EFFECT OF CH/π INTERACTION ON THE CHIROPTICAL PROPERTIES OF OLEFINS AND DIENES

Shin-ichi ARAKI, Taizo SEKI, Kazuhisa SAKAKIBARA, Minoru HIROTA,*
Yoshio KODAMA[+] and Motohiro NISHIO[+]

Department of Synthetic Chemistry, Faculty of Engineering,
Yokohama National University, Hodogaya-ku, Yokohama 240, JAPAN
+ Pharmaceutical Research Center, Meiji Seika Kaisha Ltd.,
Morooka-cho, Kohoku-ku, Yokohama 222, JAPAN

Abstract: Rotatory strengths of exo-methylenesteroids, α-phellandrene and related compounds were calculated on the basis of Rosenfeld theory by using AM1 molecular orbitals. Calculation showed that a considerable change in intensity of CD band is expected to occur for the conformers where CH/π interaction is possible. Chiroptical properties of asymmetric olefins and dienes were interpreted from the viewpoint of CH/π interaction.

As a result of recent progress in spectroscopic and X-ray crystallographic methods aided with computational techniques, conformations of a large number of organic compounds have been determined. During this process, some molecules were shown to prefer the conformations in which bulky hydrocarbon groups are located close to each other.[1] We found that *t*-butyl and phenyl groups are located *synclinal* to each other in 1-phenylethyl *t*-butyl sulfoxides[2] and ketones.[3]

The generality of the phenomenon was then explored for other molecules. It was found that the *synclinal* alkyl(R)/phenyl conformations are common for series of PhCHMe-X-R and $PhCH_2$-X-R compounds.[4] Thus, the folding tendency of the chain seems quite general for a wide variety of aliphatic molecules. We assumed that a weak hydrogen-bond-like attractive force, which we named the CH/π interaction, plays an important role in stabilizing the alkyl/phenyl *synclinal* conformations.[5]

This paper is dedicated to the memory of late Professor Gunther Snatzke; the authors sincerely regret the immeasurable loss of an outstanding figure in the field of chemistry.

The CH/π interaction has long been known phenomenologically. The interactions of two acetylene molecules[6] and chloroform with benzene[7] are the typical examples. Our suggestion is that this type of interaction not only is possible with activated CH groups, but also is important with *normal non-acidic CH groups* such as those in alkyl groups. Although the energy of the CH/π interaction is rather small, CH groups have a possibility of participating simultaneously in interactions with multiple atoms. In addition, this type of interaction is entropically advantageous with the CH group incorporated in certain symmetric structures such as methyl or isopropyl groups, etc.

The very decisive criterion for specific hydrogen-bond-like interaction should be the presence of delocalizative interaction between the "non-bonded" hydrogen atom of C-H and the carbon atom bearing π-electrons. Thus the molecular orbital or other quantum mechanical approach takes a very important role in discriminating whether the observed attractive CH/π interaction is worth being called a CH/π hydrogen bond or not.

Parallel to the experimental progress revealing the facts that the compounds carrying acidic C-H groups can interact with the π-bases,[6] several model calculations have been carried out with binary systems consisting of acidic C-H and π-component with the aim of characterizing the interaction involved. Thus *ab initio* calculations on acetylene[6] and benzene[8] dimers showed that the "T-shaped" geometries are the most stable. In such arrangement of molecules, one of the C-H bonds is located just above the π-orbital so as to obtain a maximal overlap between the interacting orbitals. Kodama and coworkers[9] reported the interaction energy for the most stable methane-benzene system to be -3.5 kJ/mol by CNDO/2 calculations. Recently Takagi and coworkers[10] reported *ab initio* calculations on the CH_4-C_2H_4 supermolecular system (1) in which one of the C-H bonds of methane is fixed perpendicular to the molecular plane of C_2H_4 and passing through the center of the C=C bond with optimization of the intermolecular distance R_{CC}. Detailed analysis on the results showed that the charge transfer from ethylene to methane contributes largely to stabilize the supermolecule. As to the intramolecular interaction, we carried out *ab initio* 4-31G calculations on the several conformers of 1-phenyl-2-propanol.[11] The population analysis gave positive bond populations between H in methyl and aromatic C atoms. The bond populations are about a half as large as the case of well characterized OH/π interaction. This suggests the participation of the delocalizative, or charge-transfer, force between CH_3 and the π-electrons of the aromatic ring in the CH/π-contiguous conformers, which can be the evidence for the

presence of CH/π interaction.

Even if there is some evidence to support the presence of CH/π interaction as stated above, the effect due to the CH/π interaction is small, i. e. 0.5-1.5 kcal/mol in energy. Thus, it is rather difficult to detect very conclusive effect of CH/π interaction from the change in observed spectrum and overlap population from molecular orbital
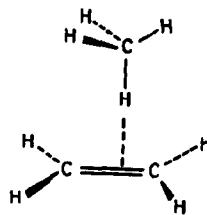
(1)

calculations. In this situation, it is necessary to find out other physical properties which reflect the effect of CH/π interaction more sensitively. Rotational strength (spectral change of CD spectrum) is thought to be an appropriate probe to detect the interaction because it is originated from rather a weak perturbation on the shape of electron cloud.

The delocalization due to CH/π interaction should induce the asymmetry of π-electron cloud when the interacting CH group approaches from the direction other than on the plane of symmetry. Thus CH/π interaction can induce the (additional) optical rotatory power of the (π,π^{*}) transition of ethylenic, dienic, and aromatic chromophores. In this paper, we wish to propose a new index to measure the contribution of CH/π interaction to the rotational strength and to interpret the anomalies observed in the chiroptical properties of several olefinic and dienic terpene and steroid compounds from the viewpoint of CH/π interaction.

Calculation of Rotational Strength Induced by CH/π Interaction.

