45). No starting material or 1,3-dimethylenecyclopentane could be detected. However, the presence of a small amount of 1-fluorobicyclo[2.2.1]heptane was confirmed by ^{19}F NMR. The remaining four components of the crude product mixture could not be unambiguously identified.

Treatment of 1,4-Dibromobicyclo[2.2.1]heptane (2; X = Y = Br) with *tert*-Butyllithium. A solution of the dibromide (2; X = Y = Br; 0.37 g, 1.45 mmol) in dry diethyl ether (5 mL) was treated with *tert*-butyllithium (2 equiv) as described above for the fluoro iodide (2; X = F, Y = I). After allowing the reaction mixture to warm to room temperature, saturated aqueous ammonium chloride was added followed by a standard workup. The crude reaction product was analyzed by VPC, mass spectrometry, and ^{13}C NMR. No starting material could be detected. The major product was 1-*tert*-butylbicyclo[2.2.1]heptane: mass spectrum, *m/e* 152 (M$^+$); ^{13}C NMR (CDCl$_3$, relative Me$_4$Si) δ 54.50 (C1), 30.12 (C2), 30.94 (C3), 37.03 (C4), 38.40 (C7), 27.20 (C(CH$_3$)$_3$), 31.64 (C(CH$_3$).

A small amount of 1-bromobicyclo[2.2.1]heptane was also detected.

Registry No. 2 (X = Y COOCH$_3$), 15448-76-7; 2 (X = COOH, Y = COOCH$_3$), 15448-77-8; 2 (X = Cl, Y = CO$_2$H), 123463-09-2; 2 (X = Cl, Y = Br), 123463-10-5; 2 (X = Cl, Y = I), 123463-11-6; 2 (X = Y = Br), 40950-22-9; 2 (X = Br, Y = I), 62947-51-7; 2 (X = Y = I), 40950-21-8; 2 (X = Br, Y = COOH), 15448-85-8; 2 (X = I, Y = COOCH$_3$), 123463-12-7; 2 (X = I, Y = COOH), 123463-13-8; 2 (X = F, Y = I), 84553-45-7; 2 (X = CH(OH)CH$_3$, Y = C(CH$_3$)$_3$), 123463-14-9; 2 (X = H, Y = C(CH$_3$)$_3$), 29339-31-9; Me$_3$SnLi, 17946-71-3; acetaldehyde, 75-07-0.

Interactive Computer Modeling of the Octant Rule: Applications to the CD of Floppy Molecules

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Computer-assisted structure–property studies of molecules involves the computer construction of a model and the use of this model to deduce the properties of a real molecule. Computer graphics, molecular mechanics, and conformation search methods have been combined with rule-based techniques to assist the prediction of CD properties from the geometric characteristics of a molecule. A computer package for CD–structure relationship studies has been developed which includes two main modules: CDexpert and RELATE. The octant rule for ketones has been implemented and tested on a number of rigid molecules. Application to CD studies of conformationally flexible molecules using the auxilliary program RELATE on the Boltzmann distribution of low-energy conformations allows excellent correlation with the temperature dependance of the CD.

Circular dichroism (CD)[1,2] is a common chiroptical method used to determine the absolute configuration of a compound as well as in conformational analysis,[3] and for determination of secondary structural changes in proteins or nucleic acids.[4] Interpretation of the CD spectrum involves the correlation of the CD with a geometric property such as absolute configuration. Most chemists use Dreiding models to construct the structural models.

We report in this paper a new computer package for CD studies which combines computer graphics and molecular mechanics with rule-based techniques to assist the prediction of CD properties from the three-dimensional structure of a molecule. Although computer programs have been used to calculate wave functions and transition moments in theoretical studies of CD,[5–7] no computer program for CD exists to make full use of techniques developed in recent years, such as interactive computer graphics and molecular mechanics. Our CDexpert program is a graphical implementation of empirical rules built around the well-known molecular modeling program MODEL.[8] An example of using CDexpert to predict the CD sign for a simple ketone is illustrated by the graphics output from an actual run on 2-decalone (Figure 1).

True theoretical approaches, except for quite simple molecules, usually do not give reliable numerical estimates of the Cotton effect or even the correct sign.[2] Our approach is a qualitative one and a natural implementation of the empirical rules. These rules predict the CD sign of a molecule based on certain geometric characteristics.[9]

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(1) (a) Djerassi, C. *Optical Rotatory Dispersion*; McGraw-Hill: New Yrok, 1960. (b) Crabbe, P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965. (c) Velluz, L.; Legrand, M.; Grosjean, M. *Optical Rotatory Dispersion*; Verlag Chemie: Weinheim, 1965. (d) *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Snatzke, G., Ed.; Heyden: London, 1967.

(2) Kirk, D. N. *Tetrahedron* **1986**, *42*, 777.

(3) Rassat, A., in ref 1d, pp 314–328.

(4) Watanabe, S.; Saito, T. *Biopolymers* **1987**, *26*, 625.

(5) Moscowitz, A. *Adv. Chem. Phys.* **1962**, *4*, 67.

(6) Wagniere, G. *J. Am. Chem. Soc.* **1966**, *88*, 3937.

(7) Pao, Y. H.; Santry, D. P. *J. Am. Chem. Soc.* **1966**, *88*, 4175.

(8) MODEL, Kosta Steliou, University of Montreal. The CDexpert program will be made available as an auxiliary routine of MODEL. Interested parties should contact Dr. Steliou.

(9) Sector rules divide the space into certain sectors divided by the nodal surfaces of the chromophore. Examples are the "octant rule" for ketones,[1] the "left-handed octant rule" for chiral olefins[10] and the "lactone sector rule" for the five- and six-membered lactones.[11] Helicity rules relate the helicity of the structure or part of the structure to the CD sign an example being the rule for α,β-unsaturated ketones,[12] which relates the CD sign to the helicity of the C=CC=O chromophore. Chirality rules relate certain chiral characteristics of the geometry to the CD sign. Two rules which belong to this group are the allylic axial chirality rule[10] for chiral cyclohexene and "Ogura sign rule" for seven-membered lactams and lactones.[13] The exciton chirality method[17] developed by Nakanishi is an unique rule for relating the CD sign to the geometry of a molecule. It is derived from the molecular exciton theory[14] and deals with the Cotton effect resulting from the spatial interactions between two or more chromophores.

