*Tetrahedron* Vol 37, No. 24, pp. 4123 to 4142, 1981
Printed in Great Britain.

0040–4020/81/244123–20$05.00/0
Pergamon Press Ltd

# TETRAHEDRON REPORT NUMBER 118

---

# CIRCULAR DICHROISM OF MOLECULES WITH ISOTOPICALLY ENGENDERED CHIRALITY

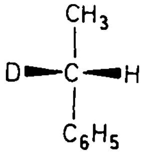
GÜNTER BARTH and CARL DJERASSI
Department of Chemistry, Stanford University, Stanford, CA 94305, U.S.A.

## CONTENTS

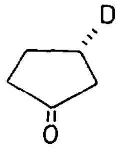
1. Introduction . . . . . . . . . . 4123
2. Isotopically-induced Cotton effects associated with various chromophores . . . . . . . . . . 4124
    2.1 The carbonyl group . . . . . . . . . . 4124
        2.1.1 α-Deuterium substituted ketones
        2.1.2 β-Deuterium substituted ketones
        2.1.3 γ-Deuterium substituted ketones
        2.1.4 Additivity of deuterium octant contributions
        2.1.5 Conformationally mobile ketones
        2.1.6 $^{13}C$ and the octant rule
        2.1.7 Theoretical considerations
    2.2 Diketones . . . . . . . . . . 4130
        2.2.1 The α-dicarbonyl chromophore
        2.2.2 The β-dicarbonyl chromophore
    2.3 β,γ-Unsaturated ketones . . . . . . . . . . 4131
    2.4 Carboxylic acids and esters . . . . . . . . . . 4131
    2.5 Thioketones . . . . . . . . . . 4132
    2.6 Azides . . . . . . . . . . 4132
    2.7 Olefins . . . . . . . . . . 4132
    2.8 Dienes . . . . . . . . . . 4133
    2.9 The benzene chromophore . . . . . . . . . . 4133
3. Conformational isotope effects . . . . . . . . . . 4135
    3.1 Cyclohexanones . . . . . . . . . . 4135
    3.2 Cyclopentanones . . . . . . . . . . 4139
4. Future developments . . . . . . . . . . 4141
5. Literature references . . . . . . . . . . 4141

## 1. INTRODUCTION

Shortly after the discovery in 1932 of the heavier isotope of hydrogen by Urey *et al.*,[1] the question was raised whether a molecule could be synthesized whose chirality was solely due to deuterium substitution vs hydrogen and whether such a molecule would exhibit the chiroptical properties commonly observed for substances of structural asymmetry. This question was answered in the affirmative by Eliel[2] who synthesized chiral (R) (2-$^2H_1$)ethylbenzene (1) for which he measured an $[\alpha]_D$ value of −0.30°.



1



2

Numerous other examples have been reported subsequently as shown by Verbit[3] in his 1970 review. In general $[\alpha]_D$ values of less than 1° were observed and with one exception (see sect. 2.4) no optical rotatory dispersion (ORD) or circular dichroism (CD) data were available at the time that review was written. Attention should be drawn to the unsuccessful attempt by Djerassi and Tursch[4] to measure the ORD spectrum of(S) (3-$^2H_1$)cyclopentanone (2) in the spectral region of the $n \rightarrow \pi^*$ transition of the C=O chromophore; no Cotton effect was observable under conditions where a rotation of >42° would have been detectable. This lack of sufficiently meaningful chiroptical data made it difficult to draw any empirical or theoretical conclusions as to the relationship between molecular structure and chiroptical properties.

With the availability of more sensitive instrumentation this situation has changed dramatically and during the past decade several research groups have reported the CD spectra of various carbonyl compounds (and subsequently also other chromophores) whose chirality is solely due to isotopic substitution. These experimental results, together with recent theoretical studies, have led to a more profound understanding of the phenomenon of isotope engendered chirality.

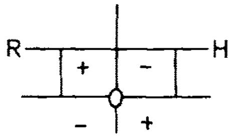
The present review is intended to provide a summary of this development and is divided into two portions. The first deals with isotopically-induced Cotton effects, associated with various chromophores, and with assignments of numerical sector contributions to isotopic substituents. The second portion deals with the application of CD spectroscopy to the determination of conformational isotope effects.

## 2. ISOTOPICALLY-INDUCED COTTON EFFECTS ASSOCIATED WITH VARIOUS CHROMOPHORES

### 2.1 *The carbonyl group*

The C=O chromophore has been of central importance in the development of ORD and CD as spectroscopic techniques for the investigation of molecular structure.[5] The octant rule[6] provided the first firm basis on which a relationship between the experimentally observed sign and amplitude of the Cotton effect associated with the $n \rightarrow \pi^*$ transition of the C=O group and the spatial disposition of extra-chromophoric atoms could be established. Briefly stated, each atom is assumed to make a partial contribution whose sign and magnitude is a function of its relationship with respect to three planes which divided the molecule into eight sectors.[7] The observed Cotton effect is then the sum of the partial contributions from all atoms comprising the molecule. Intensive experimental efforts have been made[8] to obtain numerical values for these partial atom or group contributions. The availability of these values made it possible to draw definitive conclusions regarding the absolute configuration or comformation of a molecule from its ORD or CD spectrum.

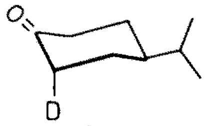
As a logical extension of these studies, several investigations have focused on those molecules which would provide information on the magnitude and sign of isotopic octant contributions. Before discussing these studies, it seems appropriate to clarify briefly the meaning of experimentally determined octant contributions and in particular the definition of the consignate/dissignate nomenclature.[9] As an example consider the octant projection of cyclohexanone, substituted with R in the $\beta$-equatorial position:



Since all other contributions cancel by symmetry, the experimentally observed Cotton effect results from the difference between the partial octant contributions of R and H in the $\beta$-equatorial positions. It is only this difference, and not the absolute contribution of either R or H, which is experimentally observable. By convention, partial octant contributions of such substituents (e.g. R) are given on a scale where hydrogen is assumed to make a zero contribution and they can, therefore, assume either positive (consignate) or negative (dissignate) values depending on whether the absolute contribution is larger or smaller than hydrogen.

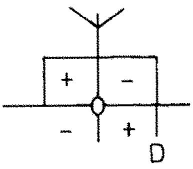
In principle it is possible, and the following discussion provides several examples, to determine isotopic octant contributions on structurally chiral molecules by measuring the difference between the Cotton effect amplitudes of the labeled and unlabeled compound. However, since even in the most favorable circumstances these differences are in the order of only a few per cent, the results are liable to large experimental errors. Therefore, it is much more desirable to obtain octant contributions from molecules which owe their chirality solely to isotopic substitution. For further consideration we point out that it is a *sine qua non* for the molecular system to be conformationally rigid and therefore quite severe limitations are placed on the number of suitable model compounds. The adamantane structure and cyclohexanones locked into one chair conformation by a bulky substituent in its 4-position probably fulfill these conditions most closely.

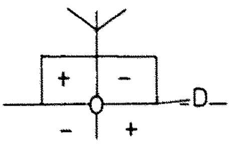
2.1.1 *α-Deuterium substituted ketones.* The Stanford group[10] reported the CD spectra of (2R,4R)- and (2S,4R)$(2-^2H_1)$4-isopropylcyclohexanone (**3** and **4**) with the deuterium in the α-axial and α-equatorial position, respectively. The negative Cotton effect observed for **3** indicates that an α-axial deuterium makes a dissignate contribution whereas an α-equatorial D (*cf* **4**) behaves in a consignate fashion although smaller by a factor of 10. The ORD spectrum of **3** has been reported by Levine and Gopalakrishnan,[11] who also observed a negative Cotton effect thus confirming the earlier CD results. From a comparison of two α-axial D substituted steroid ketones (**5a** and **6a**) with their protonated analogs (**5b** and **6b**) Meyer *et al.*,[12] arrived at the same conclusion namely that an α-axial D acts as a dissignate perturber. Partial octant contributions of $[\theta] = -364$ and $[\theta] = -495$ were observed for **5** and **6** respectively.