Most of the calculations on optical rotatory power started from the Rosenfeld equation,[12] in which rotational strength of a molecule is given as the imaginary part of the product of magnetic and electronic transition dipole moments (eq. 1).

$$R = \mathrm{Im}\{\langle\Psi_0|\mu|\Psi_e\rangle\langle\Psi_e|m|\Psi_0\rangle\}$$

(1)

Here, Ψ_0 and Ψ_e are the wave functions of the ground and the relevant excited states of the molecule, and μ and m are electric and magnetic dipole moment operators, respectively. In order to make the rotational strength independent of the choice of coordinate system, dipole velocity formalism[13] has been conventionally employed. Using this method, magnetic dipole moment part of eq.1 can be rewritten as in eq. 2.

$$\langle \phi_i | r | \phi_j \rangle = (\hbar/m) \langle \phi_i | \nabla | \phi_j \rangle / (E_j - E_i) \tag{2}$$

Here, ϕ_i and E_i refer to the wave function and the energy, respectively, of the i-th molecular orbital. Thus the rotational strength R_{ij} induced by the electronic transition from i-th to j-th MO is given by eq. 3 in which energies and distances are measured in eV and A, respectively.

$$R = (-7313/E_j - E_i) \langle \phi_i | \nabla | \phi_j \rangle \langle \phi_i | rx\nabla | \phi_j \rangle \tag{3}$$

The terms in eq. 3 can further be partitioned into those for atomic orbitals by assuming LCAO approximation.

$$\langle \phi_i | \nabla | \phi_j \rangle = \Sigma_r \Sigma_s c_{ir} c_{js} \langle \chi_r | \nabla | \chi_s \rangle \tag{4}$$

$$\langle \phi_j | rx\nabla | \phi_i \rangle = \Sigma_r \Sigma_s c_{jr} c_{is} \langle \chi_r | rx\nabla | \chi_s \rangle \tag{5}$$

Exactly speaking, eq. 3 gives the rotational strength for the virtual electronic transition between the ground and excited configuration, which can be only a rough approximation of R. The actual rotational strength is obtained after taking into account the configuration interaction.

In the aim of evaluating the contribution of the CH/π interaction to the rotational strength R, interaction-induced rotational strength ΔR_{int} was newly introduced. If we neglect all overlap integrals between the methyl CH atoms and the olefinic C atoms, the calculation gives the rotational strength R' excluding the contribution due to CH/π interaction between methyl group and the olefinic bond. The ΔR_{int} value was defined as the difference between the normal rotational strength of the whole molecule (including the contribution from CH/π interaction) and the R' value (eq 6).

$$\Delta R_{int} = R - R' \tag{6}$$

Thus, the ΔR_{int} should be a measure for the perturbation originated from the CH/π interaction. It was shown to be small when the CH/π interaction is absent between the relevant groups.

Results and Discussion
*Chiroptical properties of olefinic compounds*
    The simplest example of the effect of CH/π interaction on the chiroptical properties could be found with steroids carrying isolated ethylenic bonds. The (π, π^*) transitions of these steroids appearing at

ca. 200 nm is optically active due to the chiral environment around the chromophore. CD spectra of steroids and related compounds carrying isolated ethylenic chromophores were reported by Fetizon and Hanna,[14] and by Hudec and Kirk.[15]

Table 1. CD Spectra of several exo-methylene steroids.[14,15]

Compound	$\Delta \varepsilon$	λ/nm
1-methylene-5α-androstane (2)	-2.2	199
2-methylene-5α-androstane (3)	+10.5	197
3-methylene-5α-androstane (4)	+6.4	193
4-methylene-5α-estrane (5)	-4.1	199
4-methylene-5α-androstane (6)	-10.5	200
6-methylene-5α-estrane (7)	-0.3	205
6-methylene-5α-androstane (8)	+4.2	197
6-methylene-5α-cholestane (9)	+5.6	200
6-methylene-5α-spirostane-3β-ol (10)	+9.0	198
deoxyonocerine (11)	-14.5	202
16-methylene-5α-androstane (12)	-7.9	193
17-methylene-5α-androstane (13)	+3.8	193

Dreiding models of these steroids suggest that a five- or six-membered CH/π interaction is possible in cases where a significant enhancement of CD is observed. This is illustrated for representative cases of 2-methyleneandrostane (3) and an 8-methylene compound, deoxyonocerin (11). Such an interaction does not easily occur in 1- and 17-methylene steroids 2 and 13.
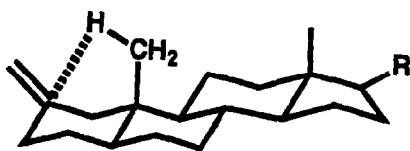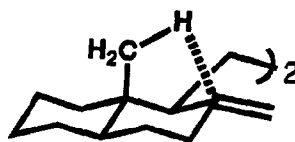
(3)   (11)

If we compare 4-methylene-5α-androstane (6) with its 10-demethyl analogue 5, the geometries are entirely similar in spite of the absence of 10-axial-methyl group in the latter compound. 6-Methylene-α-andros-

tane (8) and 6-methylene-5α-estrane (7) are also a similar pair.   Thus
we set forth the calculation of rotational strengths of these compounds.
Results are given in Table 2.   In these cases, the contribution by CH/π
interaction (measured by ΔR_{int} value) can be obtained by subtracting the
R of methylene-estrane from that of relevant methyleneadrostane.

Table 2. (π,π^*) Transition Energies (ΔE) and Rotational Strengths (R)
          of Some Exo-methylenesteroids.

Compound	ΔE/eV	λ/nm	$R/10^{40}$esu	ΔR_{int}	$\Delta \varepsilon$	$\Delta \Delta \varepsilon$
5	6.08	203.8	−36.61		−4.1	
6	6.01	204.4	−40.71	−4.10	−10.5	−6.4
7	6.07	204.1	−11.17		−0.3	
8	6.05	205.0	+0.93	+12.10	+4.2	+4.5

Molecular mechanics calculations on these four compounds showed no
indication of the deformation of geometry of the estrane-skeletone by the
introduction of 10β-methyl substituent.   The calculated ΔR_{int} values
agree, at least qualitatively, with the observed $\Delta \Delta \varepsilon_{int}$ value, which is
defined as the similar difference between the $\Delta \varepsilon$ values of methylene-
estranes and methylene-androstanes.   Thus, the changes in rotational
strengths can be rationalized by taking into account the perturbation on
the (π,π^*) transitions by the through space CH/π interaction.   Previ-
ously, we proposed the D, P and θ parameters as the criteria to measure
the strength of CH/π interaction.[4h]   When D is in the range from 2.5 to
2.9 A and θ (or P) is small, CH/π interaction becomes favorable.   AM1 MO
calculations on 6 and 8 showed that one of the methyl hydrogens occupies
a position nearly above the ethylenic bond.   As shown in Table 3, the
hydrogen atom suffices the above criteria for the formation of CH/π
interaction.

Table 3. D, P, and θ Parameters for Methyleneandrostanes.

