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Unexpected Behavior of the Retinylidene Chromophore in the Exciton Interaction of Chiral 1,2-Cyclohexanediamine Schiff Bases

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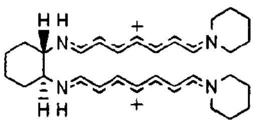
Abstract: The bis-chromophoric Schiff Bases derived from (1*R*,2*R*)-(-)-*trans*-1,2-cyclohexanediamine and two conjugated polyenes, 2,4-hexadienal and all-trans-retinal, show opposite exciton coupling patterns in the CD - without any apparent reason.

The exciton chirality method has become a valuable tool in stereochemistry for the assignment of the absolute configuration and conformation of organic compounds. The idea behind this method is simple: electronically excited states of formally isolated chromophores which are part of a chiral molecule or have been attached to it *via* suitable functional groups may interact leading to exciton states that are delocalized over the chromophores. Spectroscopically exciton states are revealed by the appearance of new bands and intensity shifts in the UV and the appearance of bisignate exciton bands in the CD. Signs and magnitudes of CD exciton bands are correlated with the relative orientation of the chromophores in space according to well-established rules.[1] With chromophores whose excitations are sufficiently separated from the rest of the molecule the results are reliable provided the possible orientations of the chromophores with respect to the molecule can be worked out. However, the method can lead to misleading results when this provision is not met which we intend to show in this communication.

In a recent paper[2] Nakanishi, Harada *et al.* applied the exciton chirality method to the biscyanine dye obtained from chiral (1*S*,2*S*)-(+)-*trans*-cyclohexanediamine and 7-piperidinohepta-2,4,6-trienal, **1**. The negative exciton coupling observed in the CD spectrum of **1** was shown to be consistent with a conformation in which the orientation of the C=N double bonds of the two all-*E*-configurated chromophores is eclipsed with respect to the α-hydrogens of the bis-equatorially substituted cyclohexane in its chair form.



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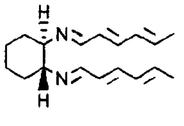

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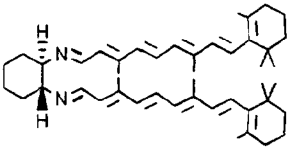

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These results are in accord with our findings on the analogous compound **2**, in which the long cyanine-type chromophore has been replaced by a short triene system. The CD-spectrum of **2** in i-pentane (Fig.1, left) shows two exciton bands, one at 275, the other at 250 nm (room temperature). The positive sign of the former and the negative sign of the latter band are indicative of a p-helical relationship between the two chromophores. Lowering the temperature results in an increase of the amplitudes of both bands by about 30 % and a bathochromic shift of 20 nm; this shift is observed likewise in the UV-spectra of **2** (not shown).

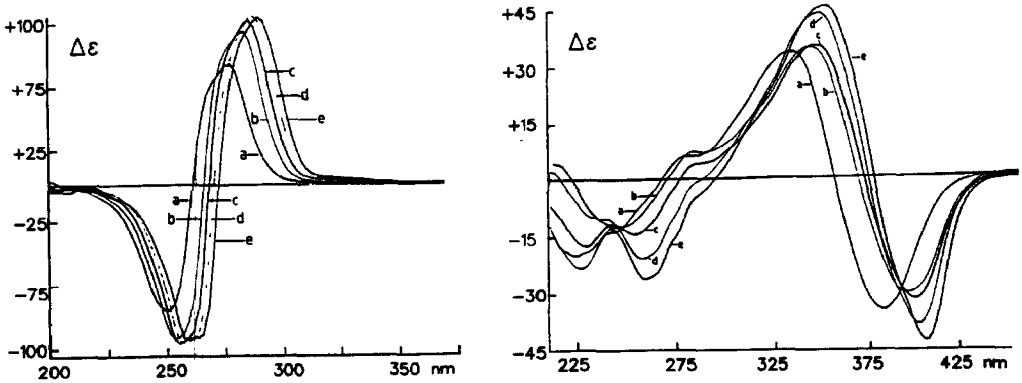

Fig. 1. Temperature dependent CD-spectra of **2** (left, 2·10^{-4} M) and **3** (right, 3·10^{-4} M) in i-pentane. Temperatures are 293 (a), 233 (b), 193 (c), 153 (d), and 113 K (e)

The CD spectra of Schiff base **3** prepared in the same manner as **2**[3] exhibit an almost mirror-image shape in the low-energy region of the spectra (Fig. 1, right), the order of signs being minus/plus coming from the low-energy end of the spectrum. The extrema of the exciton couplet at 335 and 380 nm correlate with the maximum at 342 nm and a shoulder at 370 nm in the UV. The bathochromic shift at lower temperature is a well-known effect and probably a consequence of changing solute-solvent interaction. The amplitudes of the two exciton states are less than half of those found in **2**. The CD-absorptions in the region between 200 and 280 nm are due to interactions between higher excited states of the retinylidene chromophore; their changes are possibly an indication of dynamic processes which are manifest also in the intensity changes of the long wavelength couplet.

These spectra are reproduced in other solvents such as methanol/ethanol with only minor differences. Also, the doubly protonated species of both **2** and **3** show the same peculiarity, namely a close to mirror-image structure of the main exciton couplet.