3

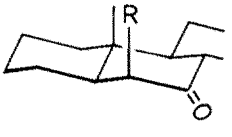
4

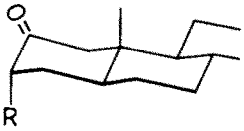




[Θ] = −298

[Θ] = −30



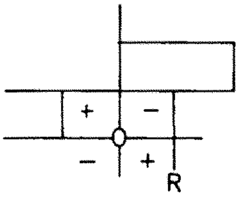


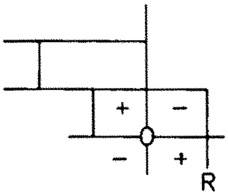
5a R=D,[Θ]=−2904

5b R=H,[Θ]=−2540

6a R=D,[Θ]=7458

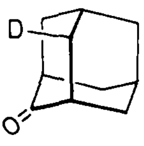
6b R=H,[Θ]=7953



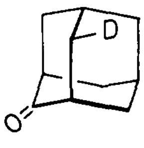


2.1.2 *β-Deuterium substituted ketones.* Two groups[13,14] reported almost simultaneously the CD spectra of (4R)-(**7**) and (4S)-(**8**) $(4-^2H_1)$adamantanone. In both instances a positive Cotton effect was observed indicating that D in the β-equatorial as well as β-axial position behaves as dissignate perturber and that the magnitude of the contribution is approx. 5 times larger for the β-equatorial position (**8**). Sundararaman and Djerassi[10] determined β-D octant contributions using as a model system, the cyclohexanone ring locked into a rigid chair comformation by a 4-t-Bu substituent, i.e. they reported the synthesis and CD spectra of (3R,4R) and (3S,4R) $(3-^2H_1)$4-t-butylcyclohexanone (**9** and **10**). In agreement with the results from the adamantanone system they observed a strong dissignate behavior for the β-equatorial D (*cf* **9** vs **8**) but in contrast a small but consignate behavior for the β-axial analog (**10** vs **7**).

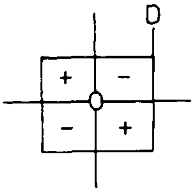
Another relevant example[15] is provided by the CD spectra of (1S-exo (**11**) and (1S)-endo (**12**) $(2-{}^2H_1)$bicyclo[2.2.1]heptan - 7 - one. In both instances a positive Cotton effect was observed indicating that



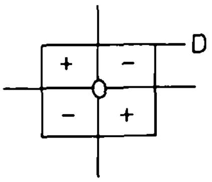
7



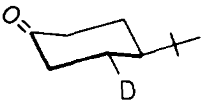
8



[Θ] = 72

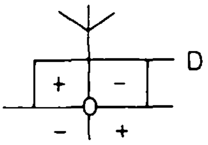


[Θ] = 378

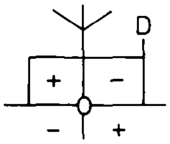


9

10

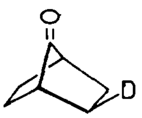


[Θ] = 290

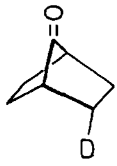


[Θ] = −28

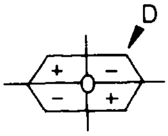
D behaves as a dissignate perturber. Although the deuterium position with respect to the C=O chromophore is not identical as compared to the previously mentioned 6-membered ring analogs, the analogy is evident in that D in the exo position (**11**) makes a larger contribution as compared to its endo (**12**) counterpart. We also note that the authors[15] were able to measure the Cotton effects associated with the $\pi \rightarrow \pi^*$ transition at 195 nm; in both cases negative Cotton effects of almost identical amplitude ($[\theta] = -330$) were observed. Two further examples where the D substituent is in a $\beta$ relationship to the C=O grup have been reported by the Stanford group.[16] Through careful comparison of the Cotton effect



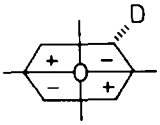
11



12

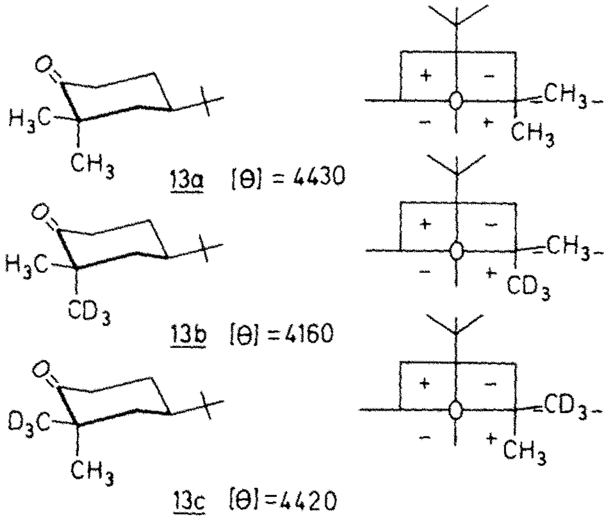


[Θ] = 101



[Θ] = 437

amplitudes of the structurally (rather than just isotopically) chiral molecules **13a**, **b** and **c** they noted that perdeuteration of the $\alpha$-axial Me group (**13b**) leads to a dissignate contribution ($[\theta] = -270$). On the other hand deuteration of the $\alpha$-equatorial Me group (**13c**) has, within experimental error, no effect on the Cotton effect amplitude. This latter observation is entirely reasonable considering that the $CD_3$ group is now located close to a nodal surface.

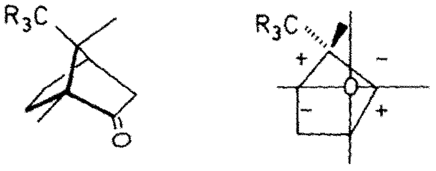


13a $[\theta] = 4430$

13b $[\theta] = 4160$

13c $[\theta] = 4420$

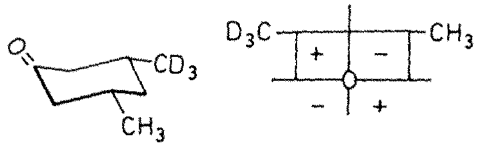
2.1.3 *$\gamma$-Deuterium substituted ketones.* In an early study Meyer and Lobo[17] reported that D(+)-(9,9,9-$^2H_3$) camphor (**14b**) exhibited a 3% smaller ORD Cotton effect amplitude compared to its undeuterated analog **14a**. Since the site of deuteration is located in a positive octant the authors concluded the D behaves as a dissignate perturber. On the average, therefore, each D atom makes a dissignate contribution of $[\theta] = -150$. However, as we have pointed out in Section 2.1, the experimental uncertainty associated with this value may be fairly large.



14a R = H , $[\theta] = 4950$

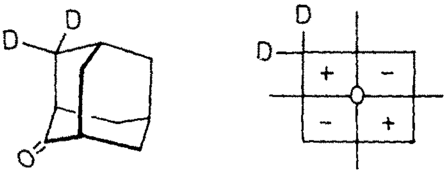
14b R = D , $[\theta] = 4490$

More recently, Pak and Djerassi[18] reported the CD spectrum of (3S,5R) (8,8,8-$^2H_3$)3,5-dimethylcyclohexanone (**15**), a molecule which predominantly exists in the chair confromation with both Me groups in the equatorial position. Here again, the observed negative Cotton effect supports the conclusion that D in the $\gamma$ position behaves as a dissignate perturber.



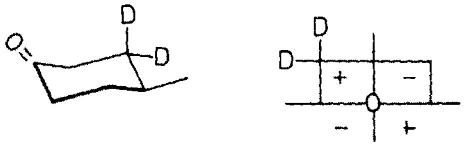
15 $[\theta] = -82$

2.1.4 *Additivity of deuterium octant contributions.* As pointed out in the introduction to Section 2, one of the basic assumptions of the octant rule is the proposition that partial octant contributions are additive. Three examples have been reported in the literature which provide a test as to the validity of this assumption for molecules containing more than one D. Numan and Wynberg[14] reported the CD spectrum of (1S) (4,4-$^2H_2$)adamantanone (**16**) and found its Cotton effect amplitude to be *ca* 20% smaller than the sum of the partial octant contributions obtained from the mono D substituted analogs **7** and **8**.



16 [Θ] = -375

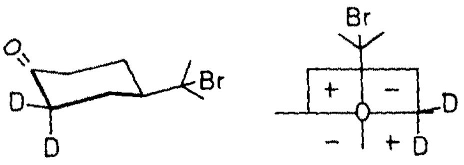
The Stanford group[19] measured the CD spectrum of (4S) (2,2-$^2H_2$)4-methylcyclohexanone (**17**) and noted that its Cotton effect amplitude is equal within 5% to the sum of the partial octant contributions as obtained from **9** and **10**. It should be noted that the conformation of **17** is not strictly rigid and that at



17 [Θ]=-276

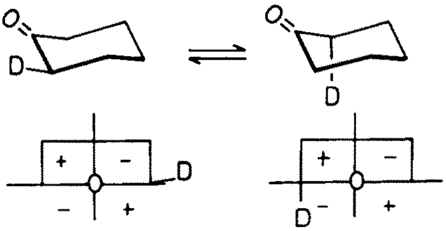
room temperature the conformation with the 4-Me group in the axial position participates to the extent of *ca* 15%. Therefore, measurements were carried out at 77 K where the conformational equilibrium is nearly completely shifted towards the conformation with the 4-Me group in the equatorial position.

Still another example is provided by the ORD spectrum[11] of (R) (2,2-$^2H_2$)4-(2-bromo-2-propyl)-cyclohexanone (**18**) whose Cotton effect amplitude equals within 8% the sum of the partial D contributions derived from **3** and **4**. All of these data lead to the conclusion that within the accuracy of measurements, the additivity rule is obeyed for poly-D substituted molecules.