Compound		D/A	P/A	θ/°
6	H(Me)−C(4)	2.65	0.63	13.8
8	H(Me)−C(6)	2.72	0.54	11.4

In order to make clear of the origin and the trend of the induced increment of rotational strength, simple model calculations on methane (CH-donor)-ethylene(π-acceptor) supermolecular system was carried out. As illustrated in Fig. 1, carbon atom of methane was fixed at a point 3.6 A above the plane of the ethylene molecule and one of its C-H bond was kept perpendicular to the plane and opposing the π-electron of ethylene. The distance (3.6 A) was chosen so as to keep the H---C(sp^2) distance suitable to form intermolecular CH/π interacted complex.
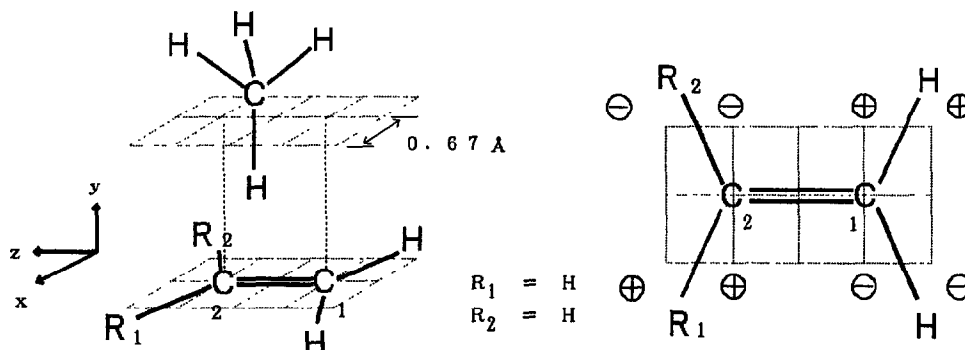

Fig. 1. Optical rotatory power of the chromophore of ethylene induced by a methane molecule approaching from various direction. When H approaches to the + sign region, positive CD is expected to be induced, and vice versa.

As expected, non-zero induced rotational strength was obtained when the CH bond was located off the symmetrical planes of the ethylene molecule. As the both components are apparently achiral in the absence of interaction, the calculated rotational strength of the π,π^* transition should be originated from chiral distortion of the π-electron cloud due to the interaction with a CH-bond of the methane molecule. As in the case of the octant rule, the sign of the induced rotational strength agrees with the signs of xyz-product in the coordinate domains (octant) if we assume that the C=C bond lies on the z-axis of a right-handed rectangular coordinate system.

Conformations and Chiroptical Problems of 1,3-Cyclohexadienes
The axial allylic and homoallylic effects
     In the aim of explaining the chiroptical properties of compounds with a conjugated double bond, Moscowitz and coworkers presented an empirical rule.[16] This is called the diene helicity rule and states that
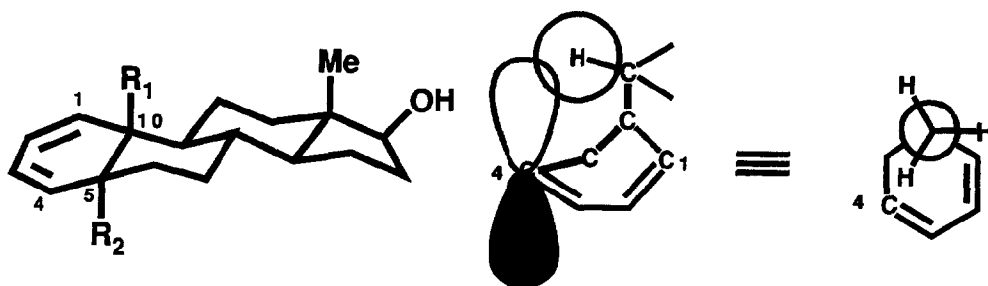
the sense and the amount of skewness of the chromophore in a 1,3-cisoid
diene determines the sign of the Cotton effect (CE) and the rotational
strength of the compounds. According to this rule, a left-handed helix
(*M*-helicity) of levopimaric acid (**14**, a tricyclic diterpene, produces a
negative CE at the long wavelength (π,π^*) transition, whereas 2,4-
cholestadiene (**15**) having the right-handed helicity (*P*-helicity) shows a
positive CE.[16b]

Table 4. CD Spectra of Some 1,3-Cyclohexadienes and Axial-Methyl Effect.

Compound	$\Delta\varepsilon$	Number of ax-alkyl Allyl[a]	Homoallyl
Levopimaric Acid(**14**)	-12.2	0	1
2,4-Cholestadiene(**15**)	+12.4	1	1
5α-Estra-1,3-dien-17β-ol(**16**)	+3.8	0	0
5α-Androsta-1,3-dien-17β-ol(**17**)	-2.8	1	1
5α-Methylandrosta-1,3-dien-17β-ol(**18**)	-11.1	2	2
6β-Methyl-5α-cholesta-1,3-diene(**19**)	-5.5	1	2
6α-Methyl-5α-cholesta-1,3-diene	-1.4	1	1
1,1,4,4-Tetramethyl-1,2,3,4,9,10- (20°C)	+0.8	0	0
hexahydronaphthalene(**20**) (-169°C)	-3.5	0	2
5β-Methylandrosta-1,3-dien-17β-ol(**21**)	+27.6	1	4
5α-Methyl-10α-androsta-1,3-dien-17β-ol(**22**)	+14.7	1	3

a) Allylic axial-methyl group on the same ring is always homoallylic
to the other end of diene. Figures in the third column include the
numbers of them.

Later, Burgstahler and coworkers presented evidence that the contri-
bution of an axial alkyl substituent allylic to the double bond outweighs
the effect of the skewness of the diene chromophore.[17] To illustrate
this, they showed that the introduction of an axial methyl group on C(10)
of 5α-estra-1,3-dien-17β-ol (**16**) inverted the sign of the CE of the
non-substituted steroid from plus to minus. The introduction of a second
methyl group on C(5) of 5α-androsta-1,3-dien-17β-ol (**17**) intensifies
further the negative CD amplitude (See **18**). The helical sense and the
amount of twist remain practically unchanged throughout the substitution
steps. Our calculations reproduced the trend of methyl-substitution
effect. This is known as the axial allylic chirality contribution.[18] The
chiroptical properties of cisoid 1,3-dienes have since been explained
against this background.[19]

H - C : ca. 2.5Å

Fig. 2. Schematic Illustration of the participation of homoallylic methyl H to CH/π interaction.

