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Chiroptical Properties and Conformation of 4,5-Saturated Derivatives of 5-Aryl-1,4-benzodiazepin-2-ones

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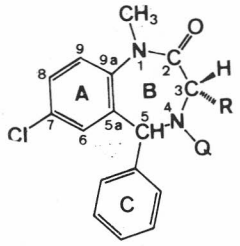
CD spectra of a series of 5-aryl-7-chloro-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one derivatives having different substituents at positions 1, 3, 4, and 5 were studied. The absolute configuration at C-5 of two homochiral analogues, *1* and *2*, having enantiomorphous ring conformations was determined on the basis of chiroptical correlations and theoretical calculations. The latter have shown that the optical activity mainly originates from the one-electron mechanism and is determined by the helicity of the diazepine ring, *i. e.* by the inherent chirality of the partial chromophore 4-chloro-*N*,2-dimethyl-formanilide. Exciton interactions between transitions of the two aromatic chromophores A and C also give a significant contribution to chiroptical properties. By applying simple chiroptical rules deduced from experimental spectra and supported by calculations, the stereochemistry (absolute conformation and configuration), of 3,5-disubstituted *cis* and *trans* epimeric pairs *(7—17)* was revealed.

INTRODUCTION

For more than two decades 1,4-benzodiazepine derivatives have been in the focus of pharmacological interest.[1] The geometry of such molecules, like *e. g.* 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, the well known diazepam, and the role of the conformation in their binding to serum proteins have been investigated by many authors.[2–7] CD spectroscopy proved to be an especially effective method for studying conformational equilibria in this field.[3–7] Besides the phenomenological relationships between CD spectra and conformation, a complete assignment and analysis of the CD bands of 1,4-benzodiazepines have been recently given by Snatzke and coworkers.[8]

The 5-aryl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one derivatives, like *1*, which are saturated at positions 4 and 5 have a centre of chirality at C-5. Resolution of the racemate of *1* led to optically pure enantiomers[9] which were transformed with potassium cyanate into their 4-carbamoyl derivatives *2*.[10] It was found that the 4-carbamoyl compound prepared from the *laevorotatory* enantiomer of *1* ($[\alpha]_D = -224$) showed a high *positive* value of optical rotation ($[\alpha]_D = +618$).[10,11] In principle, homochiral analogues must not be expected to have optical rotations of the same sign. It was, nevertheless, rather surprising that two homochiral derivatives differring only slightly in their constitution showed specific rotations of such high absolute values but of opposite signs. (The inversion of configuration at C-5 upon carbamoylation can be excluded with certainty).



1: R = H, Q = H

2: R = H, Q = $CONH_2$

3: R = CH_3, Q = H

To clarify this unexpected situation the crystal structures of (—)-*1* and (+)-*2* were determined by X-ray diffraction.[11] According to this study, which did not include the determination of absolute geometry, the conformation of the diazepine ring is almost identical in the two molecules (with slight differences around N-4 which is sp^3 in *1* and sp^2 in *2*); however, the phenyl group at C-5 is quasiequatorial (equatorial in the following) in *1* and quasiaxial (axial in the following) in *2*. This difference in the structure of the two 5-homochiral molecules can only be explained by assuming that the boat-shaped seven-membered ring of *1* was inverted upon introducing the carbamoyl group at N-4. With such an inversion molecule *2* can escape the unfavourable steric proximity which would occur between the planar carbamide moiety around N-4 and the equatorial phenyl group at C-5 in the other conformation.[11]

The chiroptical studies were undertaken with the aim of determining the absolute configuration of chirality center C-5 and finding out the general relationships between CD spectra and absolute geometry of 4,5-saturated benzodiazepin-2-one derivatives. The results are presented in this paper.

RESULTS AND DISCUSSION

Determination of the Absolute Configuration of 1—3

(a) CD spectra — Most of the compounds discussed in this paper have been prepared and studied in both enantiomeric forms. In order to avoid confusion and simplify discussion of the relationship with derivatives having

two centres of chirality, in the following (+)-*1* and (—)-*2* will be considered instead of their originally studied[11] enantiomers (—)-*1* and (+)-*2*.

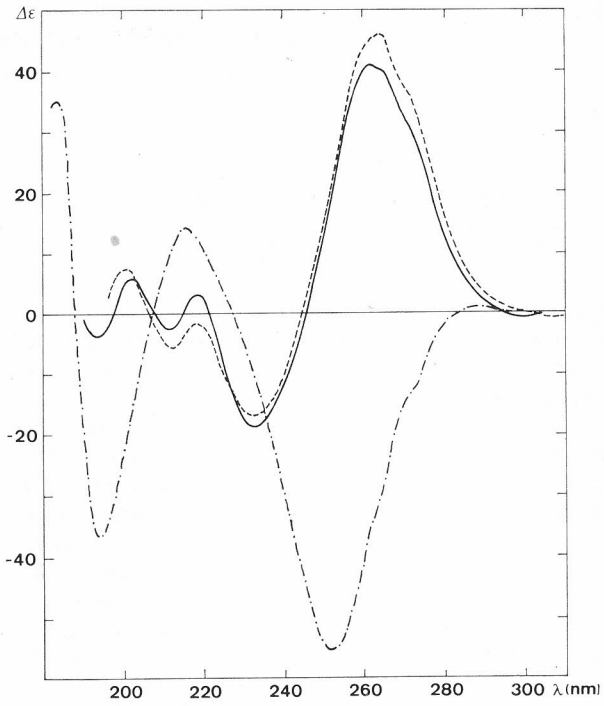


Figure 1. CD spectra of (+)-(5*S*)-*1* (———), (—)-(5*S*)-*2* (—·—), and (+)-(3*S*, 5*S*)-*3* (— — —) in cyclohexane solution.

The CD spectra of the two homochirally analogous compounds (+)-*1* and (—)-*2* are enantiomorphous with some characteristic differences (Figure 1). The most striking feature of the spectrum of (+)-*1* is a couple of bands with opposite signs: a strong positive band at 261 nm ($\Delta\varepsilon = +40.8$) and a weaker negative one at 232 nm ($\Delta\varepsilon = -19.1$). On the other hand, (—)-*2* exhibits an even stronger negative band ($\Delta\varepsilon = -55.8$) appearing at a somewhat shorter wavelength (251 nm) than the strong positive band of (+)-*1* and a weaker positive band at 215 nm ($\Delta\varepsilon = +14.0$). In the spectrum of (—)-*2* a weak positive band can also be found at 289 nm ($\Delta\varepsilon = +1.1$). A similar but almost two orders of magnitude weaker negative band occurs in the spectrum of (+)-*1* at 298 nm ($\Delta\varepsilon = -0.04$). The CD bands at lower wavelengths can be seen in Figure 1. These will not be considered in detail in the following. (Data of CD spectra for all substances discussed in this paper are collected in Table II.)