(10) Hudec, J.; Kirk, D. N. *Tetrahedron* **1976**, *32*, 2475.

(11) Klyne, W.; Scopes, P. M. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Snatzke, G., Ed.; Heyden: London, 1967; pp 193–207.

(12) Burnett, R. D.; Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1460.

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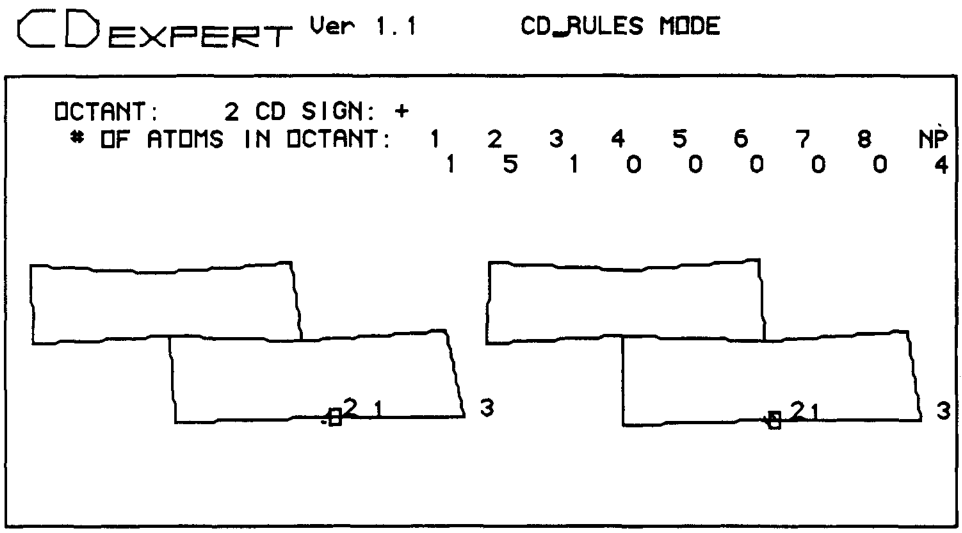

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CDEXPERT Ver 1.1        CD_RULES MODE

