent oxygen atom (O), while X is methylene group (CH_2) with the compounds **9a** and **9b** in Table 4. All coordinates were optimized whenever conformations are stable (*i. e.*, located at potential minima).

Table 2. Steric energies of *cis*- and *trans*-4-hydroxy-2-chromancarbaldehydes (**10a** and **10b**) obtained by MM calculation[a)]

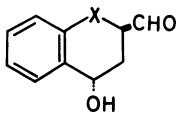
	Conformations of **10a**							Conformations of **10b**			
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
E_c	3.35	3.10	3.85	3.22	3.77	3.43	3.77	3.18	3.39	3.31	3.60
E_b	9.46	10.04	12.22	13.22	7.15	8.28	26.90	9.33	9.67	14.06	11.38
E_{sb}	0.75	0.67	0.79	1.13	0.67	0.63	1.59	0.59	0.92	0.96	1.05
E_{vdw}*	43.05	40.67	48.41	44.69	44.60	43.05	52.05	42.76	42.34	44.77	48.28
E_{vdw}	−7.53	−8.58	−9.92	−9.33	−7.70	−8.49	−7.07	−9.12	−8.66	−9.08	−10.08
E_w	15.69	14.69	27.99	27.49	20.75	21.59	25.98	14.14	14.85	27.91	27.95
E_{tb}	−0.04	−0.04	−1.59	−1.67	−0.29	−0.33	−5.40	−0.08	−0.04	−1.63	−1.63
E_d	5.61	12.05	8.62	12.80	9.54	12.51	10.50	9.67	17.03	12.09	13.93
E	70.33	72.59	90.42	91.55	78.91	80.67	108.32	70.42	79.41	92.38	94.47
ΔE	0	2.26	20.09	21.22	8.58	10.34	37.99	0.09	9.08	22.05	24.14

a) All energies are given in kJ mol^{-1}.

was carried out in order to predict the preferred conformations of the esters **5a** and **6a**. As to *cis*-4-hydroxy-2-chromancarbaldehyde (**10a**), the steric energies were calculated on the seven conformationsin Fig. 1: I, half-chair carrying 4*a*′-OH and 2*a*-CHO; II, half-chair carrying 4*e*′-OH and 2*e*-CHO; III, half-boat carrying 4*a*′-OH and 2*e*-CHO; IV, half-boat carrying 4*e*′-OH and 2*a*-CHO; V, sofa carrying 2*a*-CHO; VI, sofa carrying 2*e*-CHO; and VII, planar conformations (illustrated in Fig. 1). Calculated steric energies (E)



(**9a**) X=CH_2
(**10a**) X=O



(**9b**) X=CH_2
(**10b**) X=O

and their components were given in Table 2, where E_c, E_b, E_{vdw}*, E_{vdw}, E_w, and E_d denote compression (stretching) energy, bending energy, van der Waals energy due to 1,4-interaction, van der Waals energy of other than 1,4-interaction, torsional energy, and dipole interaction energy terms, respectively. E_{sb} and E_{tb} are stretch-bend and torsion-bend cross terms. Similar calculations were carried out on the following four conformations of the trans isomer **10b**: VIII, half chair carrying 4*a*′-OH and 2*e*-CHO; IX, half-chair carrying 4*e*′-OH and 2*a*-CHO; X, half-boat carrying 4*e*′-OH and 2*e*-CHO; XI, half-boat carrying 4*a*′-OH and 2*a*-CHO (illustrated in Fig. 1).