The above-mentioned data were measured in cyclohexane. A change of the solvent to ethanol or even to water does not significantly influence the main features of CD spectra. With increasing solvent polarity a small hypsochromic shift can be observed in the position of the strongest band. However, its intensity remains almost unchanged for most substances. Low temperature

measurements have shown that the CD spectrum of the 3-methyl derivative of *1* (*3*, see later) is almost identical at 25 °C and at — 198 °C. From the stability of chiroptical properties against solvent and temperature changes it can be concluded that in the solution of *1*, as well as of *2*, the conformational equilibrium is dominated by one of the two possible ring conformations. It is reasonable to assume that the same conformation is realized in solution as in the crystalline state.

(b) Comparison of CD and ^{13}C-NMR Spectra — The determination of absolute configuration at C-5 of *1* and *2* can be attempted in two different ways. The one is a comparison of their CD spectra with that of a reference compound with known absolute geometry. The other is a direct theoretical calculation of the CD spectra. Both methods have been applied with identical results.

The CD spectrum of the (3*S*)-methyl derivative of *1*, *i. e. 3* prepared from L-alanine,[12] was found to be almost identical with that of (+)-*1* (Figure 1). This indicates that the absolute geometry of (+)-(3*S*)-*3* and of (+)-*1* must also be very similar. According to X-ray data the conformation of the diazepine ring in molecule *1* containing the 5-phenyl ring in equatorial position is similar to that of the corresponding 4,5-unsaturated derivative 7-dechlorodiazepam.[11,13] As it is well known,[5,7,8,13] the 3-alkyl derivatives of diazepam assume that of the two enantiomeric ring conformations in which the C-3 substituent gets into the *exo* (quasiequatorial) position. It seems, therefore, probable that also in the case of the 4,5-saturated derivative *3* the ring conformation will be realized in which the 3-methyl group is in *exo* position. Furthermore, since the CD spectrum of (+)-*3* is almost identical with that of (+)-*1* and differs in the wavelengths and relative intensities of the bands significantly from that of (+)-*2*, the heterochiral analogue of (+)-*1*, it is quite reasonable to assume that the 5-phenyl group in (+)-*3* is in equatorial and not in axial position.

These assumptions relating to the relative stereochemistry of *1*—*3* were strongly supported by the ^{13}C-NMR spectra.[14] The most important signals are shown in Table I.

TABLE I

Selected signals of the ^{13}C-NMR spectra of 1—3 (δ, ppm)

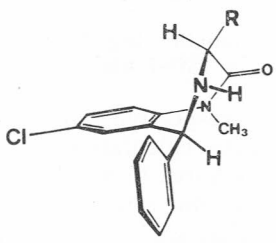
N°	N / CH_2 > C^2O	N^4 / NH_2 > CO	C^3H_2	$C^5HC_6H_5$	N^1—CH_3	C^3—CH_3
1	170.7	—	50.2	60.0	34.6	—
2	157.8[b]	166.1[b]	48.3	62.2	34.6	—
3	172.9	—	52.0	59.5	35.0	16.0
Δδ[a]	+2.2		+1.8	—0.5		

[a] $\Delta\delta = \delta\,(3) - \delta\,(1)$

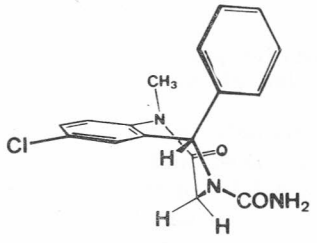
[b] The assignment of the carbonyl signals is based on a comparison with the ^{13}C-NMR spectra of carbamide and tetramethylcarbamide, where corresponding signals can be found at $\delta = 161.2$ and 165.4 ppm, respectively.[15] Thus, the signal at $\delta = 166.1$ ppm can be assigned to the carbonyl carbon bound to N-4 and that at $\delta = 157.8$ ppm to C-2.

The δ values of the signals in the spectra of *1* and *3* are near to one another, and the differences ($\Delta\delta$) are in agreement with the expected substituent effects of the 3-methyl group in *3*. There is, however, a significant difference in the spectral position of the C(2)=O carbon signal in *2* as compared with those in *1* and *3*. The upfield shift of the amide carbonyl signal of *2* is in accord with the expected axial position of the phenyl group getting nearer to C-2 than the equatorial phenyl in *1* and *3* and thus exerting a stronger field effect on its resonance. The stereochemistry of the 3-methyl group in *3* cannot be unambiguously determined from the ^{13}C-NMR spectrum. Nevertheless, its very small γ-substituent effect on the signal of C-5 is in agreement with its assumed *exo* position. An *endo* methyl group pointing towards the diazepine ring should have a stronger field effect on the signal of C-5. Furthermore, an axial methyl should have a negative α-substituent effect on the signal of C-3 and not that of +1.8. Thus the ^{13}C-NMR spectra support the assumption that the 5-phenyl group is equatorial in both *1* and *3* but axial in *2*, and that the methyl group at C-3 of *3* occupies an *exo* position.

Since the configuration of chirality centre C-3 in (+)-*3* is known to be *S* and the methyl group is assumed, with good reason, to be in *exo* position, the diazepine ring in (+)-(3*S*)-*3* must be of *M* helicity.[16] The equatorial phenyl group at C-5 of the diazepine ring of *M* helicity results in *S* absolute configuration for this centre of chirality. Thus, the absolute configuration of (+)-*3* is 3*S*,5*S*. The 5*S* absolute configuration of (+)-*1* and of (—)-*2* follows from that of (+)-*3*. According to their CD spectra (+)-*1* and (+)-*3* must be homochiral at C-5. For (—)-*2*, the synthesis ensures the homochirality with (+)-*1*, though they assume enantiomeric ring conformations.



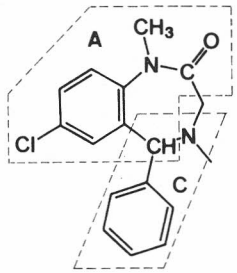
(+)-(5*S*)-*1*: R = H
(+)-(3*S*,5*S*)-*3*: R = CH_3



(—)-(5*S*)-*2*

(c) *Theoretical Calculation of CD Spectra*[17] — Although the assignment of absolute configuration at C-5 in *1*—*3*, which was based on correlations of CD and ^{13}C-NMR spectra, is quite straightforward, it was desirable to have a better insight into the mechanisms[18] responsible for the chiroptical effects. Since a direct quantum chemical calculation of the optical activity of the whole molecules was, unfortunately, beyond our possibilities, separate calculations on the effects of different mechanisms were performed. It was assumed that the main source of optical activity in molecules *1* and *2* is due to the inherently chiral chromophoric system consisting of the substituted benzene ring A and the amide moiety bound to it non-coplanarly through N-1. According to X-ray data,[11] the torsion angle around the C(9a)-N(1) bond

is —47.7° in (5*S*)-1 and +49.1° in (5*S*)-2-(Figure 2). The smallest moiety comprising all the atoms that can have an influence on the chiroptical properties of the common chromophore of *1* and *2* was »cut out« of the molecules and the dangling bonds were saturated with hydrogen atoms. The model



chosen was thus 4-chloro-2,*N*-dimethyl-formanilide (chromophore A). The second inherently chiral chromophore (chromophore C) was a noncoplanar benzylamine consisting of the phenyl group, of chirality centre C-5, and N-4 representing the chiral surrounding. For each chromophore two geometries