OCTANT:     2 CD SIGN: +
 * OF ATOMS IN OCTANT:  1  2  3  4  5  6  7  8  NP
                        1  5  1  0  0  0  0  0  4
```

Figure 1. CDexpert analysis of 2-decalone (octant projection in stereo).

A typical procedure employed by the chemist to predict CD sign for a rigid molecule has three major steps. First, a structural model of the molecule is built with a Dreiding model and is optimized by manually adjusting the dihedral angles to release any obvious strain. Secondly, the model is rotated to the usual orientation to inspect the geometrical characteristics of the model. The CD sign is predicted by referring to an empirical CD rule which relates the geometrical character of the structural model to the CD property.

Looking at this empirical procedure, one can see that it is a natural candidate to be assisted by a computer program. The structural model building and examination procedure could be assisted by interactive computer graphics, and structure optimization can be done by molecular mechanics. The determination of geometric characteristics, such as the number of atoms in each octant, the helicity of a segment of the structure, or the distance between a substituent and the chromophore in a molecule, could be readily calculated from the *xyz* coordinates of the model. CD rules are then implemented as IF-THEN statements and applied to the structural model. Most important, *computerized conformational search procedures makes the CD study of conformationally flexible molecules possible.*

The CDexpert package is designed to be used by the organic chemist in CD-structure studies (Figure 2) and should enable a chemist who does not have experience with CD spectroscopy to deduce the absolute configuration and the most stable conformations of the molecule from its CD spectrum or to predict the CD properties of a molecule from its structure.

Molecular Graphics and Molecular Mechanics. As in any computer-assisted structure-property study, the first step is to build a structural model. This is accomplished by interactive three-dimensional computer graphics routines and structure optimization routines using molecular mechanics.[15] For conformationally rigid molecules, a single stable conformation can serve as the structure model while a *group* of low-energy conformations is needed as the structural model for flexible molecules. The structural model is stored in a structure database (i.e. a single or multiple data file) for further use. For conformationally flexible molecules, there will be a certain number of stable conformers in equilibrium, their populations determined by a Boltzman distribution. The CD spectrum recorded at that temperature is derived from this *group* of conformers. It is for this reason that a careful conformational analysis must be done before the empirical rules are applied to conformationally flexible molecules. In the present case this analysis is carried out using conformation search routines (see Methods).

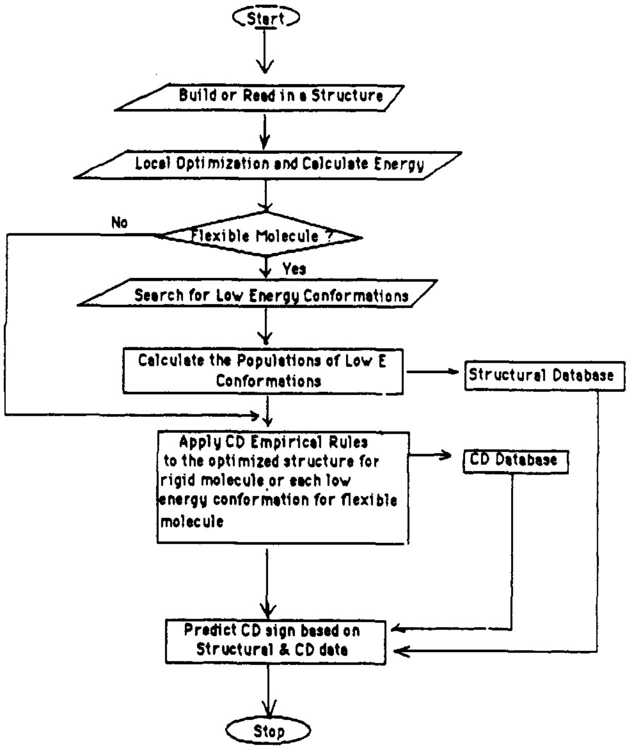

Figure 2. Flow chart of the CDexpert program.

Implementation of CD Empirical Rules. The central part of the CDexpert program is the rule base in which the empirical rules of CD are implemented in a way that could be readily applied to our computer model. A tremendous amount of experimental CD data has been accumulated, and a number of empirical rules have been proposed and tested. However, due to the complexity of the substituent effect on the CD spectrum, the scope of these rules are limited and an expert with detailed knowledge of CD

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(13) Klyne, W.; Kirk, D. N.; Tilley, J.; Suginome, H. *Tetrahedron* **1980**, *36*, 543.

(14) Davydov, A. S. *Theory of Molecular Excitons*; McGraw-Hill: New York, 1962.

(15) Burket, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph Series Vol 177; American Chemical Society, Washington, DC, 1982.

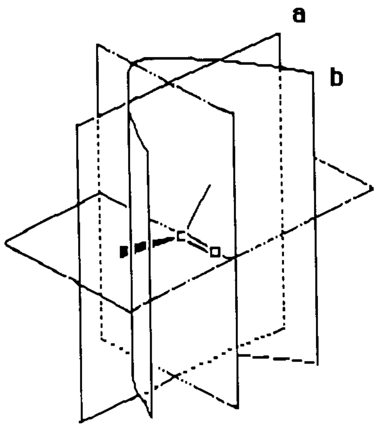

Figure 3. (a) Original octant rule nodal plane. (b) Bouman/Lightner modified nodal plane.

spectroscopy and conformational analysis is needed to interpret a CD spectrum of the moderately complicated compounds on which a practical organic chemist often works. Although some efforts have been made to comprehensively organize CD data and empirical rules, there are no general rules that can be applied to different chromophore systems, and each rule has its limits and exceptions. As our first attempt to implement empirical rules into a computer program, a preference was given to the rules that are well established and could be applied to a large number of compounds. The octant rule[1,2] for ketones and exciton chirality method[16] for coupled chromophores were chosen based on these considerations and can be readily implemented by computer.

The Octant Rule. The n → π^* transition of a carbonyl chromophore leads to a Cotton effect, which is dependent upon the spatial orientation of the molecule. The space around the chromophore is divided into eight octants, and the sign of the CD is predicted by determining whether the positive or negative octants contain the greater number of non-hydrogen atoms. In its original form, the octant rule made the division of space around the C=O group shown in Figure 3a. The octants are separated by the two symmetry planes of the n and π^* orbitals, respectively, and by a third boundary surface perpendicular to the first two planes and bisecting the C=O bond. It is customary to present an "octant projection" of the molecule as viewed down the carbonyl O → C axis (cf. figure 1). The four octants behind the third boundary surface are called rear octants while the four octants in front of the third boundary surface are called front octants. The upper left and lower right "rear" octants are positive.