(16) R_1 = R_2 = H
(17) R_1 = CH_3, R_2 = H
(18) R_1 = R_2 = CH_3

The above phenomenon can be accommodated in terms of the CH/π interaction.[5] We suggest that the so-called axial allylic effect operates primarily through the dissymmetric perturbation of the π or π^*-orbital of the diene chromophore by virtue of the CH groups, which are oriented suitably for this interaction to take place. This situation is illustrated in Fig. 2. If an axial alkyl group is present at the allylic position to an sp^2 carbon (C(1)) in a cyclohexadiene, it is, at the same time and inevitably, homoallylic to another sp^2 carbon (C(4)) which is positioned at the other terminal of the diene system.[20]

In this disposition, a hydrogen atom in the alkyl group can interact, in a through-space manner, with the π or π^*-orbital on the sp^2 carbon which is separated by four bonds from it. Inspection of Dreiding models suggests that the hydrogen atom is oriented above the molecular plane of the diene system, and thus is capable of forming a five-membered CH/π interaction with an sp^2 carbon; the interatomic distance between the relevant nuclei is ca. 2.5 A. Therefore, the important and essential condition for the enhancement of CD amplitude is not that the alkyl group is allylic to a double bond system, but that it is homoallylic to it.

Returning again to the example presented by Burgstahler,[17] we see that a CH hydrogen in the 10β-methyl group of compound 18 can participate in a five-membered hydrogen-bond with C(4) which is four-bonds apart from it, but probably not with C(1) to which the methyl group is allylic. Similarly, the 5α-methyl group can interact with C(1) from the rear side of the molecular plane. In view of this, the so-called allylic chirality contribution may, more appropriately, be termed as the homoallylic chirality rule. Gawronski and Kielczewski[21] already reported an important

contribution of groups homoallylic to a double bond in a series of exo-
methylene steroids. Burgstahler and associates[22] compared the CD spec-
trum of 6β-methyl-5α-cholesta-1,3-diene (19) with its 6α-isomer and
found that the CE magnitude of the 6β-methyl (axially homoallylic to the
diene system) isomer 19 was much larger than that of the equatorial
congener ($\Delta\varepsilon$ -1.4). They found also that, in compound 20, the presence
of a methyl group at the homoallylic position exerted a significant
influence on its CD spectrum. The two axial methyl groups are situated
at positions capable of participating in five-membered hydrogen-bonds, if
the cyclohexane ring is frozen in a chair conformation. The weak CD band
with a positive Cotton effect in fact showed an inversion of sign and an
increase in its amplitude on cooling (Table 4).

(19)   (20)
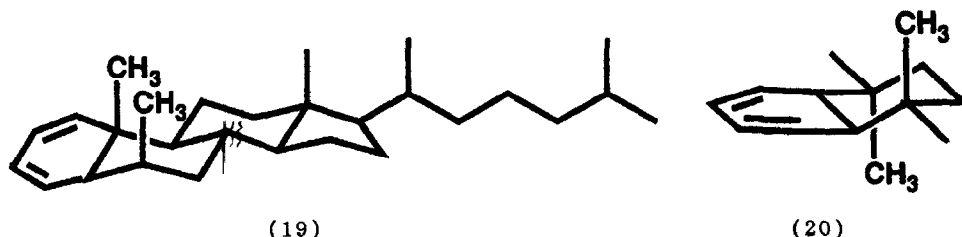
The CD amplitude of diene 21 has been reported[17] to be larger than
that of compound 22. They attributed this to the difference in polariza-
bility of the groups positioned axially allylic with respect to the diene
system. However, the explanation becomes more straightforward if the
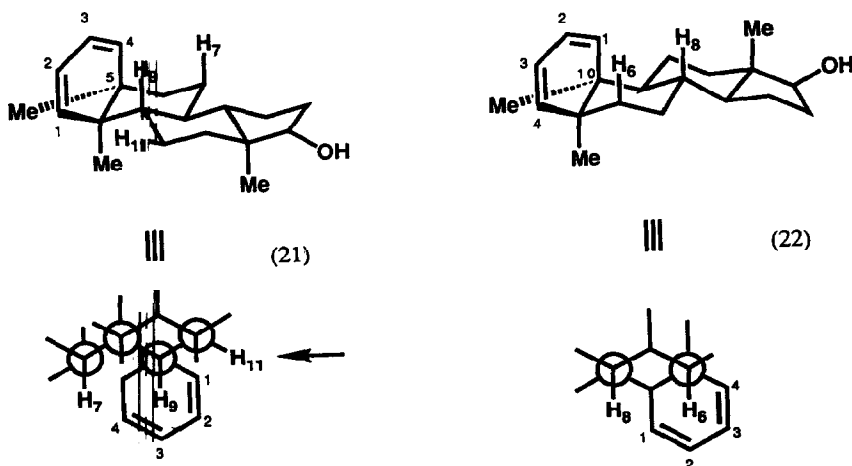phenomenon is interpreted in terms of the CH/π interaction (Figure 3).

(21)   (22)

Fig. 3. Hydrogen atoms interacting with the diene chromophores of 21 and
22 (shown by Newman projections).

In compound **21**, the number of CH groups which can interact simultaneously in a through-space manner with the diene system is three (7α, 9α, and 11α-H), whereas in compound **22** it is only two (6β and 8β-H); other situations (e. g., the skew sense and the contribution from the axial methyls) are similar for both compounds. Note that in **21** an extra CH (11α-H) is present, which is capable of participating in CH/π interaction with C(1).

Conformational behaviors of α-phellandrene and related compounds

A cyclic monoterpene compound, α-phellandrene (**23**), has been shown to be a mixture of quasi-equatorial and quasi-axial conformers.[16a] A substantial proportion of the quasi-axial form exists at room temperature, and it is known that the rotational strength of the quasi-axial conformer (M-helicity: negative CD) is considerably larger than that of the quasi-equatorial one (P-helicity), as evidenced by low-temperature CD measurements.[23] Larger rotational strength of the quasi-axial conformer may also be originated from the CH/π interaction. The axial isopropyl methine as well as the CH's in methyls can interact with an sp^2 carbon in the diene system by forming a five- or six-membered weak hydrogen-bond-like interaction.
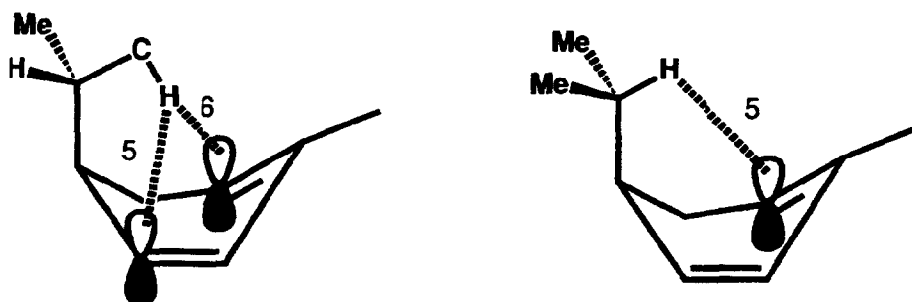

Fig. 4. Intramolecular CH/π interaction in α-phellandrene.