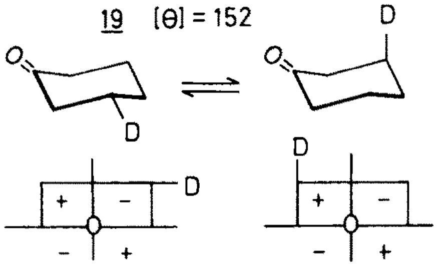


18 [Θ] = -305

2.1.5 *Conformationally mobile ketones.* Although we defer the discussion of the chiroptical properties of various conformationally mobile ketones to Section 3, two examples will be presented here which serve to confirm the results obtained with conformationally rigid systems. Djerassi *et al.*[10b,20] reported the CD spectra of (2R) (2-$^2H_1$) and (3S) (3-$^2H_1$)cyclohexanone (**19** and **20**). Both can be considered to exist in a dynamic conformational equilibrium between their two chair conformations with the D located in the equatorial and axial positions, respectively. Assuming that the equilibrium distribution between both chair conformations is unaffected by the deuterium substitution, the observed Cotton effect amplitudes should be the average of the contributions from each conformer. By taking the [θ] values obtained fo the conformationally rigid analogs **3**, **4**, **9** and **10** as reference values one arrives at estimates which ar



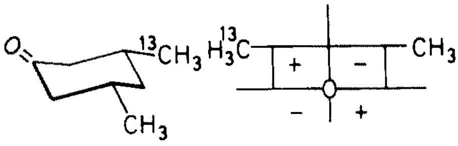
**19** $[\theta] = 152$



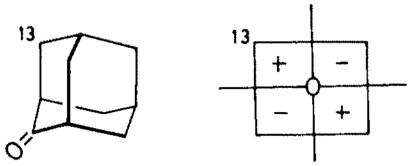
**20** $[\theta] = 143$

within 10–13% of the experimental values. In fact this line of argument has been used to establish the absolute configuration of **19** which was obtained enzymatically by Kergomard *et al.*[21] and by Benner and Rozell[22] prior to our unambiguous synthesis[10b] of **19**.

2.1.6 $^{13}C$ *and the octant rule.* Two conformationally rigid ketones have been reported whose chirality is solely due to the replacement of $^{13}C$ vs $^{12}C$. Pak and Djerassi[18] reported a negative Cotton effect for (3S,5R) (7-$^{13}C_1$)3,5-dimethylcyclohexanone (**21**) and a similar observation was made[23] with (1S) (4-$^{13}C_1$)adamantanone (**22**). Both molecules exhibit Cotton effects whose amplitudes are smaller by a factor



**21** $[\theta] = -13$



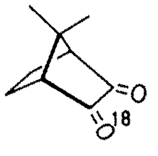
**22** $[\theta] = -17$

of ~10 compared to those which owe their chirality to D vs H substitution. These results confirm the intuitive assumption that the intensity of the Cotton effect is related to the relative mass difference. The negative Cotton effects recorded for both molecules indicate that $^{13}C$ must be considered as the weaker perturber in comparison to $^{12}C$. Thus, there appears to exist a direct analogy with the results obtained for the D substituted ketones. Although it would be premature to generalize these observations, we note that they are entirely consistent with the theoretical expectations summarized in Section 2.1.7. The CD spectrum of a molecule whose chirality is due to tritium vs hydrogen substitution would provide an ideal example on which to test this theory, i.e. one might predict that tritium behaves as a stronger dissignate perturber in comparison with D. The substantial experimental difficulties associated with the extraordinarily high radioactivity of such a substrate have so far precluded the synthesis of such a molecule.

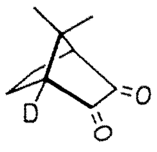
2.1.7 *Theoretical considerations.* It is not surprising that the experimentally obtained relationships between the location of the isotopic perturber with respect to the C=O group and the sign as well as amplitude of the asociated Cotton effects have been viewed with great interest by theoreticians. The chiroptical data obtained during the past 4 years provide a much more stringent basis than the earlier available sodium D line rotations on which to test the validity of any theory which attempts to describe the physical origin of the observed effects. In agreement with earlier theoretical interpretations made by Ficket,[24] Lightner and Bouman[15] argue that the ***equilibrium*** geometry of a molecule, which is chiral due to isotopic substitution, is achiral. However, when the anharmonicity of the vibrational potentials are taken into account, the ***average*** molecular geometry will be chiral. As a simplified assumption they have taken the average bond distance between C and D to be foreshortened by 0.02 Å vs the C–H bond length. The physical reality of this isotope effect on the average bond length due to anharmonicity had been earlier verified experimentally by Bartell *et al.*[25] who obtained bond length differences on the order of 0.004 Å upon substitution of H by D. Lightner and Bouman[15] used this concept to calculate the rotational strengths of ketones **3**, **4**, **7**, **8**, **9**, **10**, **11** and **12** by a computational method (CNDO/S) which they have previously shown[26] to yield reliable results for a series of Me substituted ketones. The calculated values were in surprisingly close agreement with the experimental ones, the only exceptions being those molecules in which the D substituent is in close proximity with respect to one of the sign-determining surfaces (e.g. **4**, **7** and **10**); this discrepancy is attributed to inaccuracies in the assumed molecular geometry. A somewhat different view was taken by Meyer *et al.*,[12] who assumed that the differences in electronegativity between H and D (D being assumed to be more electronegative) is the fundamental quantity which determines the Cotton effect sign and amplitude. Using this concept together with CNDO/2 calculations they also arrive at the conclusion that D should in general behave as a dissignate perturber.

### 2.2 *Diketones*

2.2.1 *The $\alpha$-dicarbonyl chromophore.* Isotopically labeled molecules containing the $\alpha$-dicarbonyl chromophore were the first compounds for which CD spectra have been reported in the literature. Kokke and Oosterhoff[27] synthesized (1R) (2-$^{18}$O$_1$) and (1R) (1-$^{2}$H$_1$)$\alpha$-fenchocamphochinone (**23** and **24**) for which they were able to measure the Cotton effects associated with the transitions at 480 and 300 nm. Whereas 24 exhibits Cotton effects of positive sign for both transitions, the CD spectrum of **23** is more complicated in that the vibrational components of the long wavelength transition display an alternating sign pattern.



23

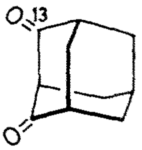


24

A theoretical interpretation of these spectral data has been attempted by Dezentje and Dekkers.[28] Starting with the basic assumption that the average molecular geometry gains chirality through the anharmonicity in the vibrational potential of the nuclei (see Section 2.1.7) and using CNDO/2 CI wave functions, their calculated rotational strengths are found to be in qualitative agreement with the experimental results. These calculations assume the $\alpha$-dicarbonyl chromophore to be planar. However, Kokke *et al.*[27b] have pointed out that even in such apparently rigid structures as **23** and **24**, some flexibility as to the dihedral angular relationship of both C=O groups may exist. If true, then the chromophore will assume inherent chirality, whereupon the sense of the twist could be preferentially affected by a conformational isotope effect. No low temperature CD measurements were carried out on either **23** or **24** which could have provided support for this assumption.

2.2.2 *The $\beta$-dicarbonyl chromophore.* The CD spectrum of the recently synthesized[23] (1S) (4-$^{13}$C$_2$)adamantane-2,4-dione (**25**) is characterized by three Cotton effects of alternating sign in the 240–340 nm wavelength region. The observation that the band intensities remain unchanged at 77 K was attributed to the presence of three distinct electronic transitions arising from the splitting of the $n \rightarrow \pi^*$

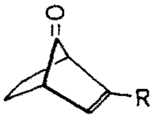
transition due to the interaction between both C=O groups.[29] It should also be pointed out that the observed Cotton effect amplitudes of $[\theta] = 300, -240$ and 110 are remarkably large for a molecule which owes its chirality solely to $^{13}$C vs $^{12}$C asymmetry (see Section 2.1.6).



25

### 2.3 *β,γ-Unsaturated ketones*

Lightner *et al.*,[30] reported the CD spectrum of (1R) (2-$^2$H$_1$)bicyclo[2.2.1]hept-2-en-7-one (**26a**), which exhibits two negative Cotton effects at 272 and 220 nm respectively. The band at longer wavelength corresponds to the standard $n \rightarrow \pi^*$ carbonyl transition. The presence of a second transition around 225 nm had previously been proposed in the literature based on the appearance of a weak shoulder in the absorption spectrum of 7-norbornenone (**26b**). The CD spectrum of the deuterated analog such as **26a** provided the first unambiguous proof for the existence of such a band. Based on (STO–4G) SCF calculations the authors[30] show that this transition contains substantial charge transfer ($\pi_{C=C} \rightarrow \pi^*_{C=O}$) character.