When the total steric energies (E) are compared among the conformations, half-chair conformations are always more stable than other conformations assumed in the calculations. As expected, the half-chair conformation (VIII) carrying 4*a*′-OH and 2*e*-CHO groups is the most stable conformer of the trans isomer **10b**. Quite unexpectedly, the half-chair conformation (I) carrying 4*a*′-OH and 2*a*-CHO groups is estimated to be the most stable for the cis-chroman derivative **10a** by the calculation. The dihedral angles between H(4) and two H(3)'s are calculated to be 50.8° and 68.6°. The J_{vic} values for these dihedral angles from the modified Karplus equation[16] are 5.70 and 4.64 Hz, which reproduces the experimental results for **6a** and **8a** qualitatively. However, the steric energy difference between the most and the next stable conformations is relatively small. From the energy difference (2.26 kJ mol^{-1}), **10a** is expected to exist as a mixture of the two conformers I and II in 69% and 28% abundances, respectively, at room temperature (298 K) by assuming the Boltzmann distribution a priori. Under the conditions of fast equilibrium between the conformers, a similar doublet of doublets is expected as the first order spectrum for H(4).[17] In both cases the triplet-like band shape can be explained if the central two lines is assumed to overlap to each other by broadening.

The results of force field calculations on the two half-chair conformers corresponding to I and II of methyl *cis*-4-hydroxy-2-chromancarboxylate (**6a**′), another model compound for **6a**, are also given in Table 3. As mentioned above, the force field parameters for the ester group is less trustworthy. However, the conformation I is again the most stable. The conformer I becomes more stable relative to the conformer II in this calculation, suggesting higher abundance of the diaxial conformer I. This is also in line with the triplet signal observed.

In order to find out the reason for the stability of the conformer I, the energy terms in Table 2 were examined more carefully. The dipole interaction terms concerning OH, CHO, and ring oxygen are 6.44 kJ mol^{-1} more favorable for the conformer I than for the next stable conformer II. In contrast, van der Waals interaction energy disfavors conformer I considerably when compared with that of the conformer II. Conformations other than the two half-chairs are remarkably disfavored by the contribution of larger repulsive van der Waals and torsional energy terms. After all dipole interaction energy is the most important factor in determining the most stable conformation.

In order to discuss the difference in the conformational preference observed with *cis*-4-hydroxy-2-tetralincarboxylate **5a** and its 1-oxa anolog **6a**, the steric

Table 3. Steric energies of methyl *cis*-4-hydroxy-2-chromancarboxylate (**6a'**) obtained by MM calculations[a)]

	Conformers of **6a'**						
	I	II	III	IV	V	VI	VII
E	92.55	101.67	118.45	115.31	98.58	106.94	137.07
ΔE	0	9.12	25.90	22.76	6.03	14.39	44.52

a) All energies are given in kJ mol^{-1}.

Table 4. Steric energies of *cis*- and *trans*-4-hydroxy-2-tetralincarbaldehydes (**9a** and **9b**) obtained by MM calculation[a)]

	Conformations of **9a**							Conformations of **9b**			
	I'	II'	III'	IV'	V'	VI'	VII'	VIII'	IX'	X'	XI'
E_c	3.05	2.64	3.51	3.14	3.39	2.89	3.22	2.94	2.92	2.95	3.56
E_b	5.73	6.23	7.28	9.12	6.11	6.44	24.52	5.27	6.44	10.01	7.71
E_{ab}	0.38	0.42	0.54	0.54	0.33	0.42	1.46	0.38	0.44	0.68	0.50
E_{vdw}*	42.55	36.69	44.02	40.75	40.88	37.53	49.41	40.56	38.10	40.62	44.53
E_{vdw}	−8.41	−8.12	−7.15	−7.61	−7.41	−7.91	−5.40	−8.56	−8.34	−7.32	−8.11
E_w	17.53	16.11	20.54	20.59	17.24	17.03	31.00	16.74	16.86	20.82	20.72
E_{tb}	−0.59	−0.59	−0.67	−0.67	−0.71	−0.75	−6.36	−0.49	−0.58	−0.85	−0.65
E_d	−3.72	1.67	−2.68	1.80	−2.63	1.38	0.46	2.74	3.62	3.24	−0.10
E	56.48	55.02	65.40	67.66	57.15	57.03	98.32	59.59	59.45	70.14	68.16
ΔE	1.46	0	10.38	12.64	2.13	2.01	43.30	4.57	4.43	15.12	13.14

a) All energies are given in KJ mol^{-1}.