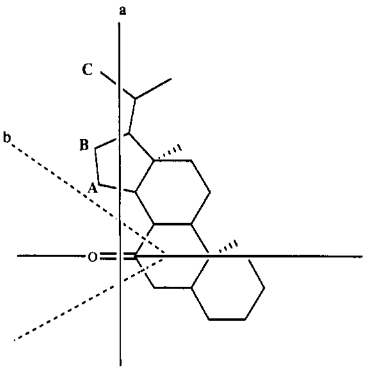

Figure 4. Projection of compound **2** using the normal (a) and Bouman/Lightner (b) boundary surfaces.

The three boundary surfaces of the original octant rule work for most of the ketone systems we have tested. Different views exist as to the location and shape of the third boundary surface. Using CNDO/S calculations. Bouman and Lightner proposed that the third boundary surface should be concave toward the oxygen atom and predicted small spatial "pockets" of sign reversal in rear octants (Figure 3b).[18] Both boundary surface models have been implemented in the program.

Special Substituent Effects. The original octant rule does not consider the nature of the substituent and fails to predict the correct CD sign for ketones with special substituents at particular positions. A group of subrules were implemented to count these effects. The program subroutines Atom_Characters, Ring_substituent, and Ring_conformation recognize the nature and stereochemical characteristics of substituents and can be modified to include other special rules. The nature of the substituent and its polarizability is important to the Cotton effect and is taken into account in this way.

Results

We have tested the CDexpert program with various types of rigid molecules. Because the octant rule was well established for predicting CD signs and the structural model built by molecular mechanics routines is expected to be as good as or better than those built by Dreiding models, the success rate for the prediction of CD signs for *rigid* molecules by CDexpert was expected to be high.

Steriodal ketones provide the widest range of polycyclic structures with known absolute configuration and chiroptical properties. This group of ketones appear in the structural skeleton of a large number of natural products and are the most widely used group when seeking structural analogues for new compounds of unknown absolute configuration. CD data from 22 steroidal ketones were taken from the literature (Table I, supplementary mate-

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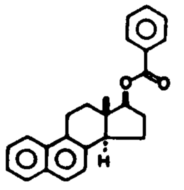
(16) The exciton chirality method, formulated as an empirical rule in which the helicity of coupled chromophores is related to the CD sign, is implemented by a chromophore chirality projection. The vector linking the ends of the two coupled chromophore vectors is placed on the *Z* axis and the molecule is reoriented by rotating around *Z* so that the vector in the rear is in the *YZ* plane. If the *X* component of the front vector is negative, then the helicity of the coupled choromophores is clockwise (positive chirality), otherwise, anticlockwise (negative chirality). For example, compound *i* was examined in EXCIT mode by CDexpert to present the projection shown and give confirmation of a negative chirality.

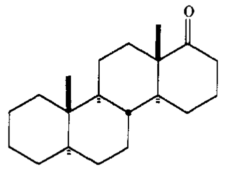


i

(17) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic and Bioorganic Chemistry*; University Science Books: Mill Valley, CA, 1983.

(18) Bouman, T. D.; Lightner, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 3145.

rial). Only one case of failure was found, compound 1 (Table I, entry 22). The observed $\Delta\epsilon$ for compound 1 was reported to be zero in MeOH and −0.2 in hexane.[19] The Cotton effect predicted by CDexpert is a strong positive one.



1

An example of the effect of boundary surfaces is given by applying CDexpert to a 7-oxo-5a-steroid 2 (Table I, entry 12), which was observed to have a negative Cotton effect. The original boundary surface system gives a wrong prediction for the CD sign of this compound, while the Bouman and Lightner boundary surface system gives a correct one (Figure 4).

According to the original octant rule, atoms A, B, and C are in octant 7, which is a positive octant. The ratio of atoms in negative octants is larger than that in positive octants (8/11), thus a positive CD sign is predicted for this molecule. Atoms A, B, and C move to octant 3, which is a negative octant, using the nodal surface system of Bouman and Lightner. The ratio of the number of atoms in negative octants over that in positive octants is 11/8, thus a negative CD sign is predicted for this molecule, which is in agreement with experimental data.

Fifteen relatively rigid ketones of various structural types were also tested using CDexpert (Table II). The failure of CDexpert in two cases (entries 5 and 15) is due to the fact that the octant rule implemented in CDexpert is qualitative, and when the numbers of atoms located in positive and negative octants are equal, CDexpert predicts a zero Cotton effect.

Conformationally Flexible Molecules. The application of CDexpert to conformationally flexible molecules is more complicated than to rigid ones. There are two major difficulties in predicting CD properties for flexible molecules. First, a complete conformational search[20,21] consumes a large amount of computer time but must be done in order to collect the complete group of conformers on which to apply the rules. Secondly, there are no established empirical rules for the estimation of the *relative intensity* of the Cotton effect for each conformation.

