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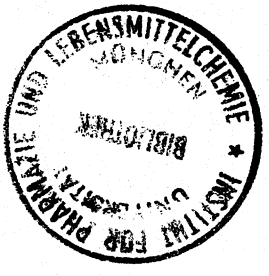

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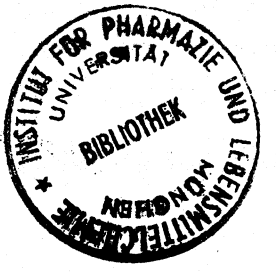

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Original Communications

Solvent Induced Circular Dichroism in Conformational Analysis: Bile Pigments

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Solvent Induced Circular Dichroism, Conformation, Enantiomerization, Purpurines, Bilatrienes

The applicability of solvent induced circular dichroism (SICD) for the conformational analysis of bile pigments has been investigated. The S-(—)-ethyl lactate induced rotational strengths for octaethylbilindion (**4**) and its dihydroderivative **5** are remarkably high. Related compounds, *e.g.* the isomeric purpurines **1** and **2** and formyltripyrrinon **3** exhibit an optical activity which is smaller by more than one order of magnitude. **1–3** are essentially free from steric strain so that a flat arrangement of the chromophore is most likely. On the other hand the closed conformations of **4** and **5** experience considerable steric repulsion of their terminal rings, so that a helical topology is energetically favoured. This distinction is reflected in the magnitude of the SICD observed and demonstrates its applicability for the conformational analysis of bile pigments.

Introduction

Recently it has been shown that SICD of bile pigments can be useful in their conformational analysis. Thus, for all-Z-all-syn biliverdindimethylester (**6**) and the XIIIα isomer, for which a helical conformation has been established by various methods [1–5], a remarkably large $\Delta\varepsilon$-value is observed in S-(—)-ethyl lactate [3, 5], while for an E,Z,Z isomer [6] no SICD could be observed under the same conditions. Hence, SICD seems an attractive method in conformational analysis. In this report more direct evidence is given for this empirical approach. It will be shown, that under appropriate conditions this method is useful for bile pigments in general.

Materials and Methods

Compounds **1–3** [7], **4** and **5** [8] and **6** [3] were prepared according to the literature. CD spectra were recorded on a Jobin Yvon Mark III instrument in thermostated ($\pm 1°$) quartz cuvettes of variable path length (0,01–2,0 cm) and $c = 10^{-4}$–10^{-5} M. Absorption spectra were measured on a Cary 15 spectrometer in 0,5 cm quartz cuvettes at ambient temperature. (S-(—)-ethyl lactate ($[\alpha]_D^{20} = -11{,}1°$, neat) was purchased from Fluka and distilled twice over a Vigreux column prior to use.

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Results and Discussion

Since the magnitude of the SICD observables is dependent on the inducibility of the optically active solvent employed [5], measurements routinely were performed in S-(—)-ethyl lactate at 20 °C. The SICD effects exhibited by the pigments **1–6** in the spectral region 300–800 nm are outlined in Table I.

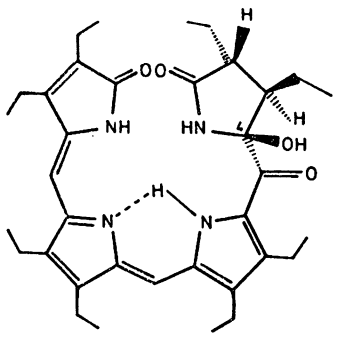
The induced optical activities of the purpurines **1** and **2** as well as that of the formyltripyrrinon **3** are exceedingly small, while the data obtained for all-Z-octaethylbilindion **4** closely resemble those of all-Z-all-syn-biliverdin-IXα-dimethylester (**6**) exhibiting an induced optical activity of $\Delta\varepsilon = +5{,}9$ and $-2{,}9$ at 377 and 680 nm, respectively [5]. Likewise, the ellipticities observed for the dihydroderivative **5** (*cf.* Table I) are similar to the values reported for the structurally related racem. phytochromobilindimethylester [9]. These results are in agreement with geometric considerations. There is one striking difference between the two groups of compounds **1–3** and **4–6**, respectively. In the compounds **1** and **2** a planar structure of the chromophore is readily accessible due to a lack of steric hindrance between rings A and D. In contrast to the situation in bilatrienes the fourth ring A of the purpurines has virtually no influence on the conformation of the connected chromophore consisting of rings B, C, D. Similar arguments hold for **3**, as its molecular skeleton involves only three pyrrolic units. A planar,

Table I. $\Delta\varepsilon_{max}$-values [M^{-1} cm^{-1}] of the bile pigments **1–6** in S-(—)-ethyl lactate at 20 °C determined at the wavelength λ ([nm]).

1	2	3	4	5[a]	6[b]
+ 0,2 (550)	— 0,2 (540)	— 0,2 (510)	— 3,4 (667)	— 5,2 (610)	— 2,9 (675)
— 0,2 (500)			+ 6,9 (366)	+ 8,7 (348)	+ 5,9 (378)

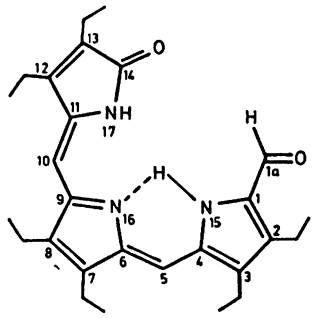
[a] The corresponding data for the two synthetic isomeric phytochromobilin-dimethylesters are reported to be + 5,1 (372) and — 2,6 (610) and + 3,5 (375) and — 2,2 (610), respectively [9]. (The values at 610 nm do not represent the maximum of the long wavelength band but the edge of the recorded wavelength range.)
[b] Values taken from ref. [5]; for the temperature dependence *cf.* Fig. 1.

closed conformation has been suggested for **3** in solution [10] and has been determined in the crystal state of an analogue [11]. By contrast, the non-bonded-interactions between the peripheral rings force all-Z-all-syn-biliverdindimethylester (**6**) and related compounds such as **4** and **5** into a helical arrangement. **4–6** can flip between two enantiomeric sets of conformations, which are both inherently chiral and separated by an activation barrier of approx. 42 kJ/mol [12].