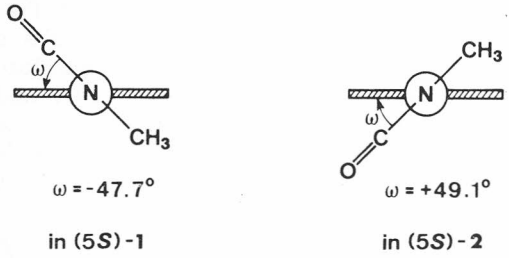


Figure 2. Relative position of the plane of the aromatic ring A (shaded bar) and that of the amide moiety of ring B in (5*S*)-*1* and (5*S*)-*2*.

were used, namely those corresponding to the respective parts of the X-ray structures of (5*S*)-1 and (5*S*)-*2*. A CNDO/S—TDA calculation was performed for both geometries of the two separate chromophores to obtain the transition properties (energies and transition moments) and the rotational strengths originating from the so-called one-electron mechanism.[19] (For details of the calculations see Experimental.)

The results are summarized in Figures 3 and 4. The two columns of horizontal lines represent calculated transition energies in eV's for the two chromophores. The numbers written above the lines are the calculated one-electron rotational strengths in 10^{-40} c. g. s. units. It is to be mentioned that while the calculated aromatic transitions are at about the expected energies (with an overestimation of about 0.5 eV), the $n \rightarrow \pi^*$ transition of the amide moiety of chromophore A and the $\pi \rightarrow \sigma^*$ transitions appear at unreasonably low energies. This fact can be attributed to the shortcomings of the CNDO/S method for this kind of transitions and to the incomplete TDA which is known to decrease the energy of $n \rightarrow \pi^*$ transitions too much.[20,21] These transitions, however, play only a minor role in the optical activity. Without going into a detailed analysis of the results it can be stated that their most impressive feature is the large value of the rotational strength appearing in the L_a

transition of chromophore A. This band was calculated to be positive for the geometry corresponding to the conformation of *M* helicity of the original benzodiazepinone molecule and negative for the geometry corresponding to *P* helicity. Thus, the theoretical calculations even for this simplified model gave a strong support to our experimental assignments. However, the typical differences between the shapes of the CD spectra of *1* and *2* could not be reproduced by this type of calculation. This is because the conformations of the chiral chromophores were almost enantiomeric in the two models and, therefore, the transition energies calculated for them hardly differ at all. Nevertheless, the results of this part of our calculations clearly show the validity of the assumption that the main source of the CD of 4,5-saturated benzodiazepinone derivatives is the inherent chirality of the seven-membered diazepinone ring.

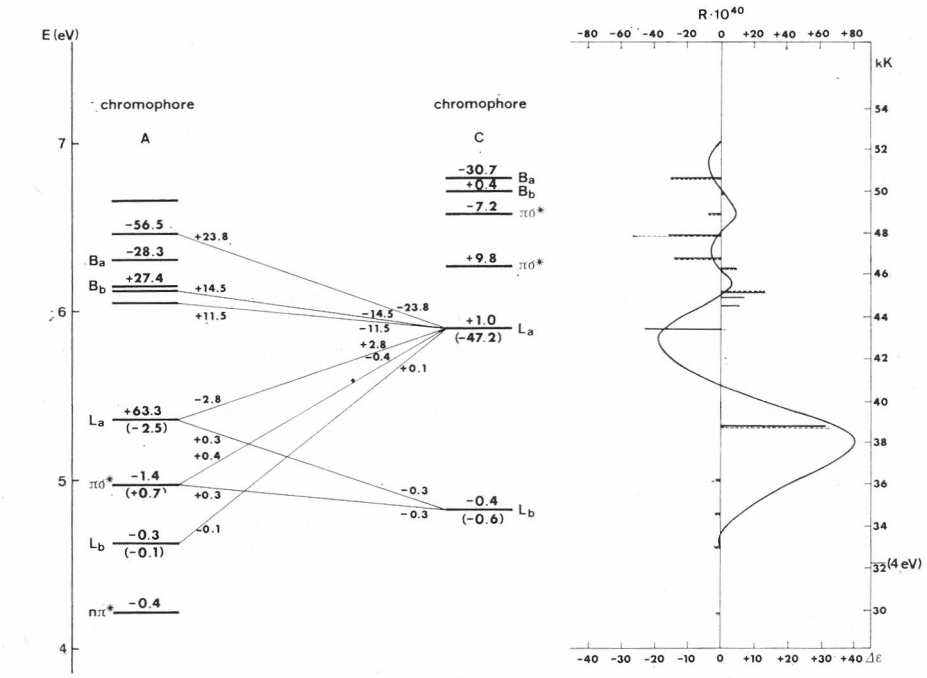


Figure 3. Results of theoretical calculations of the CD bands of (5*S*)-*1* and comparison thereof with the experimental CD spectrum. Left side: horizontal lines represent the energies of calculated transitions of chromophore A and C, numbers above the lines are one-electron rotational strengths (in 10^{-40} c. g. s. units), those in parentheses are rotational strengths originating from the coupled oscillator mechanism; thin lines connecting two transitions refer to pairwise exciton interaction, numbers written on these lines give rotational strengths due to the given coupling. Right side: full lines represent rotational strengths induced in the single transitions by the two combined mechanisms, dashed lines show the components due to the one-electron mechanism. For the calculated spectrum the energy scale in eV's is on the left margin, the intensity scale at the top of the figure; for the experimental CD spectrum the energy scale in kK (10^3 cm^{-1} units) is on the right margin (shifted by 0.5 eV to higher energies) and the intensity scale (in $\Delta\varepsilon$ units) at the bottom of the figure.