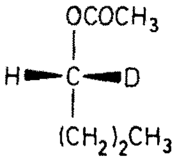


26a R=D

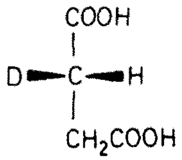
26b R=H

### 2.4 *Carboxylic acids and esters*

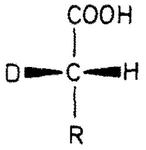
D substituted carboxylic acid derivatives were the first compounds for which ORD measurements were performed within the absorption region of the chromophoric absorption band. Verbit[31] was able to measure the positive ORD peak at 225 nm for the transition at 210 nm of (R) (1-$^2$H$_1$)1-butylacetate (**27**) and Englard *et al.*,[32] reported the partial ORD spectra for both enantiomers of (2-$^2$H$_1$)succinic acid, the (2S) enantiomer (**28**) exhibiting a positive Cotton effect. More recently, Craig *et al.*,[33] reported the CD spectrum of **28** by carrying out the measurements down to 200 nm and verified that this molecule exhibits a positive Cotton effect at 210 nm ($[\theta] = 193$). Positive Cotton effects of similar amplitude were also observed for three related carboxylic acids, (S) (2-$^2$H$_1$)propioinic acid (**29**), (R) (2-$^2$H$_1$)glycine (**30**) and (R) (2-$^2$H$_1$)glycolic acid (**31**). An attempt has been made[33] to correlate the observed Cotton effect sign



27



28

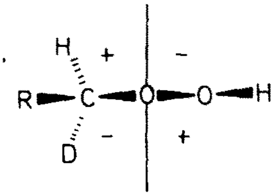


29 R = $CH_3$

30 R = $NH_2$

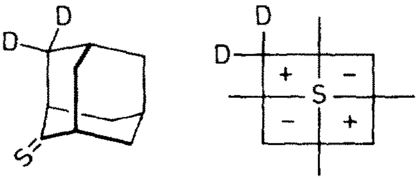
31 R = OH

of **28–31** with the molecular structure and conformation. From the three possible conformations resulting from rotation around the CO–C bond, the one with the R-group syn-periplanar with the C=O group has been shown to be energetically preferred. As shown below, the octant projection of this conformation places the D substituent into a negative sector. From the observed positive Cotton effect sign, it is again concluded that D makes a dissignate contribution.



## 2.5 *Thioketones*

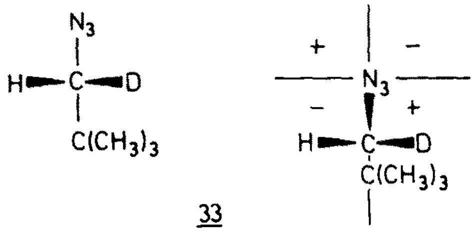
Thioketones exhibit a weak absorption band at *ca* 510 nm which has been assigned[34] to an $n \rightarrow \pi^*$ transition. However, spectroscopic evidence has been presented[35] which reveals the presence of a further transition (of singlet–triplet character) in the same spectral region. From the few examples investigated so far[36] it has been concluded that the ketone octant rule can be applied in unmodified form to this chromophore. Thus, Numan and Wynberg[37] reported that the CD spectrum of 1$\underset{\sim}{S}$(4,4-$^2H_2$)adamantanethione (**32**) exhibits a negative Cotton effect of exceptionally large amplitude ($[\theta] = -1500$). From the octant diagram representation it is seen that both D atoms are located in a positive octant and thus contribute as dissignate perturbers, in agreement with the results for the C=O analog **16**. In spite of the instability of many thioketones, the large Cotton effect amplitudes make these molecules particularly attractive substrates for further investigations.



32

## 2.6 *Azides*

Azides exhibit a weak absorption band at 290 nm which is assumed to be of $n \rightarrow \pi^*$ character. A sector rule quite similar to the octant rule for ketones has been proposed for this chromophore.[38] Mosher *et al.*,[39] have reported a positive CD Cotton effect ($[\theta] = 30$) for ($\underset{\sim}{R}$) (1-$^2H_1$)neopentylazide (**33**). The octant diagram representation of the assumed preferred conformation places the D substituent in a positive sector, which would make D a consignate perturber contrary to the observations made for the C=O chromophore. CD measurements carried out at 77 K resulted in a 25% intensity increase, indicating that conformations, other than the ones considered, participate and that their distribution is affected by a temperature-dependent conformational isotope effect.

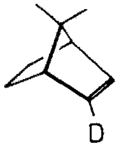


33

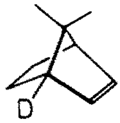
## 2.7 *Olefins*

The CD spectra of several conformationally rigid olefins, chiral by virtue of D substitution, have been investigated by Paquette and Mason[40] who were able to measure the Cotton effects associated with the

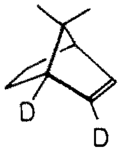
34 $[\Theta] = -660$



35 $[\Theta] = 460$



36 $[\Theta] = 500$

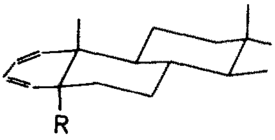


37 $[\Theta] = 760$

$\pi \rightarrow \pi^*$ transition at *ca* 200 nm for compounds **34–37**. The authors distinguish between two types of D perturbation—those which lead to Cotton effects of the same sign as introduced by a Me group replacing the D and those leading to the opposite effect. Molecules **34** and **35** with the D bound directly to the double bond were found to belong to the first class whereas **36** with D at the bridge head position belonged to the second one.

## 2.8 *Dienes*

The only example of an isotope contributing to the Cotton effect of a diene chromophore has been reported by Burgstahler *et al.*[41] Through careful comparison of the CD spectra of cholesta-1,3-diene (**38a**) and (5-$^{2}H_{1}$)cholesta-1,3-diene (**38b**) the authors observed that the Cotton effect amplitude for the $\pi \rightarrow \pi^*$ transition at 262 nm is smaller by 9% for the D substituted molecule. Since it appears very unlikely that D substitution has any effect on the twist of the diene chromophore, this observation lends proof to the proposition that extra-chromophoric perturbations can make significant contributions towards the Cotton effect amplitudes of the inherently chiral diene chromophore, a subject which has been controversial in the literature for a long time.[42]

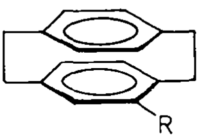


38a R = H $[\Theta] = -7820$

38b R = D $[\Theta] = -7190$

## 2.9 *The benzene chromophore*

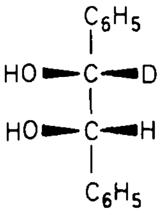
CD spectra of aromatic compounds which owe their chirality to isotopic substitution have been investigated by several groups. Weigang *et al.*[43] measured the CD spectrum of (S) (4-$^{2}H_{1}$)paracyclophane (**39a**), reporting a couplet for the $^{1}L_{b}$ band at 300 nm ($[\theta] = -70$ and $+12$) and a negative Cotton effect for the $^{1}L_{a}$ band at 255 nm ($[\theta] = -630$). From the absence of the $^{1}L_{b}$ O–O component in the vapor phase spectrum of **39a**, they conclude that the D-induced optical activity is predominantly of vibronic origin. The Me substituted analog **39b** exhibits a 100 times more intense Cotton effect amplitude in the $^{1}L_{b}$ region, which suggests that the CD intensity of **39b** arises primarily from electronic perturbation. Lowe *et al.*[44] reported the CD spectra of (1R,2S) (1-$^{2}H_{1}$) and (1R,2S) (1-$^{18}O_{1}$)1,2-dihydroxy-1,2-diphenylethane



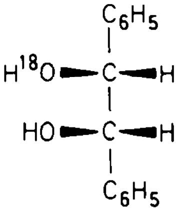
39a R = D

39b R = $CH_3$

(**40** and **41**). Both molecules exhibit negative Cotton effects for the $^1L_b$ band at 260 nm. The vibrational fine structure is particularly well resolved in the CD spectrum of **40**, which displays a different intensity distribution as compared to its absorption spectrum. Assuming that D and $^{18}O$ are weaker perturbers compared to their lighter isotopes, and applying the sector rule for the phenyl chromophore, the authors make predictions abtout the time averaged preferred conformations of **40** and

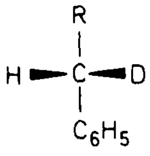


40



41

**41.** A series of $\alpha$-deuterium substituted phenylethanes were recently reported[45] and, in all examples, a positive Cotton effect was observed for the $^1L_b$ band. Earlier NMR and Raman spectroscopic studies[46]



42 R = $CH_3$

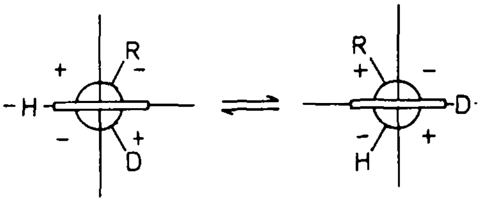
43 R = $CD_2H$

44 R = $n$-$C_3H_7$

45 R = $CH_2OH$

46 R = $CH_2Br$

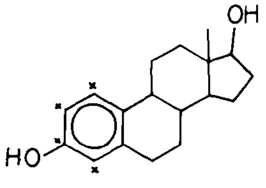
pointed to the existence in ethylbenzene of a conformation where the $\alpha$-C–H bond is nearly eclipsed with the plane of the benzene ring. Thus, for compounds **42–46** an equilibrium between conformation A and B can be assumed whose sector diagrams are shown below. The Cotton effect amplitudes for A and



A B

B are determined by the position of the substituent R (negative for A and positive for B). The observed positive Cotton effect amplitudes can then be attributed to the presence of a conformational isotope effect which biases the equilibrium towards that conformation in which the D is in the eclipsed position with respect to the phenyl ring. However, no variable temperature CD measurements were performed which could provide an experimental verification for the correctness of the interpretation.