In order to make clear the conformational behaviors and optical rotatory power of α-phellandrene, the geometries, conformational energies, and rotational strengths (R) of its six stable conformers were calculated. The geometry and conformational energy of each conformer was optimized by molecular mechanics (MM2(82))[24] and *ab initio* (4-31G//STO-3G) calculations.[25] The molecular orbitals obtained by means of the AM1[26] method were used for the calculation of rotatory strength. The results are shown in Table 5. The populations of conformers estimated

by assuming the Boltzmann law from the conformational energies showed that the total quasi-equatorial conformers (60%) predominate over the quasi-axial conformers. However, the energy difference between quasi-equatorial and quasi-axial conformers are much lower than expected. The quasi-axial conformers generally gave more strongly negative R-values than the quasi-equatorial conformers, which has less strong positve R.

Table 5. Conformational Energies, Populations, and Rotational Strengths of the Conformers of α-Phellandrene (23).

Conformer	*axial*-Isopropyl			*equatorial*-Isopropyl		
	(A)	(B)	(C)	(D)	(E)	(F)
Conformational Energy (ΔE/kcal mol^{-1})						
MMP2	0.17	0.59	0.17	0.22	0.24	0.0
4-31G//STO-3G	0.49	0.48	0.26	0.15	0.43	0.0
Population of Conformer (%)						
MMP2	17.8	8.7	17.8	16.3	15.8	23.6
4-31G//STO-3G	11.6	11.7	17.0	20.5	12.8	26.4
Rotatory Strength (R/10^{-40}esu)						
	-20.58	-20.86	-19.48	+14.29	+16.57	+16.48
Contribution of CH$_3$ (ΔR_{int}/10^{-40}esu)						
CH$_3$(9)	-2.58	+3.39	-1.99	+0.12	+1.27	-0.50
CH$_3$(10)	-0.37	-2.26	+1.09	-0.86	+0.24	+0.75
Skew Angle of Diene Chromophore (ω/$^{\circ}$)						
	-11.09	-9.97	-16.47	+12.43	+13.63	+13.97
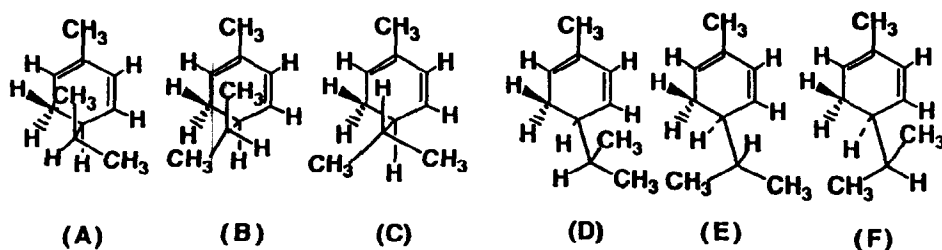
Conformers (A)-(F) of α-phellandrene (23).

The unexpected stability of axial conformers may partly come from the CH/π interaction. In the axial conformations, some hydrogen atoms are in close contacts with sp^2 carbon atoms; viz. the interatomic distances are ranging from 2.6 to 3.0 A, which are within the sum of the van der Waals' radii. These closely located C---H atom pairs were shown to have positive nonbond overlap populations. The largest value was about 10^{-2}, and the positive bond population indicates that attractive interaction is operating between them.

As the skew angles for diene-unit (Table 5) in the conformers have almost similar absolute values, the rotational strengths for the axial and the equatorial conformers are expected to have nearly identical value with the opposite sign (- for axial conformers; + for equatorial conformers) from the diene helicity rule.[16] However, the rotational strengths (R) of axial conformers have rather large absolute values comparing with those of equatorial conformers. This significant enhancement of the rotational strength in axial conformers can be ascribed to the participation of the CH/π interaction formed between a hydrogen atom of axial methyls and π-electrons of diene chromophore. The contribution of axial methyl groups to the rotational strength (ΔR_{int}) was estimated by subtracting the rotational strength obtained (R^{*}) by setting the overlap integrals for the CH/π interacted atom pairs to be zero from the overall rotational strength (R). The effect of the CH/π interacted axial methyl to the rotational strength is fairly large (C(9) methyl of conformer A and C, C(10) methyl of conformer B). Burgstahler's group[17] reported that an axial alkyl substituent proximates to a chiral diene unit showed the significant enhancement of Cotton effect. These experimental results are consistent with our calculation.

The steric requirement for the CH/π interaction is an intriguing aspect and can be best studied with the intramolecular cases. From this viewpoint, the positions of H atoms of alkyl substituent relative to olefinic sp^2 carbon atom was investigated carefully. If the H atom lies close to the olefinic π-bond, orbital overlap necessary to the hydrogen bond-like interaction becomes favorable. The $C(sp^2)$-H(alkyl) distance D and the angle θ between the axis (perpendicular to the plane of C=C double bond) of p-orbital of the olefinic carbon and $C(sp^2)$-H(alkyl) line can be appropriate indices for the geometrical criteria of CH/π interaction. The values of θ for the C(olefinic)-H(methyl) atom pairs in 6 conformers in Table 6 showed that CH/π-interacted pairs have small θ values (ca. 20°). On the contrary, non-CH/π-interacted pairs revealed larger θ values. These structural data suggest that the stabilizing orbital interaction between H of alkyl substituent and sp^2-C atoms, which

is necessary for the CH/π interaction, occurs only when the molecule can take a conformation with suitable geometrical indices (D and θ).