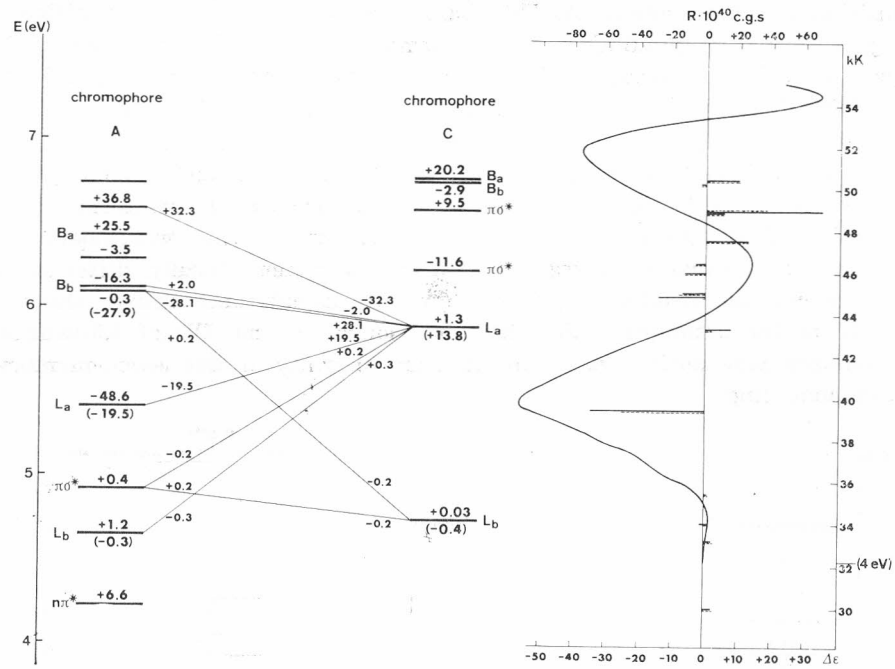


Figure 4. Results of theoretical calculations of the CD bands of (5*S*)-*2* and comparison thereof with the experimental CD spectrum. (Further legend under Figure 3.)

The other structural feature which can have a nonnegligible contribution to chiroptical properties of *1* and *2* is the exciton coupling of the two aromatic chromophores A and C. The rotational strengths originating from the exciton interaction of the transitions belonging to the two chromophores were obtained by a simple Kirkwood type calculation.[22] The electric transition moments taken from the former calculation were placed as point dipoles in the geometric centres of the two chromophores. The relative positions were taken from the X-ray structures of *1* and *2*. In this calculation couplings of the L_b and L_a transitions of chromophore C with all the transitions being lower in energy than 6.5 eV of chromophore A were taken into account. The calculated rotational strengths obtained by summarizing the pairwise interactions are given in parentheses in Figures 3 and 4. The single pairwise exciton interactions which proved to be significant are shown by thin lines connecting the participating transitions. Numbers written on these lines give the value of rotational strengths originating from the coupling of the given pair of transitions.

The results of the exciton calculation are quite interesting, some of them very instructive as well. In the case of the *equatorial model* (geometry of (5*S*)-*1*; Figure 3) the coupling between the electric moments of the two L_a transitions (L_a^A and L_a^C) which are almost coplanar and thus occupy an unfavourable relative position for exciton interaction, results, as expected, only in small rotational strengths. Therefore, the rotational strength of the

L_a^A transition originates almost entirely from the one-electron mechanism with only a small contribution, of opposite sign, coming from exciton coupling with L_a^C. The latter transition, however, interacts also with the higher energy transitions of chromophore A (with B_a^A and B_b^A among others) and gets a relatively large rotational strength of negative sign through the exciton mechanism. In this way both L_a transitions, L_a^C as well as L_a^A, will be connected with large rotational strengths of opposite signs, but these originate from different mechanisms and not from a simple direct coupling of the two transitions with each other. Nevertheless, the calculations involving both mechanisms can nicely reproduce the most important feature of the experimental spectrum of (+)-*1*, namely the presence of two strong bands of opposite signs in the wavelength range assigned to the L_a type transitions.

For the *axial model* (geometry based on the X-ray structure of (5*S*)-*2*; Figure 4) the calculations show strong exciton coupling between the L_a transitions of the two chromophores. This mechanism results in a negative rotational strength for the L_a^A and in a positive one for the L_a^C transition. This is in agreement with the experimental spectra, since the negative rotational strength originating from the one-electrom mechanism of the higher wavelength L_a transition (L_a^A) will be increased in absolute value through the exciton mechanism, and the lower wavelength L_a^C transition, the one-electron optical activity of which is negligible, gains a positive rotational strength from the exciton coupling. It is interesting to note that although the L_a^C transition interacts also with a number of other transitions of chromophore A, the rotational strengths originating from these interactions compensate each other. Thus, apparently, almost the whole exciton optical activity of the latter transition originates from the coupling between L_a^C and L_a^A. The combined results of the two calculations surprisingly well reproduce the main feature of the experimental spectrum, namely the very strong negative band at longer and the weaker positive one at shorter wavelengths.

The rotational strengths induced in the different transitions by the two mechanisms can be seen on the right hand side of Figure 3 and 4. Full lines, represent the total magnitude of the rotational strengths given by the two types of calculations, while dashed lines show the contribution of the one-electron mechanism. (A longer dashed line means that the exciton contribution is of opposite sign, therefore the sum is smaller in absolute value.) The experimental spectra of (+)-(5*S*)-*1* and (—)-(5*S*)-*2* can be seen superposed on the rotational strength diagrams. The energy scale given in kK's (10^3 cm^{-1} units) is shifted by 0.5 eV to get a good correspondence between the calculated and experimental bands. This means that the simplified calculation, at least in the range of lower energies, has overestimated the transition energies by about 0.5 eV. Nevertheless, the overall results can be regarded to be in good agrement with experiment.

However, one important difference in the CD spectra of *1* and *2* was not revealed by either of the calculations. This is the small but significant blue shift of the first two CD bands when going from *1* to *2*. Although this difference was found experimentally to be characteristic of the equatorial or axial position of the 5-aryl group in the benzodiazepinone derivatives studied by us (see below), it cannot be expected to be reproduced by simplified

calculations. The CNDO/S calculation gives, as mentioned above, almost the same energies for the two nearly enantiomeric geometries of the chromophores. In the simple Kirkwood calculation[22] of the exciton interaction of two *non-degenerate* transitions the excitation energies are held fixed. The solution of this problem could be attempted by a more sophisticated calculation on the whole molecules or at least on models comprising both aromatic chromophores. Because of the large size of these models, however, such a study is beyond our computational facilities for the time being.

It could be objected to our simplified calculations using only fragments of the whole molecules as models that the difference in the hybridization of the N-4 atom in *1* and *2* was completely ignored. In principle, it cannot be excluded that the differences in the CD spectra are to be attributed, at least in part, to this structural feature. However, it was found experimentally that a 4-unsubstituted benzodiazepinone derivative (*c-8*, see later) gave CD bands at 255 and 216 nm because its 5-phenyl group is in axial position, whereas a 4-carbamoyl derivative (*c-15*, see later) with equatiorial 5-aryl group exhibited CD maxima at 262 and 240 nm. Based on these facts, the difference in the wavelength of the first two intensive bands must be assigned, even if this cannot be supported by the simplified calculations, to the equatorial or axial position of the 5-aryl substituent and not to the different hybridization of the N-4 atom.