Wynberg and Drayer[47] have measured the CD spectrum of (1,2,3,4-$^{13}C_4$) estradiol (**47**) (the labeled positions are indicated with * in the structure) and report a substantial ($\Delta[\theta] \sim 2000$, at 240 nm) difference in the CD amplitudes in comparison to the unlabeled molecule. Provided that these observations are not due to experimental error—easily possible in such comparative measurements—the magnitude of this $^{13}C$ isotope effect would be very unusual.



47

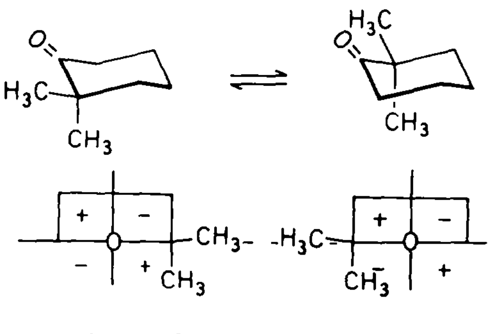
## 3. CONFORMATIONAL ISOTOPE EFFECTS

Because of the intimate relationship between molecular conformation and the sign and amplitude of Cotton effects, CD spectroscopy provides an ideal tool for the investigation of conformational equilibria; measurements at various temperatures yield quantitative values of conformational energy differences.[48] Therefore, the interesting question arose whether CD could be utilized to determine the effect of isotopic substitution on the composition of conformational equilibria. As has been pointed out in previous sections, several authors have considered the possibility that Cotton effect amplitudes of conformationally flexible molecules may to some degree be determined by the presence of conformational isotope effects. Unambiguous proof for the existence of such an isotope effect has so far been established only with cyclic ketones.

### 3.1 *Cyclohexanones*

In Section 2.1.5 we mentioned two conformationally flexible cyclohexanones, **19** and **20**, in which deuterium is substituted in the $\alpha$ and $\beta$ positions respectively. Both molecules exist predominantly in chair conformations where the D substituent assumes either an equatorial or an axial orientation. These two positions are quite different as far as non-bonded interactions are concerned and one might expect, therefore, that the degeneracy of the equilibrium is perturbed due to the introduction of D. However, careful CD measurements revealed[10b,20] that, within experimental error, the Cotton effect amplitudes of **19** and **20** remain unchanged over a temperature range of *ca* 220 K. This negative result to detect the presence of conformational isotope effects in these two molecular systems is not very surprising. In the first place one might estimate that, since the energy difference between the two participating confirmations is probably on the order of a few cal/mol, the temperature-induced equilibrium shift will be equally small—perhaps less than 1% over the accessible temperature range. Second, and more important, if the Cotton effect amplitudes of the participating conformers are themselves small numbers, as is the case for the ketones **19** and **20**, than any variation of the CD amplitude with temperature will be below the limit of experimental detectability. Therefore, it was clear that only in those situations where the rotational strengths of the participating conformers are large numbers of opposite sign could one hope to detect the presence of such small energy differences as introduced by isotopic substitution.

A molecular system that exhibits such properties is 2,2-dimethylcyclohexanone which exists in a degenerate conformational equilibrium between two chair conformations. The rotational strengths are now large numbers of opposite signs predominantly determined by the contributions of the $\alpha$-axial Me group.



With the molar ellipticity of **13a** (Section 2.2.2) taken as reference one arrives at an estimate for $[\theta]_A - [\theta]_B \approx 8900$. Consequently, the introduction of the α-gem dimethyl group increases the magnitude of Cotton effect variation with change of temperature by a factor of *ca* 30 as compared to the unsubstituted cyclohexanones **19** and **20**.

With this concept in mind, the Stanford group[49-51] synthesized three α-dimethylcyclohexanones asymmetrically substituted with D in the β, γ and β′ positions respectively (**48**, **49**, **50**) and investigated the temperature-dependent behavior of their CD spectra. The results of these studies are given in Fig. 1 from which it can be seen that substantial variations of the Cotton effect amplitudes with temperature are observed.

A common complicating factor in the interpretation of variable temperature CD spectra is the presence of temperature-dependent solvent–solute interactions which can also give rise to variations in the Cotton effect amplitudes.[52] Furthermore, the interpretation of the data given in Fig. 1 depends crucially on the assumption that the conformational equilibria are correctly described by the presence of only two (chair) conformations. If other forms (e.g. twist or boat conformations) participate to a non-negligible extent at room temperature then they could be responsible for temperature-dependent amplitude changes. Several pieces of evidence were presented by the Stanford group which make it unlikely that the observed intensity changes are associated with either one of the above cited alternative possibilities.

First, it was shown that the intensity changes were independent of solvent polarity. Second, the conformationally rigid, deuterium substituted molecules **3**, **4**, **9** and **10** discussed in Sections 2.1.1 and 2.1.2 exhibited no temperature-dependent CD spectra. Finally, a structurally similar molecule with the dimethyl group located in the 4-position (**51**) was synthesized and its CD properties determined.[51]

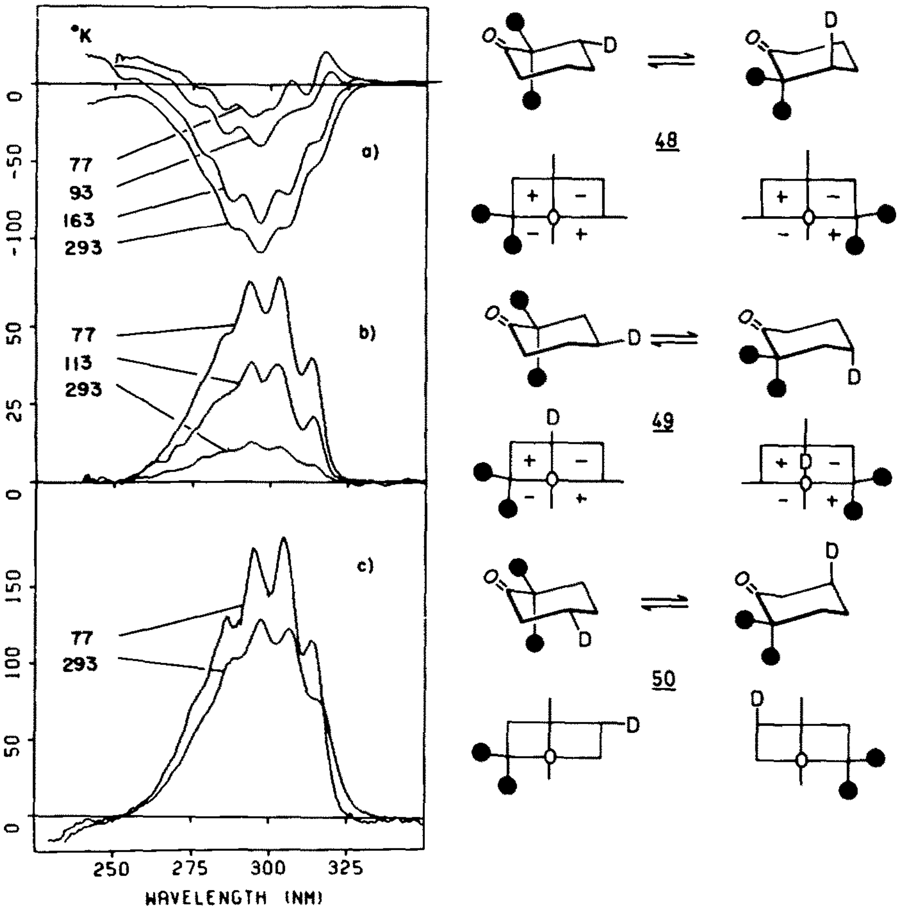
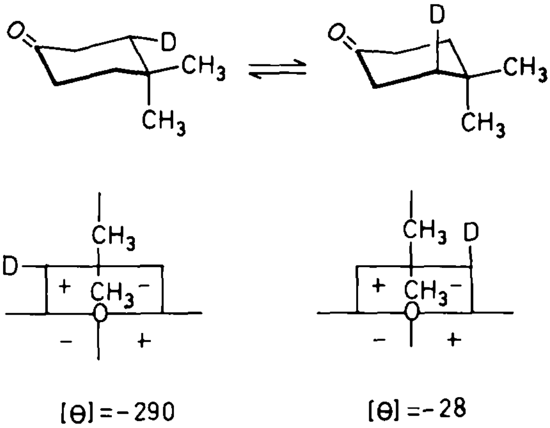


Fig. 1. Variable temperature circular dichroism spectra of (a) (R) (3-$^3H_1$)2,2-dimethylcyclohexanone (**48**); (b) (S) (4-$^2H_1$)2,2-dimethylcyclohexanone (**49**) and (c) (S) (5-$^2H_1$)2,2-dimethylcyclohexanone (**50**). Methyl groups are symbolyzed as ●.