Determining the absolute configuration for a molecule is based on the *sign* of the CD. Although the rotatory strength can be determined by measuring the area under the CD curve, it is never used in practice because there is no empirical rule relating the *magnitude* of the CD to geometric properties of molecules. For conformationally flexible molecules, estimation of the relative intensity of the Cotton effect becomes necessary because the CD spectrum observed is the combination of the contributions of all low-energy conformations. The contribution by an individual conformation to the overall CD is weighted by its *population at a given temperature* and by the *intensity of its Cotton effect*. The intensity of the Cotton effect of each conformation has to be considered in a quantitative way because the difference in the Cotton effect intensities between conformations can be large and outweigh population factors. The Relative_CE routine in the program RELATE is designed to estimate the relative intensity of the Cotton effect for each conformation of a flexible molecules. The procedures in Relative_CE for the relative intensity estimation takes the following factors into consideration: the relative number of atoms in positive and negative octants, the distance between the substituent and chromophore, the distance between the substituent and nodal planes, and the nature of the substituent.

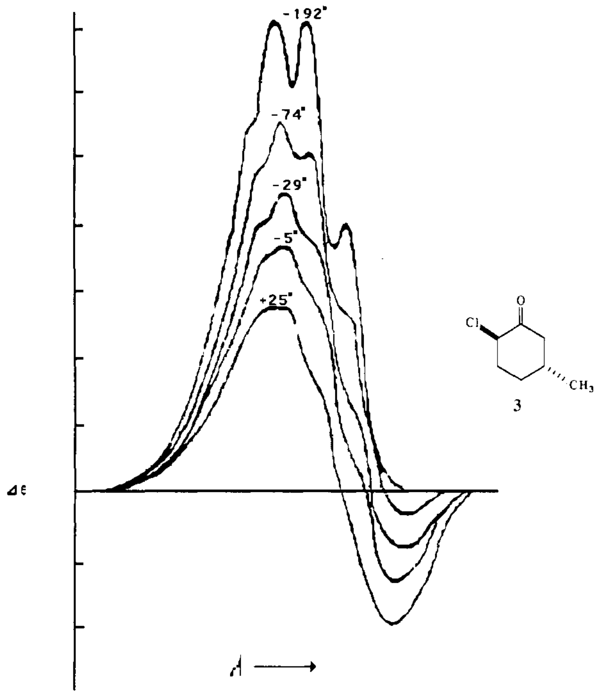


Figure 5. CD curves of compound 3 at 25, −5, −29, −74, and −192 °C (ref 1d).

It is known from CD studies of rigid molecules that there is a special substituent effect, that is halogen atoms located near the chromophore perturbs the chromophore much more than carbon atoms in the same position. The "α-halo ketone rule" states that the CD sign of an α-halo ketone is determined by the sign of the octant occupied by an α-axial halogen atom. A study of the CD spectra and conformational equilibrium of *trans*-2-chloro-5-methylcyclohexanone at various temperatures by Djerassi[25] showed that the contribution to the CD intensity by an axial chlorine atom is about 15 times larger than an equatorial one. Our studies on this system by molecular mechanics shows that this ratio should be 45. Since both of these studies were based on empirical estimations, an average value of 30 was chosen to be used as an empirical parameter for this special substituent effect. Obviously, other empirical parameters can be added for other groups as more data is accumulated.

***trans*-2-Chloro-5-methylcyclohexanone.** There are two overlapping Cotton effects with opposite signs in the CD spectrum (Figure 5) of *trans*-2-chloro-5-methylcyclohexanone, 3.[1d] It is clear that more than one conformation contributes to the overall CD spectrum significantly. The

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(19) From ref 2.

(20) For a description of the grid search approach to conformation searching: (a) Lipton, M.; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343. (b) Bruccoleri, R. E.; Karplus, M. *Biopolymers* **1987**, *26*, 137.

(21) The simulated annealing approach to conformation searching: Wilson, S. R.; Cui, W.; Moskowitz, J. W.; Schmidt, K. E. *Tetrahedron Lett.* **1988**, *29*, 7343.

(22) Moscowitz, A.; Wellman, K.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 3515.

(23) Sato, T.; Minato, H.; Shiro, M.; Koyama, H. *J. Chem. Soc., Chem. Commun.* **1966**, 363.

(24) Kuriyama, K.; Takeda, K. *J. Chem. Soc. C.* (*London*) **1967**, 420.

(25) Djerassi, C. *Proc. Chem. Soc.* **1964**, 314.

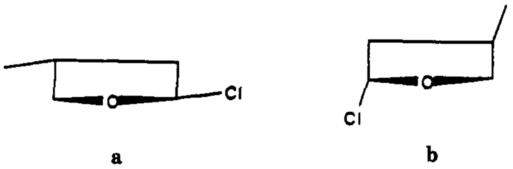


Figure 6. Octant projections of conformation a and b of *trans*-2-chloro-5-methylcyclohexane (3).

question is, how many conformations contribute and what are the relative intensities of their Cotton effects?

From the data listed in Table III, it is clear that the third conformation and those conformations of higher energies can be ignored because their populations are too small. The overall CD curve is thus the result of the overlapping Cotton effects of only conformations a and b. The contribution of ring atoms in any of these two conformations are canceled because of the symmetry of these conformations (Figure 6).

In conformation a, the chlorine atom is in a negative octant but located very close to two nodal planes (distance to XZ, XY, and YZ planes: 0.13, 0.52, and 2.80 Å) and gives a weak negative contribution, while the methyl group is in a positive octant and not close to any nodal plane and expected to give a normal positive contribution. The overall CD for this conformation is a weak positive Cotton effect (ca. $\Delta e = +0.84$). Both methyl and chlorine substituents are in negative octants and far away from any nodal plane (distances from Cl to XZ, XY, and YZ planes: 1.56, 2.25, and 1.55 Å) in conformation b and enforce each others' perturbation of the chromophore's orbitals. The Cotton effect of this conformation is negative and much stronger than that of conformation a (ca. $|\Delta e_2/\Delta e_1| = 45$). The calculations are based on the following equation

$$R_{\mathrm{obs}}(T) = P_1(T)R_1 + P_2(T)R_2$$