1

2 : C-4-epimer



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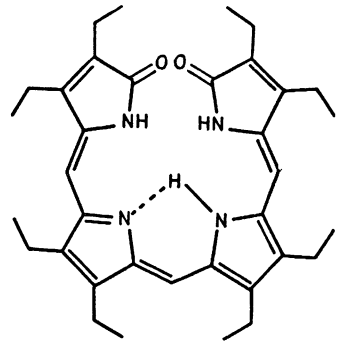

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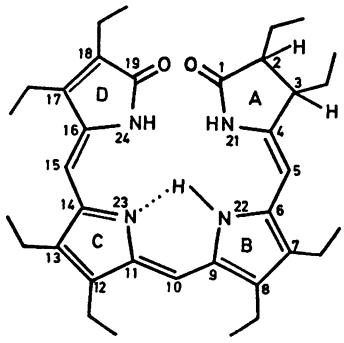

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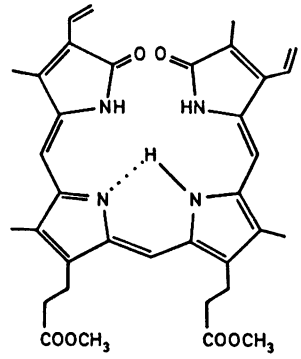

6

The finding of a large SICD in the twisted species of **4**–**6** is reminiscent of the effects observed in natural optical activity: the rotational strengths of inherently chiral chromophores are generally larger than the pertinent values for chirally perturbed symmetrical chromophores [13, 14].

Hence, the large SICD of **4**–**6** as compared to **1**–**3** is rationalized by the induction of an excess population of one enantiomeric helix, which originates from diastereomeric interactions of the optically active solvent with easily interconverting antipodal conformations of the solute. Therefore the equilibrium constant between P- and M-helices is no longer unity, but is shifted to the one or other side, so that one enantiomeric, inherently chiral species predominates. Thus, this process represents an asymmetric transformation of the first kind or enantiomerization [15]. A similar mechanism has been suggested for the intense CD in bilirubin and biliverdin induced by binding to serum albumen [16, 17].

Of course, the amount of the excess population in a given optically active solvent is not known, and it is even probable that the solute involves an ensemble of different diastereomeric conformations. In other words, although a large induced ellipticity as compared to a related non-helical molecule is indicative of a considerable amount of twisted conformers in the sample, it is by no means a proof for conformational homogeneity. For **6** *e.g.* it has been shown by fluorescence spectroscopy that its solvatochromic and thermochromic properties are due to different populations of coiled and stretched conformers [5]. Accordingly, on lowering the temperature the amount of the coiled species of **6** should increase. In fact, the SICD of **6** in ethyl lactate exhibits an extraordinarily strong temperature dependence with respect to the intensity, whereas the position and shape of the band remains unchanged (*cf.* Fig. 1). The increase of the effect on lowering the temperature reflects a shift of the conformational equilibrium to helical species, which exhibit a much larger contribution to the SICD observed than other conformers. The dependence of an induced CD on the conformation of the substrate has further been supported by incubation of **6** in liposomes of optically active lecithines [18]. In this matrix **6** exhibits chronochromic properties, which are due to a conformational transition [19].

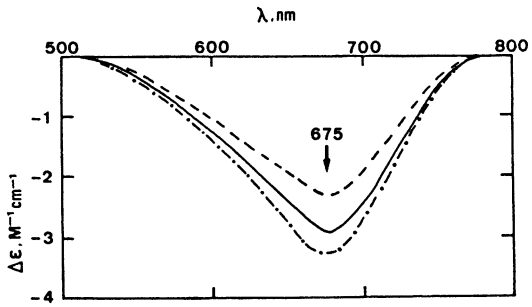

Fig. 1. SICD in the VIS absorption region of **6** in S-(—)-ethyl lactate (10^{-4} M) at 35 °C (– – – –), 20 °C (————), and 9 °C (–·–·–). The temperature-dependence observed is fully reversible.

On the basis of these considerations the small SICD of **1**–**3** is not surprising. The arguments given above explain as well the negligible SICD of E,Z,Z-biliverdin [6], in which the steric repulsion between the peripheral rings is removed and of a biliverdin bridged between N-21 and N-24, in which the ready interconversion between enantiomeric helices is hindered at ambient temperature [20].

Concluding Remarks

In order to identify twisted chromophore conformations by means of SICD the induced rotational strength of a related molecule with a similar chromophore of established conformation should be known. A chromophore independent criterion based on the anisotropy factor (*g*), which has been fruitfully applied in natural optical activity [14], cannot be given.

Although the electronic transitions stemming from helical conformations of **4**–**6** and other bilatrienes should be electrically and magnetically allowed the condition $g \approx 10^{-2}$ [14] will scarcely be met. Even in the case of conformational homogeneity the enantiomeric excess population – the analogue of "enantiomeric purity" in natural optical activity – will not necessarily reach unity. Its value is not known for any given case, and it additionally changes with the optically active solvent employed.

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