energies for the seven conformations I'—VII' of the model compound **9a** (corresponding to the conformation I—VII, respectively, of **10a**) were calculated as given in Table 4. The most stable conformation of **5a** is estimated to be the half-chair conformation II' in which both 4-hydroxyl and 2-carbonyl groups are equatorial by calculation. The H(4*a'*)/H(3*e*) and H(4*a'*)/H(3*a*) dihedral angles of the conformer II' were calculated to be 50.0° and 166.3°, respectively, from which the spin-spin coupling constants ($J_{a'e}$ and $J_{a'a}$) are estimated to be 5.76 and 8.96 Hz, respectively. The results reproduce the observed coupling constants fairly well. Even in the case of **9a**, the conformation I' (carrying 4*a'*-OH and 2*a*-CHO groups) is considerably favored by the contribution of dipole interaction term. The stabilizing contribution is overcome by the increase in repulsive van der Waals interaction in **9a**. Apparent difference between the molecular structure of **10a** and **9a** is the presence of pseudoaxial hydrogen atom in **9a**, which is supposed to disfavor the axial conformation of formyl group. The sums of E_{vdw} terms between ring 1-CH_2 and 2-CHO groups (inclusive of 1,4-interaction terms) are nearly identical, however. Repulsion between the axial groups causes flattening of the cyclohexene ring, which, in turn, brings about large repulsive 1,4-interaction terms between the atoms in the ring.

The next stable (diaxial) conformer (I') of the aldehyde **9a** has a steric energy only 1.46 kJ mol^{-1} higher than the most stable (diequatorial) conformer (II'). This suggests the possibility for the coexistence of conformers other than II' to a considerable extent. Infrared spectrum of ethyl *cis*-4-hydroxy-2-tetralincarboxylate **5a** shows an absorption band assignable to axial hydroxyl group at 3621 cm^{-1}, which renders a support to the presence of 4*a'*-hydroxy-2*a*-alkoxycarbonyl conformer (I').[18)]

Similarly the model calculations on the trans aldehyde **9b** showed that the half-chair conformer (VIII') carrying 2*e*-formyl and 4*a'*-hydroxyl groups is the most stable, which is again in line with the triplet signal with relatively small J_{vic} values of H(4) for the *trans*-esters **5b** and **7b**.

The molecular force field calculations were carried out by HITAC M-200H computers of the Institute for Molecular Science and, in part, of the University of Tokyo to which the authors are grateful. The authors also thank Prof. Eiji Osawa, Hokkaido University, for his permission to use the MM1/MMP1 program.

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16) In general, the Karplus type equations containing only quadratic term of cosϕ tend to underestimate the J_{vic} values when the dihedral angle ϕ is near 90°. Thus the following modified equation to estimate J_{vic} was proposed by M. Karplus (*J. Am. Chem. Soc.*, **85**, 2870 (1963)):

$$J_{vic}=4.22-0.5\cos\phi+4.5\cos^2\phi$$

from which the J_{vic} values were calculated to be 5.1 Hz assuming the dihedral angle to be 60°.
17) The ring reversal from I to II causes the change in dihedral angles from 68.6° to 167.0° for a pair of coupling protons and from 50.8° to 48.5° for the other pair. Thus the J_{vic} values were calculated to be 5.74 and 5.89 Hz, respectively, from the modified Karplus equation[16] as the averages weighted by the abundances of the conformers I and II from MM.
18) Infrared absorption spectra of **5a**, **5b**, and **6a** in the OH stretching region were determined as follows: **5a**, 3621 cm^{-1}(21) and 3599 cm^{-1}(52); **5b**, 3618 cm^{-1}(63); and **6a**, 3610 cm^{-1}(42) and 3596 cm^{-1}(31). Molar absorbances in 1 mol^{-1} cm^{-1} are given in parentheses. No other absorptions were observed in the OH stretching region even with the *cis*-compounds **5a** and **6a**, which excludes the possibility of strong intramolecular hydrogen bonding. See, K. Hanaya, T. Muramatsu, S. Onodera, Y. Ikegami, and M. Hirota, *Bull. Chem. Soc. Jpn.*, **57**, 1695 (1984).