where $R_{\mathrm{obs}}(T)$ is the observed rotational strength at temperature T, R_i is the rotational strength of individual conformation, which is not dependent on temperature, and $P_i(T)$ is the population of conformation i at temperature T. The Cotton effect intensity ratio of 45 calculated by this procedure is higher than that of 15 by Djerassi and co-workers based on estimated ΔG value,[17] but in the same order of magnitude. Considering the fact that both calculations are based on rough estimation of rotational strength and the population distribution is also based on the energies calculated by empirical methods, the average value of 30 was taken as an empirical parameter for further applications to compounds having similar geometrical characteristics as this model compound.

Perhydroazulene Compound 4. The seven-membered ring makes the perhydroazulene derivative 4 conformationally flexible. It was shown by X-ray analysis[24] that this molecule occurs in the crystal in a conformation having an pseudoequatorial bromine. According to the octant projection of this conformer (Figure 8a), one should expect a positive CD for this compound. However, a negative CD is actually found in solution,[25] which indicates that the bromine is pseudoaxial (Figure 8b). Measurement at −180 °C led to reversal of the sign of CD with a simultaneous shift of $\lambda_{\max}$ to 294 nm (Figure 7).

It is clear that the usual practice that relates to CD only to the most stable conformation of a molecule is not valid in this case. The question arising from the conflicting experimental data is how many low-energy conformations should be considered for their contributions to the overall CD curve and how the combination of the CD of these individual conformers could result in the CD sign reversal with temperature change.

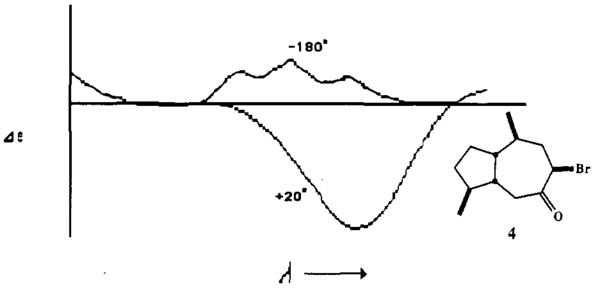


Figure 7. CD curves of compound 4 at +20 and −180 °C (ref 25).

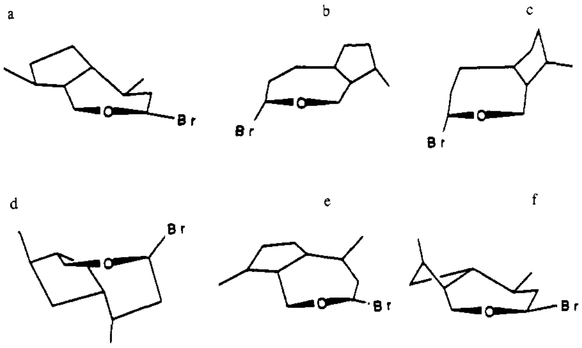


Figure 8. Octant projections of low-energy conformations of the perhydroazulene derivative (4).

Using the empirical parameters for the relative intensity of Cotton effect derived from the study of *trans*-2-chloro-5-methylcyclohexanone, the combination of the CD contributions of these six conformation correctly predicted the reverse of CD sign for this molecule from 20 to −180 °C. The most stable conformation a has an equatorial bromine atom located near a nodal plane in a positive octant thus gives *weak positive* Cotton effect while the much less stable conformation b and c (Figure 8) have axial bromine atoms in negative octants and not close to any nodal plane, thus give very *strong negative* Cotton effect.

The reversal of the CD sign from 20 to −180 °C is the result of the population changes of these conformations as seen in Table IV. Although the combined population of the two negative CD conformations (b and c) is only 14.4% at 20 °C the strong negative Cotton effects of these conformations (ca. 80% of overall Cotton effect) effectively cancels the positive Cotton effect (ca. 20% of overall Cotton effect) of the much more stable conformation a (population at 20 °C: 83.5%). The Δe for the overall Cotton effect at 20 °C is predicted to be −1.0 (experimental data: −2.5). At −180 °C, the population of conformations b and c are small and the major contribution (97.1%) to the overall Cotton effect is from conformation a (population at −180 °C: 99.9%). The Δe for the overall Cotton effect at −180 °C is predicted to be +1.21 (experimental data: +0.8). The correct prediction of the sign and relative magnitude of CD for this flexible molecule supports the empirical parameter for the relative intensities of α-halo ketones and the general strategy of CDexpert.

(−)-Menthone. The CD curves of (−)-menthone 5 shows a weak negative Cotton effect at room temperature in decalin. If the temperature is increased, the sign and maginitude of the CD does not change very much. However, the sign and maginitude of the CD changes dramatically when the temperature decreases (Figure 9). A published[25] CD–structure analysis based on low-energy conformations built by examing Dreiding models (cf. Figure 10a,d,e) overlooked some important conformations and could not give a consistant explaination for the Cotton effects at these temperatures.[26] The dramatic increase

Table II. Testing CDexpert with Nonsteroidal Ketones

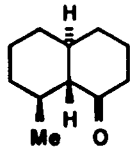
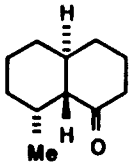
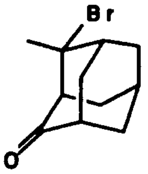
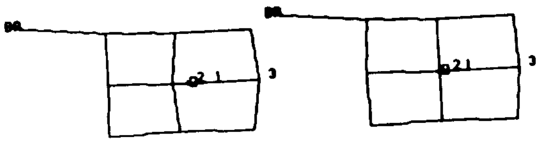
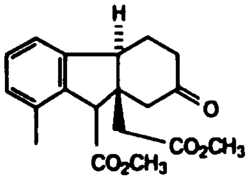
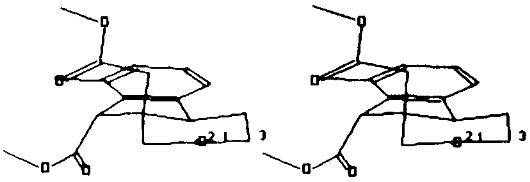
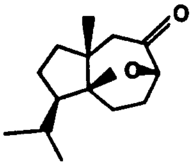
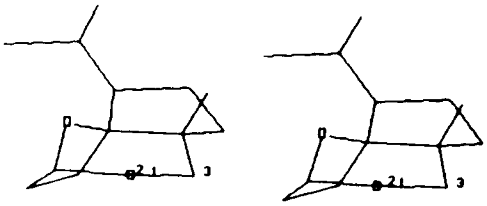
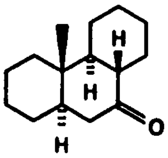
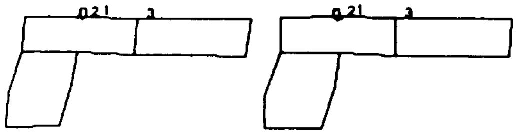
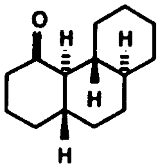
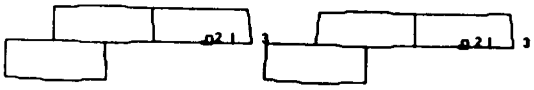
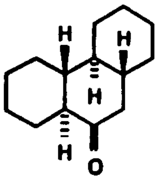
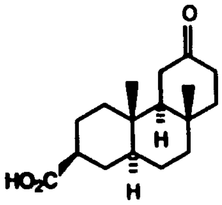
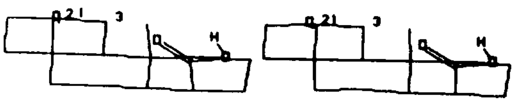
entry	structure	observed CD	predicted CD	stereo drawing of octant projection
1		-1.85	⊖	
2		-0.54	⊖	
3		+2.1	⊕	
4		⊕	⊕	
5		-0.72	0.0	
6		-0.8	⊖	
7		+2.14	⊕	
8		-0.7	⊖	
9		⊕	⊕	

Table II (Continued)

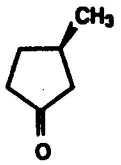
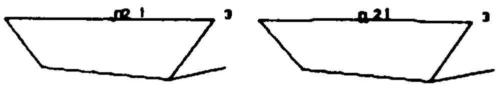
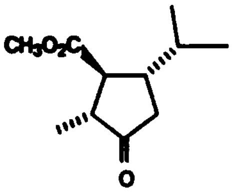
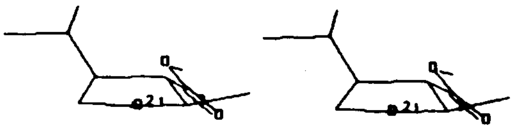
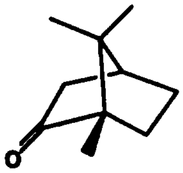
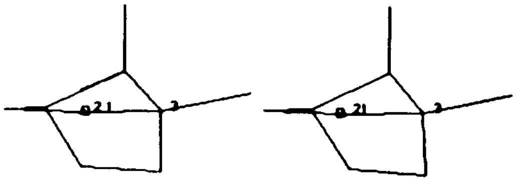
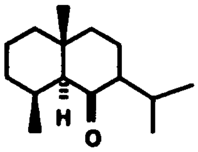
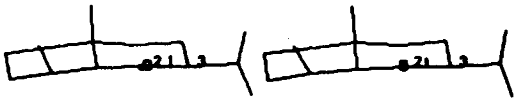
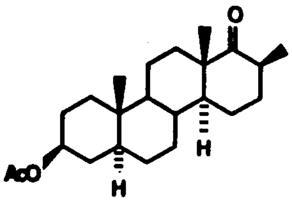
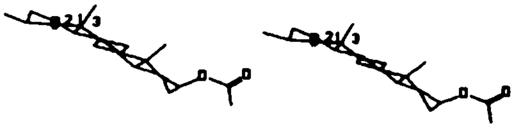
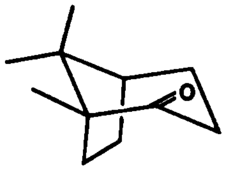
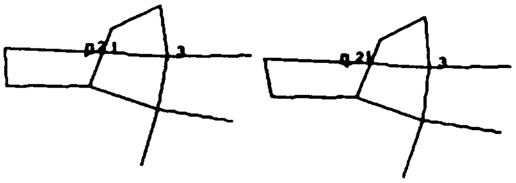
entry	structure	observed CD	predicted CD	stereo drawing of octant projection