Since both Me groups are now located on a nodal plane the rotational strengths of the participating conformers are determined by the D octant contributions alone and, therefore, are small numbers. As expected the CD spectrum of **51** ($[\theta] = -120$) exhibited no temperature dependence within the accuracy of measurement. Therefore, from the experimental data provided in Fig. 1 we feel justified in concluding that in all three examples the conformational equilibrium is shifted towards the conformation possessing a positive rotational strength, i.e. the population of the conformation with the deuterium in the axial position increases with lowering the temperature.



51

Given the rotational strengths of each conformer $[\theta]_A$ and $[\theta]_B$, estimated from the conformationally fixed reference compounds (e.g. **3**, **4**, **9**, **10** and **13a**), the equilibrium constant K can be calculated from the observed rotational strength $[\theta]_{obs}$ at each temperature.

$$C_A = ([\theta]_{obs} - [\theta]_B)/([\theta]_A - [\theta]_B); \quad K = c_a/(1 - c_a).$$

A linear fit to the data points in an Arrhenius diagram, shown in Fig. 2, permits a calculation of the enthalpy difference ΔH°.

The basic conclusion drawn from these experiments—D occupies preferentially the position of larger strain—is entirely consistent with the general view that D is of "smaller size" as inferred from kinetic studies, a property which is most likely related to its smaller vibrational amplitude.[53] However, difficulties arise in the quantitative interpretation of the energy relationships for compounds **48**, **49** and

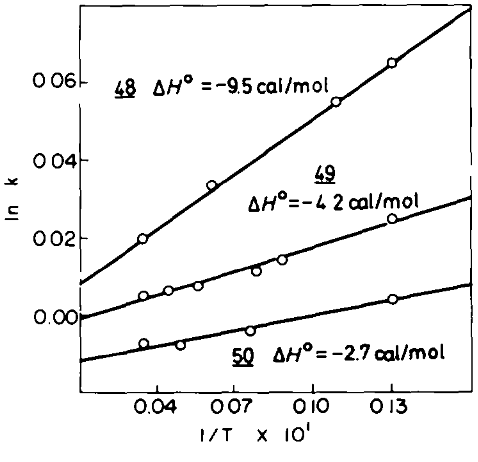
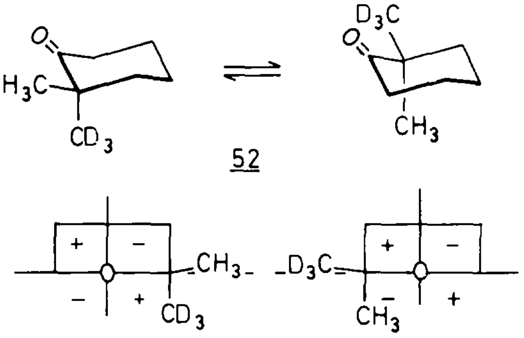


Fig. 2. Arrhenius plot for (R) (3-$^2H_1$)2,2-dimethylcyclohexanone (**48**), (S) (4-$^2H_1$)2,2-dimethylcyclohexanone (**49**) and (S) (5-$^2H_1$)2,2-dimethylcyclohexanone (**50**).

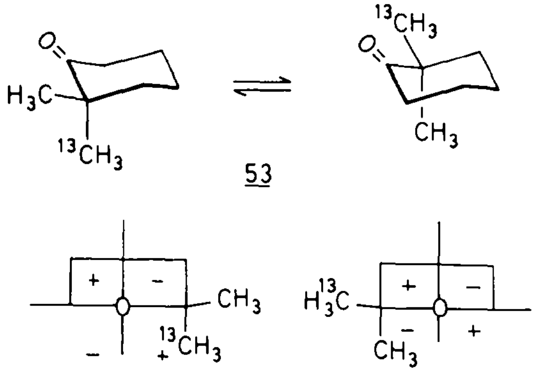
**50**. From simple model considerations one might expect the largest value to be observed for D located in the 4-position (**49**) (two 1-3 diaxial interactions) and smaller values of about the same magnitude for the 3 and 5 positions (one 1-3 diaxial interaction). Experimentally, it was shown that the cyclohexanone **47** with D in the 3 position possesses the largest (9.5 cal/mol), and ketone **50** with D in the 5 position the smallest (2.7 cal/mol) energy difference. Attempts to explain this discrepancy by assuming that the molecular geometry is somewhat distorted from the symmetrical chair form and using force field calculations which incorporate smaller non-bonded interactions for D were not entirely successful.[50]

In another study the Stanford group[16] investigated the conformational equilibria of **52** and **53** and surprisingly found that the equilibria are shifted towards the conformer with the isotopically labeled Me group in the equatorial position, i.e. the substituent of smaller size now preferentially occupies the position of smaller non-bonded strain.



52

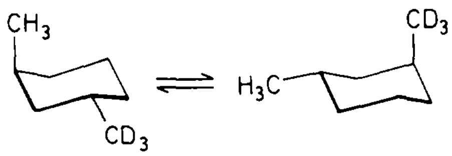
$\Delta H^\circ = -3.4$ cal/mol



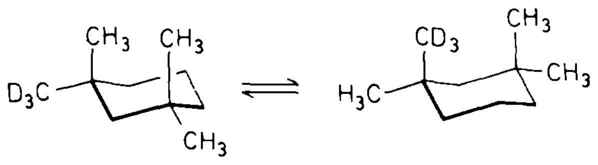
53

$\Delta H^\circ = -1.5$ cal/mol

This observation is particularly unusual considering the results of two recent NMR studies of similar equilibria,[54,55] which showed that the conformations with the $CD_3$ group oriented axially are energetically preferred.



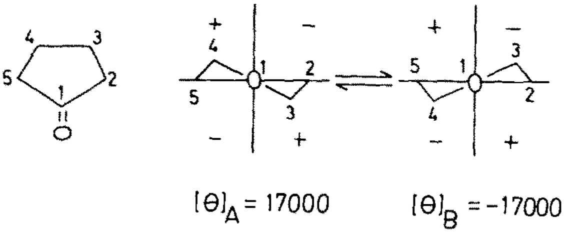
$\Delta H^\circ = -11$ cal/mol



$\Delta H^\circ = -24$ cal/mol

### 3.2 *Cyclopentanones*

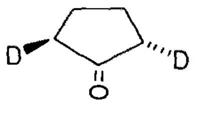
Another molecular system suitable for the detection of conformational isotope effects through variable temperature CD measurements is cyclopentanone. This ketone exists almost exclusively in a conformational equilibrium between the two possible twist conformations.[56,57] The alternative envelope conformation is, by estimates obtained from force field calculations,[58] 3.22 kcal/mol higher in energy.



As can be seen from the octant projections, in contrast to the chair conformation of cyclohexanone, no mutual cancellation of the contributions from the atoms comprising the ring system takes place. In fact such twisted structures can exhibit Cotton effect amplitudes of extraordinary amplitude.[59,60] The Stanford group[61,62] has synthesized a series of chiral cyclopentanones, substituted at various ring positions with D; these compounds, together with the octant projections of their respective conformations and their CD spectra at various temperatures, are given in Fig. 3.

The three molecules substituted in the $\beta$ and $\beta\beta'$ positions (**54**, **55** and **56**) exhibit the expected behavior based on the results obtained in the cyclohexanone analogs **48**, **49** and **50**, i.e. the conformations with the D in position of larger non-bonded strain (quasi-axial) are observed to be of lower energy as compared to those with the D in the quasi-equatorial position. Using the estimates for the rotational strength of cyclopentanone in its twist conformation provided by Kirk,[60] conformational energy differences of −1.11, −4.04 and −6.15 cal/mol were calculated for **54**, **55** and **56** respectively.