Table 6. Overlap Populations N(C,H) between sp^2-Carbons and Methyl Hydrogens and CH/π Interaction Indices (D and θ).[a]

C(sp^2)-H(Me) Pair	N(C,H)	D/A	θ/$^\circ$
Conformer (A)			
C(1)-H(23)	8.80 X 10^{-4}	2.80	17.5
C(4)-H(22)	1.13 X 10^{-2}	2.86	21.1
C(4)-H(26)	5.51 X 10^{-3}	2.86	43.8
Conformer (B)			
C(3)-H(25)	5.18 X 10^{-3}	2.97	29.6
C(4)-H(20)	-2.28 X 10^{-4}	2.62	49.8
C(4)-H(25)	9.93 X 10^{-3}	2.81	23.5
Conformer (C)			
C(1)-H(20)	1.18 X 10^{-2}	2.86	26.5
C(4)-H(20)	7.11 X 10^{-3}	2.79	44.2
C(4)-H(23)	1.18 X 10^{-2}	2.61	25.0
Conformer (D)			
C(4)-H(25)	6.91 X 10^{-3}	2.77	43.2
Conformer (E)			
C(4)-H(20)	-1.19 X 10^{-3}	2.73	54.3
C(4)-H(26)	2.42 X 10^{-4}	2.79	83.6
Conformer (F)			
C(4)-H(22)	7.58 X 10^{-3}	2.75	39.8
C(4)-H(20)	-4.63 X 10^{-3}	2.72	87.0

a) N(C,H): Nonbonded overlap population between H(methyl) and C(sp^2) by 4-31G//STO-3G calculations. D: Interatomic distance between H(methyl) and C(sp^2). θ: Approach angle, i. e. the angle between the p$_\pi$-axis and C(sp^2)-H(methyl) line.

Suitable steric arrangement necessary for proper orbital interaction was shown to be very important for CH/π interaction from the calculated results (Table 7) on the rotational strengths for the conformers of 2,5-dimethyl-1,3-cyclohexadiene (**24**), which has a 5-methyl substituent in place of isopropyl group as found in α-phellandrene. This diene has two stable conformers. MMP2 calculations showed 5-methyl equatorial conformer was more stable than 5-methyl axial one by 0.33 kcal/mol. This energy

Table 7. Conformational Energies, Populations, and Rotational Strengths of the Conformers of 2,5-Dimethyl-1,3-cyclohexadiene (24).

Conformer	*axial*-5-Methyl	*equatorial*-5-Methyl
Conformational Energy (ΔE/kcal mol^{-1})		
MMP2	0.33	0.0
4-31G//STO-3G	0.27	0.0
Population of Conformer (%)		
MMP2	33.5	66.5
4-31G//STO-3G	39.0	61.0
Rotatory Strength (R/10^{-40}esu)		
	-13.3	+13.5
Skew Angle of Diene Chromophore (ω/$^{\circ}$)		
	-15.1(*M*-helicity)	+14.7(*P*-helicity)

difference is larger than that of the α-phellandrene in spite of the fact that methyl group is less bulky than isopropyl group. As the allylic methyl group is less favorable for CH/π interaction, such interaction is expected to be weak in this compound. The rotational strengths (R) and the skew angles (ω) of both conformers are nearly the same. The diene helicity rule explained the rotatory strength of this molecule probably because the CH/π interaction was rather weak. Judging from rather large θ values in the both conformers, favorable orbital interaction between H atom and neighboring sp^{2} carbon atom might be impossible even in the axial-conformer of this molecule. H atoms occupying positions most favorable to CH/π interaction have θ-values of ca. 41° (41.1° for C(1)-H(Me(6)).

Calculations on dienes also showed that the CH/π interaction perturbs the rotational strength of optical active chromophores significantly. Thus induced enhancement or decrease in intensity is large enough to serve as a probe for the CH/π interaction.

Conformational Behaviors of 1,3-Cyclohexadienes and CH/π Interaction.

Lightner and coworkers[23c,27] studied the conformational equilibria of a series of 5-substituted 1,3-cyclohexadienes. They reported that the quasi-equatorial conformers are only slightly more stable than the quasi-axial ones; G_{ax-eq} is ca. 0.05, 0.25, and 0.4 kcal/mol for methyl, isopropyl (α-phellandrene), and *t*-butyl derivatives, respectively. Our calculation also showed that the energy differences between the axial and

equatorial conformers are nearly equal with the 5-methyl and 5-isopropyl
derivatives (Tables 5 and 7). Lack of 1,3-diaxial repulsion (in contrast
to the parent cyclohexane system) may play a part in stabilizing the
quasi-axial conformer with respect to the quasi-equatorial one. In our
view, it is more reasonable to look for other kinds of interactions which
are attractive in nature. Thus, in the 5-methyl group there are three
hydrogens which can participate (not necessarily simultaneously) in a
five-membered interaction with C(1), whereas in the isopropyl group there
is only one. The *t*-butyl group has no hydrogen of this type. On the
other hand, the number of methyl groups increases in the order from
methyl to *t*-butyl. One of the hydrogens in a methyl (in isopropyl and *t*-
butyl) group may also form a weak intramolecular hydrogen-bond with the
use of the same or another sp^2 carbon in the diene system.

Levopimaric acid (14) has been known to exist in a folded conforma-
tion in the solid state.[28] ORD and NMR studies demonstrated that this
compound also favors the folded conformation in solution.[16b] This is in
contrast to the extended conformation deduced for the configurationally
related 2,4-cholestadiene (15). To account for this, the possibility of
a specific attractive interaction in 14 was once postulated by Burgstah-
ler.[16b] However, this was later superseded by an explanation based prin-
cipally on repulsive interactions (relief of 1,3-diaxial repulsion or
4,4-dimethyl effect, etc).[28,29]

(14)   (15)
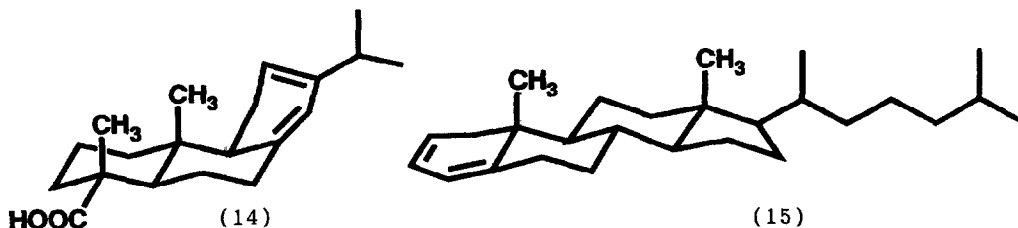
The axial 10β-methyl group (C(17)) of 14 is homoallylic to C(8),
and can interact with the diene system. This is compatible with the
strong negative CD absorption of this compound and also explains why 14
adopts the folded conformation. The folded conformation of 14, at
least in part, is a consequence of attractive interaction. In fact,
the distances between hydrogens in 10β-methyl to sp^2 carbons have been
found to be very short by X-ray crystallography.[28a]