10		**+2.1**	⊕	
11		⊖	⊖	
12		**-1.6**	⊖	
13		**+1.2**	⊕	
14		**+4.2**	⊕	
15		**-1.4**	**0.0**	

Table III. Energies and Conformation Populations of Compound 3

conformer	MM2 energy[a]	population, % at temp, °C				
		+25	-5	-29	-74	-192
a	43.64	96.9	97.9	98.6	99.4	100
b	52.22	3.0	2.1	1.4	0.6	0
c	62.63	0.01	0	0	0	0

[a] In kilojoules/mole.

Table IV. Energies and Conformation Populations of 4

conformer	energy, kj/mol	population, % at given temperature, °C	
		+20	-180
a	120.83	83.5	99.9
b	126.06	9.9	0.1
c	127.95	4.5	0.0
d	132.21	0.8	0.0
e	132.43	0.7	0.0
f	132.78	0.6	0.0

in the positive maximum upon lowering of temperature was explained as the results of the increase of the population of the diequatorial conformer a (Table V).

The relative intensities of Cotton effects of these conformations are calculated based on the distances between the atoms of substituents and the center of carbonyl group. The atoms positioned on or very close to any nodal plane

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(26) Crabbe, P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965.

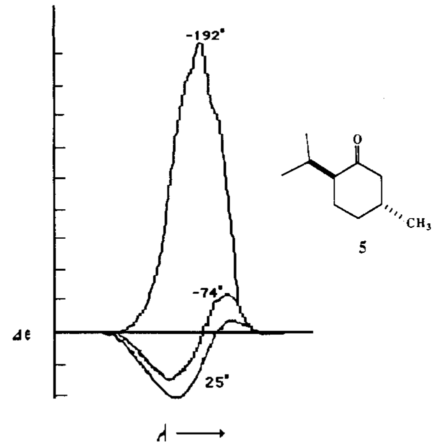


Figure 9. CD curves of (−)-menthone 5 at +25, −74, and −192 °C (ref 25).

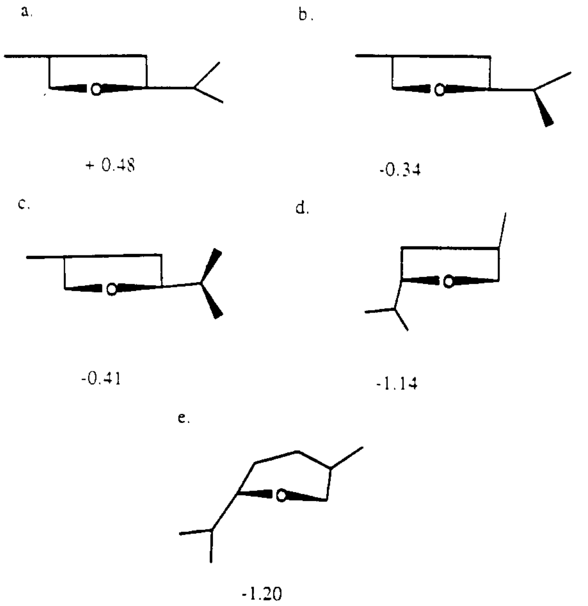


Figure 10. Octant projections and relative intensities of (−)-menthone 5.

Table V. The Energies and Conformation Populations of 5

conformer	energy, kj/mol	population, % at given temperature, °C −192	−74	25	162
a	53.89	57.2	44.6	40.9	38.0
b	54.19	36.6	37.2	36.3	35.0
c	55.38	6.2	18.1	22.4	25.2
d	65.67	0.0	0.0	0.3	1.5
e	71.02	0.0	0.0	0.0	0.3

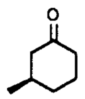
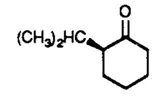
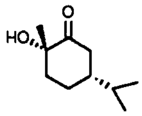
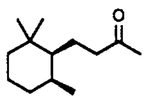
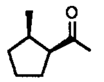
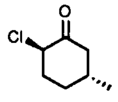
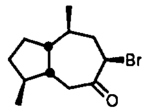
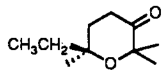
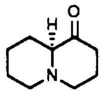
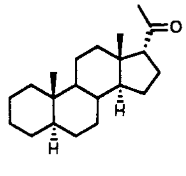
(the minimum distance between the atom and the nodal planes < 0.1 Å) are neglected for contribution to Cotton effect. The signs and magnitudes of the CD at different temperatures are calculated by combining the populations and relative intensities of Cotton effects of these low-energy conformations and are in agreement with experimental results (Table VI). The change of the CD sign and magnitude at these temperatures are the result of the change of relative populations among the three diequatorial conformations rather than the change of between diequatorial and diaxial conformations.

Table VI. The Sign and Magnitude of the CD for (−)-Menthone 5

	CD sign and magnitude			
	expt		predicted	
temp, °C	direct	relative[a]	direct	relative[a]
−192	+19.1	+4.75	+0.1232	+6.42
−74	+3.2	+0.75	+0.0164	+0.85
+25	−4.1	−1.0	−0.0192	−1.0
+162	−4.9	−1.25	−0.0562	−3.43

[a] The relative data are calculated by dividing direct data by the value of direct data at 25 °C.

Table VII. Testing CDexpert with Flexible Molecules

entry	structure	temp, °C	CD sign and magnitude observed	predicted
1		25	+5.6	+0.18
2		−192 −74 25 162	+0.57 +0.10 −0.12 −0.15	+0.12 +0.02 −0.02 −0.06
3		−74 25 156	+1.21 −1.36 −0.76	+0.48 +0.48 +0.47
4		−179 20	−0.24 −0.01	−0.15 +0.03
5		−188 20	+3.63 +2.77	+0.99 +0.58
6		−192 −74 −29 −5 +25	+0.84 +0.63 +0.43 +0.29 +0.09	+1.00 +0.81 +0.57 +0.35 +0.07
7		−180 20	+0.80 −2.50	+1.21 −1.00
8		−180 20	−1.70 −0.30	+0.13 +0.07
9		−78 60	−1.80 −1.20	−1.41 −1.37
10		25	−2.60	−0.54

Applications to Other Flexible Molecules. Besides the molecules discussed in detail in the previous section, CDexpert has been applied to several other flexible molecules whose CD at various temperatures has been reported (Table VII). Among the cases where CDexpert gives wrong prediction, two have an oxygen atom located near the chromophore. Unlike the halogen atoms, there is not enough experimental data to propose an empirical rule regarding the special effect of the oxygen atom located close to chromophore. In the third case (entry 3), none of the low-energy conformations found by molecular mechanics and conformational search routines have a hydrogen bond between the OH group and O=C group, although experimental studies of similar molecules suggest that a hydrogen bond to the carbonyl group could stabilize a conformer which would other wise be unfavored and change the CD spectra significantly.[26] Because no solvents are included, our molecular mechanics calculations may have missed a stable hydrogen bonded conformation.

Methods

The CDexpert Program. This program package consists of four major blocks: (1) structure building and optimization procedures which produce a structural database, (2) geometrical and structural characterization procedures which recognize the geometrical and structural features related to the CD properties of a molecule, (3) rule-based procedures in which empirical rules are applied to the structural models, and (4) conformational search and population distribution procedures for studying the conformational equilibrium of flexible molecules.