An additional comment concerning the geometry of the models is due here. In the exciton calculations the relative position of the two aromatic rings was fixed for both models in the geometry taken from the X-ray structures. In reality, the 5-phenyl ring is surely not fixed but, even if not freely rotating, it may change its position around its bond to C-5. This rotation, however, does not change the direction of the electric moment belonging to the L_a^C transition, since it is parallel to the C(aryl)—C(5) bond. Thus, the rotational strength originating from the coupling of L_a^C with transitions of chromophore A is not influenced by the actual position of ring C. The situation is different with the L_b^C transition, where the electric moment is perpendicular to the bond axis. The contribution of this transition, however, is negligible as compared to that of the L_a^C transition. According to this reasoning, the neglect of the possible torsional motion of chromophore C does not invalidate the results of the exciton calculations.

To sum up the results of the theoretical study, it can be stated that the simplified calculations taking into account the two mechanisms of optical activity separately reproduce the main features of experimental CD spectra of *1* and *2* and give a sound basis for further generalizations in assigning CD spectra to molecular geometry.

Chiroptical Rules

Based mainly on experimental CD spectra of several series of model compounds (see Table III), but strongly supported by the results of theoretical calculations outlined above, the characteristic features of the relationship between chiroptical properties and stereochemistry of 4,5-saturated 5-aryl-1,4-benzodiazepin-2-one derivatives can be summarized in the following simple rules.

(1) The sign of the first strong CD band appearing between 270 and 250 nm is determined by the helicity of the seven-membered 1,4-benzodiazepin-2-one ring. Positive and negative signs correspond to *M* and *P* helicity, respectively.

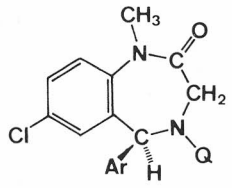
(2) For molecules having the 5-aryl group in *equatorial* position the first strong CD band appears *above* 260 nm and the second (somewhat weaker) around 235 nm, whereas for those bearing an *axial* 5-aryl group the strongest CD band can be found *below* 260 nm and the second, normally weak, band at about 215 nm.

(3) The intensity of the strongest band in the CD spectra of substances containing molecules of almost homogeneous conformation in the solution is between 40 and 60 $\Delta\varepsilon$ units. Significantly smaller values indicate the presence of more than one conformer.

By applying these rules the absolute conformation of the diazepinone ring and the absolute configuration at C-5 of the type of compounds studied can be easily established.

Derivatives with One Centre of Chirality

Starting from (+)-(5*S*)-*1* some other derivatives containing a single centre of chirality at C-5 have also been prepared in optically active form (*4*—*6*).[9] (For CD spectra see Table II).



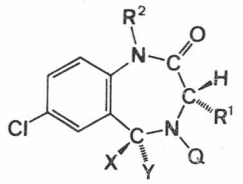
	Q	Ar
4	CH_3	C_6H_5
5	$COCH_3$	C_6H_5
6	$COC_{15}H_{31}$	C_6H_5

The CD spectrum of (+)-*4*, the 4-methyl derivative of (+)-*1*, was similar to that of (+)-*1* with a somewhat more symmetrical couplet in the wavelength range of 300—220 nm. This indicates that 4-alkyl derivatives also prefer the equatorial orientation of the 5-phenyl group. The 4-acetyl and 4-palmitoyl derivatives (*5* and *6*) containing an sp^2 hybridized N-4 atom exhibited CD spectra which were, at least in the wavelength range of the strongest band, almost identical with that of (—)-*2*, showing the 5-phenyl group to adopt the axial position.

These results allow us to generalize the experiences with *1* and *2*. 4,5-Saturated benzodiazepinones containing a single centre of chirality at C-5 assume mainly one conformation even in solution. This major conformation can be characterized by an equatorial aryl group in the case of 4-unsubstituted and 4-alkyl substituted derivatives, whereas by an axial aryl group in the case of 4-acyl compounds.

Derivatives with Two Centres of Chirality

Reduction of 3-substituted 4,5-unsaturated benzodiazepinone derivatives (whose configuration at C-3 is given by that of the amino acid used in their synthesis) leads to the formation of a pair of epimers, namely of the 3,5-*trans* and the 3,5-*cis* 4,5-saturated compounds.[12] Though the two epimers are not formed in the same amount, in most cases both of them could be prepared in pure state.[12] Starting from these substances, which are unsubstituted at N-4, the two epimers of other types of derivatives (4-carbamoyl, 4-alkyl) were also prepared.[9,12]



	X	Y	Q	R^1	R^2
7	C_6H_5	H	$CONH_2$	CH_3	CH_3
t-8	C_6H_5	H	H	$CH_2C_6H_5$	CH_3
c-8	H	C_6H_5	H	$CH_2C_6H_5$	CH_3
t-9	C_6H_5	H	H	$CH_2C_6H_5$	H
t-10	C_6H_5	H	$CONH_2$	$CH_2C_6H_5$	CH_3
c-10	H	C_6H_5	$CONH_2$	$CH_2C_6H_5$	CH_3
t-11	C_6H_5	H	$CONH_2$	$CH_2C_6H_5$	H
c-11	H	C_6H_5	$CONH_2$	$CH_2C_6H_5$	H
t-12	C_6H_4Cl (*o*)	H	H	CH_3	H
c-12	H	C_6H_4Cl (*o*)	H	CH_3	H
t-13	C_6H_4Cl (*o*)	H	H	$CH_2C_6H_5$	CH_3
c-13	H	C_6H_4Cl (*o*)	H	$CH_2C_6H_5$	CH_3
t-14	C_6H_4Cl (*o*)	H	H	$CH_2C_6H_5$	H
c-14	H	C_6H_4Cl (*o*)	H	$CH_2C_6H_5$	H
t-15	C_6H_4Cl (*o*)	H	$CONH_2$	$CH_2C_6H_5$	CH_3
c-15	H	C_6H_4Cl (*o*)	$CONH_2$	$CH_2C_6H_5$	CH_3
t-16	C_6H_4Cl (*o*)	H	$CONH_2$	$CH_2C_6H_5$	H
c-16	H	C_6H_4Cl (*o*)	$CONH_2$	$CH_2C_6H_5$	H
t-17	C_6H_4Cl (*o*)	H	C_2H_5	$CH_2C_6H_5$	CH_3
c-17	H	C_6H_4Cl (*o*)	C_2H_5	$CH_2C_6H_5$	CH_3

Based on the chiroptical rules outlined above, the whole stereochemistry, absolute conformation and configuration, of the members of these epimeric pairs could be established by CD spectroscopy.

A 4,5-saturated benzodiazepinone derivative substituted at C-3 and C-5 can assume, by inversion of the seven-membered ring, two conformations: that of *M* and that of *P* helicity.[16] Corresponding to their configurations, the substituents occupy different positions in the two conformers, as shown in Figure 5.