In 2,4-cholestadiene (15), which has *P*-helicity, the axial 10β-
methyl group (C(19)) is homoallylic to C(2), and can engage in a five-
membered CH/π interaction with this carbon. This explains why 15 has
the extended conformation and a strong positive CD absorption. In this

respect, it is noteworthy that tetracyclic triterpenes such as ergosterol (25, $\Delta\varepsilon$ -11.4), lumisterol (26, $\Delta\varepsilon$ +14), pyrocalciferol (27, $\Delta\varepsilon$ +31), and isopyrocalciferol (28, $\Delta\varepsilon$+25) are reported to have large CD at a wavelength corresponding to the (π,π^*) transition.[16a,30] All of these compounds have angular methyls (C(18) and/or C(19)) ideally positioned for the homoallylic axial effect to play a role. Interatomic distances of the relevant atoms (H(18) or H(19) to C(8)) have in fact been found to be very short.

Ergosterol (25)   Lumisterol (26)

Pyrocalciferol (27)   Isopyrocalciferol (28)
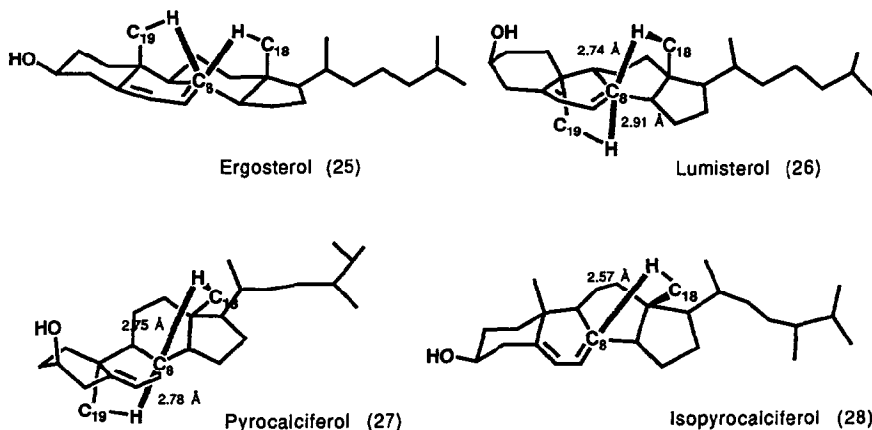
Concluding Remarks

The effect of the axial allylic and homoallylic methyl group on the Cotton effect amplitude, or rotational strength is originated by the CH groups which can interact in a through-space manner with the π-orbital of the chromophore. Thus, the effect could be ascribed to the CH/π interaction. The CH group may be located more remote than the homoallylic position if the groups are situated suitably for the orbital interaction. In summary, the perturbation on the chiroptical spectrum by CH/π interaction is governed by (1) the number and the acidity of the CH groups, (2) the distance and angle) of the hydrogen atom to the plane of the π-system, (3) the shapes and the energies of the orbitals perticipating in the interaction, and (4) the mobility of the groups involved in the interaction.

The CH/π interaction is essentially a weak hydrogen bonding.[5] Although the energy of interaction is small, this type of interaction is entropically favored because both CH and π groups can participate in interaction multiply. In some cases, the interaction becomes more advantageous because of a special arrangement of the groups having symmetric structure (Fig. 5).
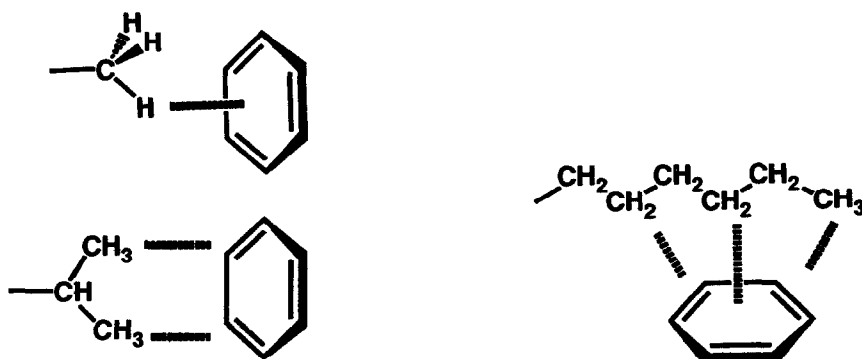
Fig. 5. Examples of entropically favored CH/π interaction.

In view of this, we emphasize the ubiquitos nature of the groups involved in the CH/π interaction. The CH groups are present everywhere in organic compounds. The π-containing molecules are also widely distributed in nature. Interactions involving these groups will thus exert a considerable influence on a variety of chemical behaviors. These include selectivity problems[31] of organic reactions, selective formation of inclusion complexes, certain solution and surface phenomena such as chromatography, higher order structure and substrate specificity of biopolymers.[4,5] As was pointed out by Watson, "Interactions which determine the subtle behavior of the dynamically interacting, complex molecules should be weak and orientation-dependent."[32]

REFERENCES:

1. a) B. Nilsson. P. Martinson, K. Olsson and R. E. Carter, *J. Am. Chem. Soc.* **96**, 8190 (1974). b) R. E. Carter, B. Nilsson and K. Olsson, *J. Am. Chem. Soc.* **97**, 6155 (1975). c) B. Aurivillius and R. E. Carter, *J. Chem. Soc. Perkin Trans. 2* 1033 (1978). d) R. E. Carter and P. Stilbs, *J. Am. Chem. Soc.* **98**, 7515 (1976). e) M. H. Lyttle, A. Streiwieser, Jr. and R. Q. Kluttz, *J. Am. Chem. Soc.* **103**, 3232 (1981).

2. a) Y. Iitaka, Y. Kodama, K. Nishihata and M. Nishio, *J. Chem. Soc.*

Chem. Commun. 389 (1974). b) Y. Kodama, K. Nishihata, M. Nishio and Y. Iitaka, *J. Chem. Soc. Perkin Trans. 2* 1490 (1976).