To study the possible reasons responsible for this behavior we have performed quantum-mechanical calculations on these systems starting with the short-chain compound **2**. Assuming a stable chair-conformation for the cyclohexane ring and an all-*E* configuration of the two carbon carbon double bonds leaves the C=N double bond as the only source for major conformational flexibility. We have optimized **2** with the semi-empirical PM3 method[4] with the only restriction that C_2 symmetry be retained, and find four stable structures, corresponding to the E/Z isomers about the C=N bond and the eclipsed/anti orientations of this bond with respect to the α-hydrogen of the cyclohexane ring. While the calculations favor the *Z*/eclipsed form, the energy differences are so small (less than 2.4 kcal/mol between the most and the least stable form) that none can be ruled out for energy reasons alone. However, for only two of the four are the calculated signs of the CD-couplet in agreement with the CD-spectrum, namely the C-H eclipsed *E*- and *Z*-isomers; [5] only in one of these two, *viz.* the former, is the high-energy exciton state of higher intensity than the lower, in agreement with experimental UV-intensities. This conformation which is depicted in Fig. 2, left, corresponds closely to the minimum energy structure obtained by Nakanishi *et al.* for **1**.

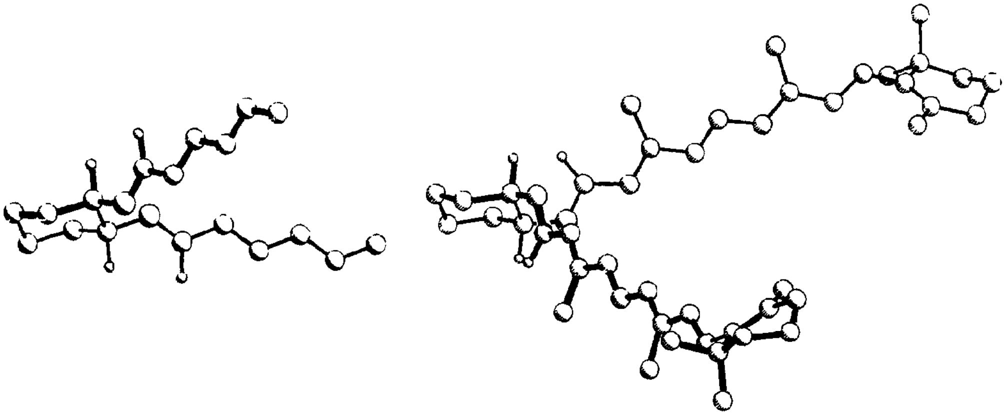

Fig. 2 Plot of the minimum energy conformations of **2** (left) and **3** (right) that correspond most closely to the observed UV- and CD-spectra. For **2**, the conformation about the two C=N-bonds is *E*/eclipsed, for **3** it is *E*/anti. The projections visualize the approximately enantiomeric relationship betwen the two chromophore pairs.

The same four minima that were found for **2** are obtained for **3**; obviously the methyl groups at C13 of the retinylidene chromophores do not interfere with each other, and neither do the terminal cyclohexenyl rings. Calculated spectral data depend somewhat on the twist of these rings with respect to the chromophore plane, but never so much as to change the signs of the exciton couplet. As for **2** we find p-chirality for the C-H eclipsed conformations and m-chirality for the C-H anti conformations. Considering the CD-spectra we have to conclude that **3** prefers the latter conformation over the former - in contrast to **2**! In one of the two anti-conformations (*viz. Z*) the relative orientation of the two chromophores is almost antiparallel, which leads to a low-energy excited state with a very high oscilator strength. In the other (*E*) both excited states share the intensity, in accord with the UV-spectrum. This structure is depicted in Fig. 3 (right).

The relative energies calculated for **3** correspond closely to the values obtained for **2**, which is not surprising considering the similarity of the structures. Thus, *Z* is found more stable than *E*, and eclipsed more stable than anti. This is not the information coming from the experiment which appears to favor *E*; also, there is no evidence from the calculations why **3** should prefer a different conformation than **2**. We have to conclude that the theoretical method we used is not adequate for the description of Schiff bases like the ones of our study.

With respect to the reasons for this apparent failure of the theory we can only speculate. One kcal which is approximately the calculated energy difference between the eclipsed and the anti forms is easily overcome by solvent effects, and this would cause, as we have shown, the chromophore chirality to change from positive to negative. This does not explain, however, why the question of solvent should be invoked for **3** but not for **2** (nor for **1**). Also, the small amplitudes in the CD-spectrum of **3** compared to **2** are not accounted for by the calculations according to which the exciton states should have more, not less rotatory strengths, as a consequence of the more extended chromophores.

The preference of PM3 for the (wrong) *Z*-form is found likewise when AM1 is employed, a semi-empirical method similar to PM3. This is in contrast to high-quality *ab initio* calculations, [6] which correctly predict the *E* form of 2-propene-1-imine, $CH_2=CH_2-CH=NH$, to be more stable than *Z*, in agreement with microwave spectroscopic data. [7]

Due to the scarcity of experimental data imines and protonated imines have not been used extensively in the development of parameters for AM1 and PM3, with the consequence that systems containing the C=N double bond are not described satisfactorily by these methods. Force-field methods suffer from the same deficiency, a problem that has been taken up recently [8] in a paper that describes the development of parameters for MM2 using *ab initio* results. In view of the importance of imines in bio-organic systems such as rhodopsin or bacteriorhodopsin a similar project seems worthwhile with respect to semi-empirical methods.

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