For a given stereoisomer the conformation can be characterized by three descriptors referring to the helicity of the ring (*M* or *P*),[16] the relative conformation of the substituent at C-5 (*equ* or *ax*) and the relative conformation of the substituent at C-3 (*endo* or *exo*). The absolute configurations can be

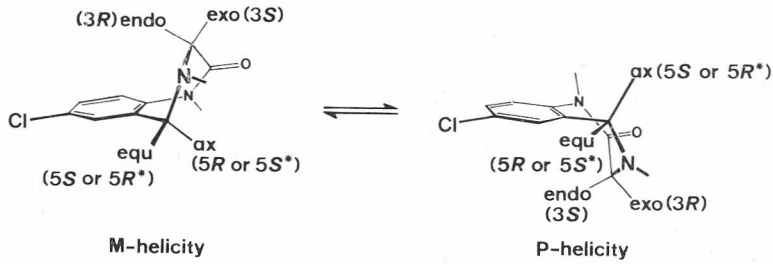


Figure 5. Conformational and configurational descriptors of the two conformations of 3,5-disubstituted derivatives of 4,5-saturated 1,4-benzodiazepin-2-ones.

specified according to the CIP conventions*. Thus *e. g.* the *trans* and *cis* epimers of a (3*S*)-methyl-5-phenyl derivative (the substituents at N-1 and N-4 are irrelevant) can assume the following two pairs of conformations:

trans epimer (3*S*,5*S*)

M-equ-exo or *P-ax-endo*

cis epimer (3*S*,5*R*)

M-ax-exo or *P-equ-endo*

The first two descriptors of the absolute conformation can be determined from the CD spectrum. These together give also the absolute configuration at C-5. The third descriptor comes from the known configuration of chirality centre C-3.

In the following several examples to the application of this method will be shown.

Compound (+)-(3*S*)-*3* was one of the models used for deducing the correlations between stereochemistry and chiroptical properties (see above). It is a 3,5-*trans* stereoisomer with conformation *M-equ-exo*. On a diazepine ring of *M* helicity both substituents can adopt a local conformation which is presumably more favourable, namely, with the phenyl group at C-5 in the equatorial and the methyl at C-3 in the *exo* position. (The *cis* epimer of *3* was not prepared in a sufficiently pure state and, therefore, could not be studied by CD spectroscopy).

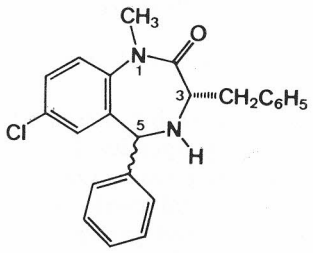
Carbamoylation[9,12] of (3*S*,5*S*)-*3* led to (—)-(3*S*,5*S*)-*7*, the (3*S*)-methyl derivative of (—)-(5*S*)-*2*, exhibiting a CD spectrum very similar to that of (—)-*2*. This indicates that in this molecule the diazepine ring is of *P* helicity, the 5-phenyl group adopts the axial orientation, and the (3*S*)-methyl group has no other choice but to assume the *endo* position. Thus, in this molecule it is the steric repulsion between the 5-phenyl and the 4-carbamoyl group, and not the more favourable *exo* position of the methyl group at C-3, that determines the major ring conformation.

From inspection of molecular models it could be expected that a methyl group in *endo* position at C-3 is sterically unfavourable, and that the diazepine ring bearing such a group must be strongly distorted. In contrast to this, Fitos *et al.*[7] have found that the »achiral« 3,3-dimethyldiazepam bound to serum

* According to the CIP conventions,[23] the descriptor of the configuration at C-5 of a 5-(*o*-chlorophenyl) derivative is opposite to that of the homochiral 5-phenyl compound. Therefore, to avoid confusion, this descriptor will be marked with an asterisk (*R** and *S**) for 5-(*o*-chlorophenyl) derivatives (*cf.* Figure 5).

albumin exhibits almost the same CD spectrum as the (3*S*)-monomethyl derivative. This observation indicates that the conformation of the 4,5-unsaturated diazepine ring of the dimethyl derivative is, despite the presence of an *endo* methyl group, almost identical with that of the monomethyl derivative having a methyl group only in *exo* position. However, the somewhat lower intensity of the strongest band of (—)-(3*S*,5*S*)-7 (about 70% of that of the corresponding band in the CD spectrum of (—)-2) can probably be explained by a smaller pucker of the seven-membered ring (smaller torsion angle within the »formanilide« chromophore). Such a small distortion of the ring conformation would relieve the steric strain caused by the *endo* methyl group. Our further experiences with other models have shown (see below) that in the molecules of the 4,5-saturated series a 3-alkyl (or 3-aralkyl) substituent can occupy the *endo* position without any significant steric strain.

As a typical example to the application of the chiroptical rules in stereochemical determinations, the two 5-epimers of the 1-methyl-(3*S*)-benzyl-5-phenyl derivative *8* will be considered. The first two strong bands in the CD spectra of the two isolated compounds A and B are as shown below. (The CD data are given in the form: λ [nm] ($\Delta\varepsilon$).)



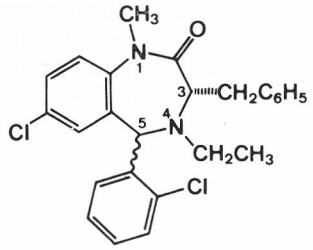
8

epimer A: 265 (+49), 234 (—19),

epimer B: 255 (+47), 216 (—26).

From these data it can be established that the diazepine ring is of *M* helicity in both epimers, and that the 5-phenyl group is equatorial in epimer A and axial in epimer B. The corresponding configurations are thus 5*S* and 5*R*, respectively. Since both epimers, prepared from L-phenylalanine, are of 3*S* configuration, epimer A is the (3*S*,5*S*)-*trans* stereoisomer of conformation *M-equ-exo*, and epimer B is the (3*S*,5*R*)-*cis* stereoisomer of conformation *M-ax-exo*. As these results show, for both epimers of compound *8* it is the *exo* position of the benzyl group at C-3 that determines the conformation of the molecules. In the *trans* epimer also the 5-phenyl group gets in the more favourable equatorial position, but in the *cis* isomer it is constrained to assume the axial position which, according to the experiences with C-3 unsubstituted derivatives (*e. g. 1*), is the less favoured local conformation for an N-4 unsubstituted compound. It is interesting to note that the crystal structures[24] of the two epimers are in agreement with their solution conformations determined by CD spectroscopy.

A strikingly different situation was found with the epimeric pair of the 1-methyl-(3*S*)-benzyl-4-ethyl-5-(*o*-chlorophenyl) derivative *17*. The main bands of the CD spectra of the two epimers A and B are as follows:



17

epimer A: 269 (—56), 241 (+37),

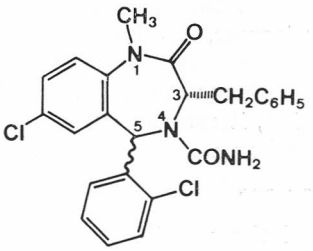
epimer B: 272 (+31), 240 (—44).