Although the direction of the equilibrium shift can again be qualitatively understood through the concept of " smaller size" for the heavier isotope, the relative magnitude of the obtained values is somewhat surprising. One would have expected that the introduction of a second D in **55** would simply result in a doubling of the energy difference as compared to **54** and that additional perdeuteration of the $\alpha$-positions in **56** would not contribute to any further stabilization of the conformer with the D in the quasi-axial position. Experimentally, however,[62] the energy differences are found to be in a 1:4:6 relationship. While these discrepancies point to deficiencies in the simple concept of steric size differences, the results obtained for (R) (2-$^{2}H_{1}$)cyclopentanone (**57**)[63] are in plain contradiction with this model. As evident from the temperature behavior of its CD spectrum shown in Fig. 3(d) and inspection of the octant diagram representation of its respective conformations, the conformation with the D substituent in the quasi-equatorial position is found to increase in population with decreasing temperature, and an energy difference of 10 cal/mol was calculated. This comparatively large value indicates that even at room temperature the contributions towards the observed rotational strength are largely determined by the conformational isotope effect rather than the differences of the partial D octant contributions in the quasi-equatorial and quasi-axial positions, respectively. Although, as we have pointed out previously, values for partial octant contributions cannot be obtained from the CD spectra of conformationally mobile systems, it is reasonable to assume that, as in the cyclohexanone series, an $\alpha$-axial D substituent makes a dissignate contribution larger in amplitude compared to an $\alpha$-quasi equatorial D substituent. Based on this assumption, and neglecting contributions from a conformational isotope effect, a positive Cotton effect would have been predicted for **57**. In fact this discrepancy has led to some difficulties in the assignment of the absolute configuration of this molecule and its related di-D substituted analog **58**. (2,5-$^{2}H_{2}$)Cyclopentanone (**58**) has been obtained by Hine *et al.*[64] through D exchange of (2,2,5,5-$^{2}H_{4}$)cyclopentanone using a chiral base as catalyst. The product exhibited a positive



58

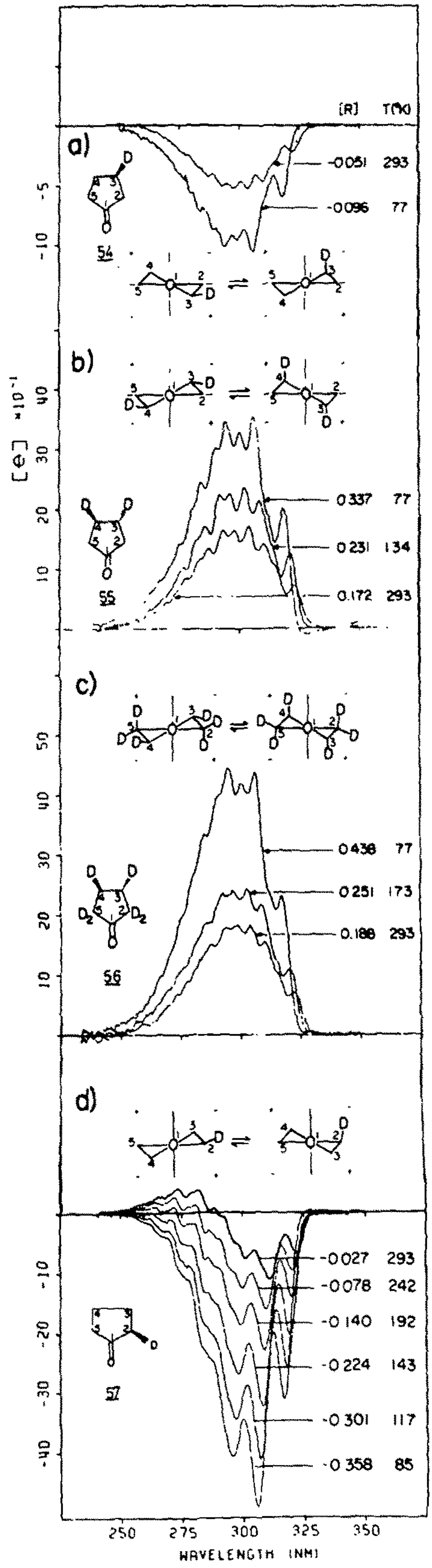


Fig. 3. Variable temperature circular dichroism spectra of (a) (R) $(3\text{-}^{2}\mathrm{H}_{1})$cyclopentanone (54); (b) (3S,4R) $(3,4\text{-}^{2}\mathrm{H}_{2})$cyclopentanone (55); (c) (3S,4R) $(2,2,3,4,5,5\text{-}^{2}\mathrm{H}_{6})$cyclopentanone (56) and (d) (R) $(2\text{-}^{2}\mathrm{H}_{1})$cyclopentanone (57).

Cotton effect which would indicate that the molecule possesses the 2R,5R configuration, whereas considerations of the transition state geometry led the authors to propose the 2S,5S configuration. (2-$^{2}H_{1}$)Cyclopentanone (**57**) was first synthesized by Kergomard *et al.*[21] through enzymatic reduction of (2-$^{2}H_{1}$)2-cyclopentenone, the product exhibiting a negative Cotton effect. By comparison with the stereochemistry of the reaction product of the 6-membered analog, the French authors assigned the R configuration to **57**. The subsequent synthesis of **57** by the Stanford group[63] via a synthetic route which established its absolute configuration unambiguously, and their interpretation that the Cotton effect sign is predominantly determined by the presence of a conformational isotope effect, has served to clarify this apparent dichotomy.

The question still remains to be answered as to which forces are responsible for the selective stabilization of the conformation with the $\alpha$-D substituent in the quasi-equatorial position. That, just as in cyclohexanone, the $\alpha$-quasi-axial position is of larger non-bonded strain is clearly demonstrated by comparison with 2-methylcyclopentanone which exists even at room temperature predominantly in a conformation with the Me group in the quasi-equatorial position.[63] Evidently the dihedral angular relationship between the vicinal C=O and C–H(D) bonds seems to be a responsible factor and a syn-coplanar conformation with the C–D bond appears to be energetically more favorable.

In conclusion, the investigation of conformationally mobile D substituted molecules through variable temperature CD measurements has led to the quantitative determination of very subtle conformational isotope effects. Whereas in a number of cases the observed equilibrium shift can be described, at least qualitatively, by assuming that the sum of the non-bonded interactions is smaller for the heavier isotope, three examples (**52**, **53**, **57**) were discovered where this simple model leads to contradiction with the experimental results.

One may, therefore, look forward to further investigations on similar systems and also to theoretical studies which hopefully will provide a better understanding of the underlying factors which determine conformational isotope effects.

## 4. FUTURE DEVELOPMENTS

As evident from the number of molecules cited in this article, the prediction made by Verbit[3] in his 1970 review entitled "Optical activity of D Substituted Compounds", that "...more use will be made of the techniques of ORD and CD to establish correlations for the rapid determination of absolute configurations of D compounds..." has certainly been fulfilled. Undoubtedly these investigations will continue and be extended to other chromophores including inorganic molecules which have not been studied so far.

An area which probably holds the greatest promise for future research is the investigation of vibrational circular dichroism (VCD)[65] and Raman optical activity (ROA).[66] The VCD[67] and ROA[68] spectra of several molecules which owe their chirality to isotopic substitution have been reported recently and theoretical calculations of the VCD band intensities for (R) (3-$^{2}H_{1}$)cyclohexanone (**20**) and (1S) (4-$^{13}C_{1}$)adamantanone (**22**) have been carried out by Moscowitz *et al.*[69] A further recent article by Hug *et al.*[70] proposes the existence of sum rules in ROA of isotopically chiral molecules.

*Acknowledgements*—This work has been supported by a grant (No. CHE 78-27413) from the National Science Foundation. The bulk of the work at Stanford was made possible through the extensive and sometimes quite complicated syntheses of ketones performed by many collaborators, whose names are cited in the bibliography. We are also greatful to Ruth Records for technical assistance in measuring numerous CD spectra.

## REFERENCES

[1a] H. C. Urey, F. Brickwedde and G. M. Murphy, *Phys. Rev.* **39**, 164 (1932); [b] E. W. Washburn and H. C. Urey, *Proc. Natl. Acad. Sci. U.S.* **18**, 496 (1932).
[2] E. L. Eliel, *J. Am. Chem. Soc.* **71**, 3970 (1949).
[3] L. Verbit, *Progr. Phys. Org. Chem.* **7**, 51 (1970).
[4] C. Djerassi and B. Tursch, *J. Am. Chem. Soc.* **83**, 4609 (1961).
[5] C. Djerassi, *Optical Rotatory Dispersion.* McGraw-Hill, New York (1960); L. Velluz, M. Legrand and M. Grosjean, *Optical Circular Dichroism.* Verlag Chemie, Weinheim and Academic Press, New York (1965).
[6] W. Moffitt, R. B. Woodward, A. Moscowitz, K. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961).
[7] For the various theoretical treatments and modifications which the octant rule has received see the recent review article by A. E. Hansen and T. D. Bouman, *Adv. Chem. Phys.* **44**, 545 (1980).
[8] For reviews see: [a] D. N. Kirk and W. Klyne, *J. Chem. Soc.* Perkin I, 1076 (1974) and [b] H. Ripperger, *Z. Chem.* **17**, 250 (1977)
[9] W. Klyne and D. N. Kirk, *Tetrahedron Letters* 1483 (1973).

[10a] P. Sundararaman and C. Djerassi, *Ibid.* 2457, (1978) Errata. *Ibid.* 4120, (1979); [b] P. Sundararaman, G. Barth and C. Djerassi, *J. Org. Chem.* **45**, 5231 (1980).

[11] S. G. Levine and B. Gopalakrishnan, *Tetrahedron Letters* 699 (1979).

[12] W. L. Meyer, A. P. Lobo, E. E. Ernstbrunner, M. R. Giddings and J. Hudec, *Ibid.* 1771 (1978).

[13] D. A. Lightner, T. C. Chang and J. Horwitz, *Ibid.* 3019 (1977) Errata. *Ibid.* 696 (1978).

[14] H. Numan and H. Wynberg, *J. Org. Chem.* **43**, 2232 (1978).