3. M. Hirota, Y. Takahashi, M. Nishio, and K. Nishihata, Bull. Chem. Soc. Jpn. 51, 2358 (1978).

4. a) Y. Kodama, S. Zushi, K. Nishihata, M. Nishio and J. Uzawa, *J. Chem. Soc. Perkin Trans. 2* 1306 (1980). b) M. Hirota, K. Abe, H. Tashiro and M. Nishio, *Chem. Lett.* 777 (1982). c) M. Nishio, Kagaku No Ryoiki, **36**, 190 (1982). d) Y. Kodama, K. Nishihata, S. Zushi, M. Nishio, J. Uzawa, K. Sakamoto and H. Iwamura, *Bull. Chem. Soc. Jpn.* **52**, 2661 (1979). e) J. Uzawa, S. Zushi, Y. Kodama, Y. Fukuda, K. Nishihata, K. Umemura, M. Nishio and M. Hirota, *Bull. Chem. Soc. Jpn.* **53**, 3623 (1980). f) S. Zushi, Y. Kodama, K. Nishihata, K. Umemura, M. Nishio, J. Uzawa and M. Hirota, *Bull. Chem. Soc. Jpn.* **53**, 3631 (1980). g) S. Zushi, Y. Kodama, Y. Fukuda, K. Nishihata, M. Nishio, M. Hirota and J. Uzawa, *Bull. Chem. Soc. Jpn.* **54**, 2113 (1981). h) S. Araki, K. Sakakibara, M. Hirota, M. Nishio, S. Tsuzuki and K. Tanabe, *Tetrahedron Lett.* **45**, 6587 (1991).

5. a) M.Nishio, *Kagaku no Ryoiki* **31**, 998 (1977); *Ibid.*, **33**, 422 (1979). b) M. Nishio and M. Hirota, *Tetrahedron* **45**, 7201 (1989). c) M. Hirota and M. Nishio, *Kagaku* **46**, 592 (1991).

6. T. Aoyama, O. Matsuoka, and N. Nakagawa, *Chem. Phys. Lett.* **67**, 508 (1979).

7. a) R. W. Reeves and W. G. Schneider, *Can. J. Chem.* **35**, 1157 (1957). b) G. J. Korinrk and W. G. Schneider, *Can. J. Chem.* **35**, 1157 (1957).

8. J. Pawliszyn, M. M. Szecesniak, and S. Scheiner, *J. Phys. Chem.* **88**, 1726 (1984).

9. a) Y. Kodama, K. Nishihata, M. Nishio and N. Nakagawa, *Tetrahedron Lett.* 2105 (1977).

10. T. Takagi, A. Tanaka, S. Matsuo, H. Maezaki, M. Tani, H. Fujiwara, and Y. Sasaki, *J. Chem. Soc. Perkin Trans. 2* 1015 (1987).

11. K. Abe, M. Hirota and K. Morokuma, *Bull. Chem. Soc. Jpn.* **58**, 2713 (1985).

12. V. L. Rosenfeld, *Z. Phys.* **52**, 161 (1928).

13. A. Imamura, T. Hirano, C. Nagata, and T. Tsuruta, *Bull. Chem. Soc. Jpn.* **45**, 396 (1972).

14. M. Fetizon and I. Hanna, *Chem. Commun.* 545 (1970).

15. J. Hudec and D. N. Kirk, *Tetrahedron* **32**, 2475 (1976).

16. a) A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *J. Am. Chem. Soc.* **83**, 4661 (1961). b) A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Am. Chem. Soc.* **83**, 4660 (1961). c) U. Weiss, H. Ziffer, and E. Charney, *Tetrahedron* **21**, 3105 (1965). d) E. Charney, *Tetrahedron* **21**,

3127 (1965).

17. A. W. Burgstahler, L. O. Weigel, and J. K. Gawronski, *J. Am. Chem. Soc.* **98**, 3015 (1976).

18. a) A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.* **92**, 7601 (1970). b) N. H. Andersen, C. R. Costin, D. D. Syrdal, and D. P. Svedberg, *J. Am. Chem. Soc.* **95**, 2049 (1973).

19. a) J. S. Rosenfeld and E. Charney, *J. Am. Chem. Soc.* **99**, 3209 (1977). b) O. E. Weigang, Jr., *J. Am. Chem. Soc.* **101**, 1965 (1979). c) R. M. Moriarty, H. E. Paaren, U. Weiss and W. B. Whalley, *J. Am. Chem. Soc.* **101**, 6804 (1979).

20. M. Nishio, *Kagaku no Ryoiki* **37**, 243 (1983).

21. J. K. Gawronski and M. A. Kielczewski, *Tetrahedron Lett.* 2493 (1971).

22. A. W. Burgstahler, G. Wahl, N. Dang, M. E. Sanders, and A. Nemirovsky, *J. Am. Chem. Soc.* **104**, 6873 (1982).

23. a) H. Ziffer, E. Charney, and U. Weiss, *J. Am. Chem. Soc.* **84**, 2961 (1962). b) G. Horsman and C. A. Emeis, *Tetrahedron* **22**, 167 (1966). c) G. Snatzke, E. sz. Kovats, and G. Ohloff, *Tetrahedron Lett.* 4551 (1966). d) D. A. Lightner, T. D. Bouman, J. K. Gawronski, K. Gawronska, J. L. Chappuis, B. V. Crist, and A. E. Hansen, *J. Am. Chem. Soc.* **103**, 5314 (1981).

24. N. L. Allinger and H. L. Flanagan, *J. Comput. Chem.* 1983, 4, 399.

25. *Ab initio* calculations were carried out by using the Gaussian 82 and Gaussian 86 programs at National Chemical Laboratory for Industry and IMS.

26. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.* **107**, 3902 (1985).

27. D. A. Lightner and J. L. Chappuis, *J. Chem. Soc. Chem. Commun.* 372 (1981).

28 a) I. L. Karle, *Acta Cryst.* **B28**, 2000 (1972). b) U. Weiss, W. B. Whalley, and I. L. Karle, *J. Chem. Soc. Chem. Commun.* 16 (1972).

29. a) A. W. Burgstahler, J. Gawronski, T. F. Niemann, and B. A. Feinberg, *J. Chem. Soc. Chem. Commun.* 121 (1971). b) G. A. Lane and N. L. Allinger, *J. Am. Chem. Soc.* **96**, 5825 (1974).

30. R. M. Moriarty, H. E. Paaren, U. Weiss, and W. B. Whalley, *J. Am. Chem. Soc.* **101**, 6804 (1979).

31. A specificity of 100:1 can be brought about by a difference in free energy of only *ca.* 2.6 kcal/mol at 25°C.

32. J. D. Watson, "The Importance of Weak Chemical Interactions", Chap. 4 in "Molecular Biology of the Gene", W. A. Benjamin, Menlo Park, Calif. (1965).