Both spectra must be assigned to conformers having the substituent at C-5 in equatorial position, but the ring in epimer A is of *P* helicity, whereas in epimer B of *M* helicity. Thus, the configurations and conformations of the two compounds are:

epimer A: (3*S*,5*S**)-*cis*
P-equ-endo,
epimer B: (3*S*,5*R**)-*trans*
M-equ-exo.

In this case it is the equatorial position of the *o*-chlorophenyl group at C-5 that determines the main conformation for both epimers, and in the *cis* isomer the 3-benzyl group occupies the *endo* position.

Based on earlier experiences it was expected that both epimers of the 1-methyl-(3*S*)-benzyl-4-carbamoyl-5-(*o*-chlorophenyl) derivative *15* would contain the 5-aryl group in axial orientation. In contrast to this, one of the two CD spectra was typical of an equatorially substituted diazepine ring of *M* helicity.



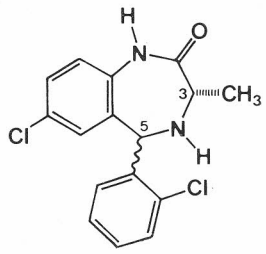
15

epimer A: 254 (—47), 215 (+29),

epimer B: 262 (—37), 240 (+23).

According to these very characteristic CD spectra, epimer A is of *P-ax-endo* conformation, hence it is the (3*S*,5*R**)-*trans* isomer, and epimer B is the (3*S*,5*S**)-*cis* isomer with the conformation *P-equ-endo*. The most surprising feature of this result is that in the *cis* epimer not only the 5-aryl group is equatorially oriented, but even the 3-benzyl group occupies the *endo* position. Apparently, it is the *endo* position of the latter substituent which is the factor determining the conformational equilibrium for both epimers.

In some cases only one of the epimers exhibits a CD spectrum which is of the typical form and intensity, and from which the presence of one major conformer can be deduced. The spectrum of the other epimer is »irregular«, containing more bands with smaller intensities than usual. These spectra indicate the presence of two conformers, *i. e.* an equilibrium which is not biased towards the one or the other of the two possible conformers. A characteristic example can be given by the two epimers of the 3-methyl-5-(*o*-chlorophenyl) derivative *12*. One of the epimers (A) exhibited a CD spectrum



12

which is typical of an *M-equ* conformation: 263 (+ 46), 235 (— 13). Since the configuration at C-3 is *S*, this is the (3*S*,5*R**)-*trans* isomer in the expected *M-equ-exo* conformation. The spectrum of the other epimer (B) contains the following weak bands between 300 and 200 nm: 274 (— 12), 249 (+ 7), 224 (— 16,) 220 sh (— 11), 201 (+ 27). From the low intensity of the bands it can be concluded that the spectrum originates from two overlapping, more or less enantiomorphous spectra. If only the first two bands are considered, the first can be assigned to a *P-equ* and the second to an *M-ax* conformation. (The maxima of the bands due to the single conformers must be, of course, nearer to each other than in the partially compensated sum spectrum.) The shorter wavelength bands cannot be assigned so simply to the one or the other typical spectrum. Although the interpretation of this irregular spectrum is by far not as clear-cut as that of the other isomer, the bands surely cannot be due to a mixture containing *M-equ* and *P-ax* conformers. Thus, the configuration of the chirality centre C-5 can be unambigously determined to be *S**. Since epimer B is also of 3*S* configuration, it cannot be but the (3*S*,5*S**)-*cis* isomer realizing the equilibrium of two conformers:

$$P\text{-}equ\text{-}endo \rightleftharpoons M\text{-}ax\text{-}exo$$

In the case of this compound neither of the substituents can shift the equilibrium towards one of the possible conformations.

At this point an important comment seems to be necessary. Many examples have shown that the substituent (methyl or benzyl) at C-3 does not significantly influence the chiroptical properties. (The CD spectra of *1*, *3* and *e. g. t-8* are almost identical.) More important is the role of the aryl group at C-5. Although the calculations have shown that the sign of the first intensive CD band is mainly determined by the helicity of the diazepinone ring (*i. e.* by the inherent chirality of the »formanilide« chromophore), the exciton interaction between the two aromatic chromophores also has a significant effect

on the shape of the CD spectra. Therefore, the chloro substitution at the *o*-position of the benzene ring, which changes the direction of transition moments, is expected to result in a nonnegligible change of the CD spectrum. In contrast to this expectation, the experimental spectra of the *trans* isomers containing a 5-phenyl or a 5-(*o*-chlorophenyl) group are very similar in many cases (compare *e. g.* the spectra of *3* and *7* with those of *t-12* and *t-15*, respectively; Table II). Based on this observation, it seems reasonable to assume that the *o*-chlorophenyl group, even if it is not freely rotating, can adopt two almost equally populated conformations with the chlorine atom occupying two »enantiomorphous« positions. In this way the chiroptical effect of the chlorine substituent could be compensated. With this assumption it can be explained that the chiral contribution of the 5-(*o*-chlorophenyl) group is equivalent to that of a phenyl group. (In special cases fixed conformations cannot be excluded, either.)

It is another question, how far the substituents can modify the geometry of the seven-membered ring. It seems possible that in molecules containing *e. g.* a 3-benzyl group in *endo* position, the pucker of the diazepinone ring will be decreased to lessen unfavourable steric proximities. This can lead to diminished intensities of the CD bands. Thus, the CD spectrum of *trans-10*, the (3*S*)-benzyl derivative of (5*S*)-*2* is typical of a *P-ax-endo* conformation [253 (— 28), 214 (+ 11)]. However, the smaller intensity of the first band can be considered as an indication of the flattening of the diazepinone ring.

If a CD spectrum does not contain bands pointing to the presence of another conformer, its smaller intensity can be explained by a distorted geometry of the single (or the major) conformer.

By similar analyses as shown on the examples presented above, configurational and conformational assignments for all the substances containing two centres of chirality could be performed from the CD spectra (see Table II).

Our results presented in this paper show that the simple correlations found between the CD spectra of 4,5-saturated 1,4-benzodiazepin-2-one derivatives and their absolute conformation and configuration can be successfully aplied in order to determine the stereochemistry of this type of substances. It is another question what sort of interaction is responsible for the actual conformation of a given compound. This question can only be answered by more sophisticated calculations relating to the exact geometry and energy of the individual members of conformers pairs.

EXPERIMENTAL

Preparations

The preparations and physical properties of the substances discussed in this paper are published elsewhere.[9,10,12]

Spectra

The ^{13}C-NMR spectra were measured on a WM-250 Bruker instrument in DMSO-d_6 using TMS as internal standard. The CD spectra were recorded with a Roussel-Jouan Dichrographe Mark III (Jobin-Yvon) in quartz cells of lengths of 0.02—1.00 cm, at concentrations of appr. 1 mg/cm^3 at ambient temperature. Data of the CD spectra are collected in Table II.