[15] D. A. Lightner, J. K. Gawronski and T. D. Bouman, *J. Am. Chem. Soc.* **102**, 1983 (1980).

[16] S. F. Lee, M. Edgar, C. S. Pak, G. Barth and C. Djerassi, *Ibid.* 102, 4784 (1980).

[17] W. L. Meyer and A. P. Lobo, *Ibid.* **88**, 3181 (1966).

[18] C. S. Pak and C. Djerassi, *Tetrahedron Letters* 4377 (1978). The first example of a molecule which owes its chirality to $^{13}$C vs $^{12}$C asymmetry has been reported by K. K. Andersen, S. Colonna and C. J. M. Stirling, *J. Chem. Soc.* Chem. Comm. 645 (1973); however, only the plain ORD curve and no Cotton effects were reported.

[19] M. T. Edgar, G. Barth and C. Djerassi, *J. Org. Chem.* **45**, 2680 (1980).

[20] C. Djerassi, C. L. van Antwerp and P. Sundararaman, *Tetrahedron Letters* 535 (1978).

[21] G. Dauphin, J. C. Gramain, A. Kergomard, M. F. Renard and H. Veschambre, *Ibid.* 4275 (1980).

[22] S. A. Benner and J. D. Rozzell, Jr., *J. Am. Chem. Soc.* **103**, 993 (1981).

[23] Y. L. Sing, H. Numan, H. Wynberg and C. Djerassi, *Ibid.* **101**, 5155 (1979) Errata. *Ibid.* **101**, 7439 (1979).

[24] W. Fickett, *Ibid.* **74**, 4204 (1952).

[25] L. S. Bartell, K. Kuchitsu and R. J. DeNeui, *J. Chem. Phys.* **35**, 1211 (1961).

[26] T. D. Bouman and D. A. Lightner, *J. Am. Chem. Soc.* **98**, 3145 (1976).

[27a] W. C. M. C. Kokke and L. J. Oosterhoff, *Ibid.* **94**, 7583 (1972); [b] W. C. M. C. Kokke and L. J. Oosterhoff, *Ibid.* **95**, 7159 (1973); [c] W. C. M. C. Kokke, *J. Org. Chem.* **38**, 2989 (1973); [d] W. C. M. C. Kokke and F. A. Varkevisser, *Ibid.* **39**, 1653 (1974).

[28] R. F. R. Dezentje and H. P. J. M. Dekkers, *Chem. Phys.* **18**, 11 (1976).

[29] R. Spafford, J. Baiardo, J. Wrobel and M. Vala, *J. Am. Chem. Soc.* **98**, 5217 (1976).

[30] D. A. Lightner, J. K. Gawronski, A. E. Hansen and T. D. Bouman, *Ibid.* **103**, 4291 (1981).

[31] L. Verbit, *Ibid.* **89**, 167 (1967).

[32] S. Englard, J. S. Britten and I. Listowsky, *J. Biol. Chem.* **242**, 2255 (1967).

[33] B. Ringdahl, J. C. Craig, R. Keck and J. Retev, *Tetrahedron Letters* 3965 (1980).

[34a] J. W. Sidman, *Chem. Rev.* **58**, 689 (1958); [b] K. J. Rosengren, *Acta Chim. Scand.* **16**, 2284 (1962).

[35] J. P. Engelbrecht, G. D. Anderson, R. E. Linder, G. Barth, E. Bunnenberg, C. Djerassi, L. Seamans and A. Moscowitz, *Spectrochimica Acta* **31A**, 507 (1975) and refs. cited.

[36a] C. Djerassi and D. Herbst, *J. Org. Chem.* **26**, 4675 (1961); [b] R. E. Ballard and S. F. Mason, *J. Chem. Soc.* 1624 (1963); [c] C. A. Emeis, Diss., Leiden (1968).

[37] H. Numan, F. Meuwese and H. Wynberg, *Tetrahedron Letters* 4857 (1978).

[38] C. Djerassi, A. Moscowitz, K. Ponsold and G. Steiner, *J. Am. Chem. Soc.* **89**, 347 (1967).

[39] P. H. Anderson, B. Stephenson and H. S. Mosher, *Ibid.* **96**, 3171 (1974).

[40] L. A. Paquette, C. W. Doecke, F. R. Kearney, A. F. Drake and S. F. Mason, *Ibid.* **102**, 7228 (1980).

[41] A. W. Burgstahler and M. E. Sanders, *Tetrahedron Letters* 2509 (1979).

[42a] A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.* **92**, 7601 (1970); [b] U. Weiss, H. Ziffer and E. Charney, *Tetrahedron* **21**, 3105 (1965).

[43] P. H. Hoffman, E. C. Ong, O. E. Weigang and M. J. Nugent, *J. Am. Chem. Soc.* **96**, 2620 (1974).

[44] P. M. Cullis, G. Lowe and P. M. Bayley, *J. Chem. Soc.* Chem. Comm. 850 (1978).

[45] B. Ringdahl, J. C. Craig and H. S. Mosher, *Tetrahedron* **37**, 859 (1981).

[46a] R. J. Ouellette, B. K. Sinha, J. Stolfo, C. Levin and S. Williams, *J. Am. Chem. Soc.* **92**, 7145 (1970); [b] L. Verdonck and G. P. van Der Kelen, *Spectrochim. Acta A.* **28**, 51 (1972).

[47] G. Zomer, H. Wynberg and N. M. Drayer, *J. Am. Chem. Soc.* submitted for publication.

[48a] A. Moscowitz, K. Wellman and C. Djerassi, *Ibid.* **85**, 3515 (1963); [b] K. M. Wellman, W. S. Briggs and C. Djerassi, *ibid.* **87**, 73 (1965); [c] K. M. Wellman and C. Djerassi, *Ibid.* **87**, 60 (1965); [d] D. A. Lightner and B. V. Crist, *Appl. Spectroscopy* **33**, 307 (1979).

[49] S. F. Lee, G. Barth, K. Kieslich and C. Djerassi, *J. Am. Chem. Soc.* **100**, 3965 (1978).

[50] S. F. Lee, G. Barth and C. Djerassi, *Ibid.* **100**, 8010 (1978).

[51] S. F. Lee, G. Barth and C. Djerassi, *Ibid.* **103**, 295 (1981).

[52] A. Rassat and A. Moscowitz, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, pp. 314 and 329. Heyden, London (1967).

[53] For a review on this subject, see R. E. Carter and L. Melander, *Adv. Phys. Org. Chem.* **10**, 1 (1973).

[54] K. W. Baldry and M. J. T. Robinson, *Tetrahedron* **33**, 1663 (1977).

[55] F. A. L. Anet, V. J. Basus, A. P. W. Hewett and M. Saunders, *J. Am. Chem. Soc.* **102**, 3945 (1980).

[56] H. Kim and W. D. Gwinn, *J. Chem. Phys.* **51**, 1815 (1969).

[57] R. L. Lipnick, *J. Mol. Structure* **21**, 411 (1974).

[58] N. L. Allinger, M. T. Tribble and M. A. Miller, *Tetrahedron* **28**, 1173 (1972).

[59] C. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci.* **48**, 1093 (1962).

[60] D. N. Kirk, *J. Chem. Soc.* Perkin I, 2171 (1976).

[61] J. W. Simek, D. L. Mattern and C. Djerassi, *Tetrahedron Letters* 3671 (1975).

[62] L. Y. Sing, M. Lindley, P. Sundararaman, G. Barth and C. Djerassi, *Tetrahedron* **37**, 181 (1981).

[63] P. Sundararaman, G. Barth and C. Djerassi, *J. Am. Chem. Soc.* **103**, 5004 (1981).

[64a] J. Hine and W. S. Li, *Ibid.* **97**, 3550 (1975); [b] J. Hine, W. S. Li and J. P. Zeigler, *Ibid.* **102**, 4403 (1980).

[65] P. J. Stephens and R. Clark, In *Optical Activity and Chiral Discrimination* (Edited by S. F. Mason), p. 263 and references cited therein. Reidel, Dordrecht, Holland (1979).

[66] L. D. Barron, In *Optical Activity and Chiral Discrimination* (Edited by S. F. Mason), p. 219 and references cited therein. Reidel, Dordrecht, Holland (1979).

[67a] G. Holzworth, E. C. Hsu, H. S. Mosher, T. R. Faulkner and A. Moscowitz, *J. Am. Chem. Soc.* **96**, 215 (1974); [b] P. L. Polavarapu, L. A. Nafie, S. A. Benner and T. Hellman Morton, *Ibid.* **103**, 5349 (1981).

[68a] L. D. Barron, *J. Chem. Soc. Chem. Comm.* **1977**, 305; [b] L. D. Barron, H. Numan and H. Wynberg, *Ibid.* **1978**, 259.

[69] C. Marcott, K. Scanlon, J. Overend and A. Moscowitz, *J. Am. Chem. Soc.* **103**, 483 (1981).

[70] B. Cuony and W. Hug, *Chem. Phys. Lett.* in press.