Conformation Searching. Two conformational search methods are employed to produce the structural database for flexible molecules. The systematic search method (Multiconformer option of MacroModel[20,27] generates the conformations for a molecule by systematically rotating all the rotable bonds and then minimizes the energy of the resulting conformations to their nearest local minimum. The simulated annealing method[21] finds conformations by a totally different global conformational search algorithm involving a Monte Carlo search of conformation space. The percentage of each low-energy conformation in the conformational equilibrium is calculated approximately by a Boltzmann distribution based on molecular mechanics energy. The low-energy conformers which would be expected to contribute significantly to the CD spectrum based on energy considerations are stored in a structural database to be further examined for CD properties by the program RELATE.

Octant Rule. The original form of the octant rule is implemented by following procedure. First, the C=O bond of the ketone to be studied is identified. The program translates the middle of the the C=O bond to the origin of the Cartesian coordinate system and aligns the C=O bond on the Z axis. The α-carbon atoms are placed on the XZ plane, and the three nodal planes for such a projected ketone system are the XZ, YZ, and XY planes of the Cartesian space. The octant location of each atom is easily determined by its coordinates, the number of atoms of each octant are counted, and the CD sign of this molecule is predicted by the sign of the octant occupied by the greater part of the molecule.

For flexible molecules, a *group* of low-energy conformations has to be found using conformation search routines described above, and the *populations* of these low-energy conformations in the conformational equlibrium at the temperature at which the CD spectrum is determined has to be calculated according to a Boltzmann distribution. The *relative intensities* of the Cotton effects for these conformations have to be established using empirical parameters. Finally, the relative Δe (difference in molar absorption coefficients) for the molecule at a given temperature is estimated by the following formula:

$$\Delta e = P_i \Delta e_i \qquad i = 1, 2, ..., n$$

where P_i is the percentage concentration of conformation i in the conformational equilibrium at the given temperature, Δe_i is the relative Δe of the conformation i, and n is the number of low-energy conformations considered.

A program RELATE estimates the CD for flexible molecules. It consists three major routines: (1) Relative_CE calculates the relative intensity for each conformation, (2) Boltz_Dis calculates the populations of the low-energy conformations according to Boltzmann distribution, and (3) the MAIN routine which combines the signs and relative intensities and populations of these low-energy conformations to predict the sign and relative maginitude for the overall CD for a flexible molecule.

Parameterizing Relative Intensities. There are no empirical rules or results from theoretical calculations for evaluation the relative intensities of Cotton effects. The formulas employed in RELATE routines were parameterized from the results of trial studies and general considerations of through space interaction between the substituents and chromophore. From the study of CD–structure relationships of rigid molecules, it is well established that the magnitude of perturbation by a substituent is inversely proportional to the distance between this substituent and the chromophore.[28] The magnitude of perturbation also depends on the closeness of the substituent to the nodal planes. It is well established from the studies on rigid molecules that a substituent positioned on nodal planes has no effect on the CD and one very close to nodal planes has a very small effect. This suggests that the magnitude of perturbation of a substituent should also be related to the distance between the substituent and nodal planes.

Based on these facts, a formula for the *chromophore distance factor* (DCi) and *nodal plane factor* (DNi) is proposed to be as follows:

$$\mathrm{CE} = \mathrm{PN}_i{}^* \, (\mathrm{DN}_i)^m / (\mathrm{DC}_i)^n, \; i = 1, 2, ..., N_{\mathrm{atoms}}$$

CE is the relative Cotton effect of a conformation, PN_i is the sign of the octant occupied by atom i, DC_i is the distance between atom i and the chromophore, DN_i is the minimum distance between atom i and the nodal planes, and N_{atoms} is the number of non-hydrogen atoms of the molecule. This simple formula has been tested on flexible molecules with different values for m and n. The set of m, n values with $n = 1$ and $m = 1$ for atoms on or very close to nodal plane (DN <0.05 Å) and $m = 0$ for other atoms gives the best prediction.

Conclusions

The encouraging results from applications of CDexpert to the study of CD–structure relationships of flexible molecules shows that the overall approach of computer-assisted CD study is effective. The simple distance factor formula we proposed gives reasonably good results in predicting relative intensity of Cotton effect. More testing and some theoretical investigations on the dependence of rotational strength on the distances between the substituent and chromophore and closeness to the nodal planes could be carried out to give better quantitative predictions in any further development of CDexpert.

Registry No. **3**, 89616-30-8; **4**, 123409-78-9; **5**, 14073-97-3.

Supplementary Material Available: Table I, detailing the testing of CDexpert with 22 steroidal ketones (6 pages). Ordering information is given on any current masthead page.

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(27) MacroModel, 1986, W. C. Still (Columbia University).

(28) Snatzke, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 363.