TABLE II

CD data for compounds 1—17

N°	Solvent[a] (*t*, °C)[b]	λ, nm ($\Delta\varepsilon$)[c]
1	C	298(—0.04), 261(+40.8), 232(—19.1), 218(+3.0), 211(—3.3), 204(+5.5), 194(—4.0)
	E	258.5(+25.5), 232(—12.9), 216(+3.0), 207.5(—4.9), 192!(—19)
	W	252.5(+16.0), 230(—2.2), 220.5(+1.2), 207(—5.4), 190(—39)
2	C	289.5(+1.1), 251.5(—55.8), 215.5(+14.0), 193(—37), 184(+35)
	E	290(+1.5), 251(—62.6), 212(+7.8), 208sh(—6.0), 195!(—30)
	W	287(+0.5), 249(—51.1), 209(+9.9), 192(—32.0)
3	C	320(—0.4), 264(+45.9), 231(—16.6), 212(—5.5), 202(+7.0)
	E	316(—0.27), 258.5(+43.4), 228(—12.9), 209(—11.0)
	W	310.5(—0.24), 252(+46.8), 231(—1.3), 222(+1.4), 206(—12.4)
	M/I (+25)	258.4(+47.5), 225.5(—17.9)
	M/I (—100)	259(+46.4), 225(—19.7)
	M/I (—198)	253(+47.8), 219(—9.8)
4	C	273.5(+33.4), 250sh(—20.6), 242(—30.0), 224(+1.9), 213.5(—18.1), 196(+26)
	E	267(+28.3), 239(—25.8), 211(—13.4), 197(+13)
	M/I (+25)	267.5(+36.0), 234.5(—32.0)
	M/I (—100)	267.5(+47.6), 231(—41.2)
	M/I (—198)	259.5(+52.8), 227.5(—39.5)
5	E	252(—64.6), 228sh(—10.9), 210(+26.4), 191(—51.2)
6	C	292(+1.5), 257.5(—62.4), 233sh(—11.1), 215(+22.7), 193(—39)
	E	289(+1.2), 252.5(—60.8), 228sh(—8.2), 211(+32.2), 195!(—27)
7	C	293(+0.65), 255(—41.3), 217.5(+17.0), 197(—31)
t-8	C	265(+49.4), 233.5(—18.7), 212(—16.4), 194!(—51)
c-8	C	254.5(+46.6), 216(—26.1), 190(+49.5)
t-9	C	262(+36.3), 233(—21.0), 208(—13.0)
t-10	E	291(+0.5), 253(—28.1), 214(+11.2)
c-10	E	259(+26.1), 223(—8.9), 214.5(—10.2)
t-11	C	290(+1.3), 248(—18.0), 222(—13.0), 209(+5.3), 193!(—36)
c-11	C	298(—0.7), 260(+14.0), 213(—12.1), 204(—26.2)
t-12	E	263(+46.1), 235(—13.3), 220(+14.9), 203(—38.6), 190!(+22.3)
c-12	E	274(—11.9), 249(+6.9), 224(—16.3), 201(+27.1)
t-13	C	263(+16.4), 234(—5.1), 221.5(+5.1), 199(—17.6)
c-13	E	275(—1.8), 248(+19.5), 224(—5.5), 209(+9.7)
t-14	C	264(+37.6), 236(—19.3), 221(+2.3), 207.5(—40.5), 185(+41)
c-14	C	279(—9.0), 255.7(+7.1), 235.5(—13.2), 226.5(—15.5), 207(+23.2), 198!(+13)

Table II continued.

t-15	E	289(+1.3), 254(—47.0), 215(+28.9)
c-15	E	262(—36.9), 240(+23.1), 225(—2.6), 200!(+30)
t-16	E	290sh(+1.7), 264(+14.1), 235(—29.5), 216(—61.0), 196!(+60)
c-16	E	295(—2.0), 258(—18.3), 231(+5.2), 217(—5.2)
	CL	290(—3.0), 253(—24.0)
t-17	E	283sh(+24.4), 272(+30.7), 240(—43.5), 223(+11.0), 207(—34.2)
c-17	E	269(—55.7), 241(+36.5), 224(—22.1), 211(+58.8)
	CL	272(—53.6), 244(+36.3)

[a] C = cyclohexane, E = ethanol, W = water, CL = chloroform, M/I = methylcyclohexane-isopentane (1 : 3).

[b] If not otherwise stated, at ambient temperature.

[c] sh = shoulder ! = last measurable value of CD (no maximum).

Methods of Calculations

The quantum chemical calculations for the excitation properties of the model chromophores were carried out at the standard CNDO/S level.[25-27] The excitation energies were calculated by the Tamm-Dancoff approximation (TDA).[28] This latter method treats the ground state as a single Hartree-Fock determinant, while the excited states are linear combinations of determinants of monoexcited configurations. That is why this procedure is also called the single excitation configuration interaction method. In our calculations 43 singly excited configurations, including all the $\pi \rightarrow \pi^*$ transitions and the low-lying $n \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ excitations, were used.

The electric and magnetic transition dipole moments were evaluated with the atomic Slater functions, including all the one- and two-centre integrals. Accordingly, the CNDO/S molecular orbital coefficients were »renormalized« in order to take into account the overlap of the basic functions.[29] The electric transition dipole moments, as well as the rotational strengths, were evaluated in the dipole velocity formalism.[30] Some details of the computational procedure can be found in the paper of Gould and Hoffman.[31] The program we used was adapted by P. Maloň.[32]

The CNDO/S calculations served first to evaluate the rotational strengths due to the inherent chirality of the two separate chromophores (»one-electron mechanism«[19]). Secondly, the calculated electric transition dipole moment components of the two chromophores were used for evaluating the contribution of the »coupled oscillator mechanism«.[22,33,34]

The final rotational strengths were obtained by summing up the one-electron and the coupled oscillator contributions.

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SAŽETAK

Kiroptička svojstva i konformacija 4,5-zasićenih derivata 5-aril-1,4-benzodiazepin-2-ona

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Studirani su CD spektri niza derivata 5-aril-7-kloro-1,3,4,5-tetrahidro-2*H*-1,4-benzodiazepin-2-ona s različitim supstituentima u položajima 1,3,4, i 5. Apsolutna konfiguracija C-5 u dva homokiralna analoga, *1* i *2*, s enantiomorfnim konformacijama prstena, određena je na temelju kiroptičkih korelacija i teorijskih računa. Ovi posljednji pokazali su da optička aktivnost potječe pretežno od jednoelektronskog mehanizma i određena je helicitetom diazepinskog prstena, tj. inherentnom

kiralnošću particajlnog kromofora 4-kloro-*N*,2-dimetil-formanilida. Ekscitonska interakcija između prijelaza za dva aromatska kromofora A i C također znatno pridonosi kiroptičkim svojstvima. Primjenom jednostavnih kiroptičkih pravila, izvedenih iz eksperimentalnih spektara i potvrđenih računima, može se odrediti stereokemija (apsolutna konformacija i konfiguracija) 3,5-disupstituiranih *cis*- i *trans*-epimernih parova *(7—17)*.