Tetrahedron Vol. 48, No. 38, pp. 8189-8198, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

CHIRAL RECOGNITION BY SULFOXIDES. INDUCED CIRCULAR DICHROISM FROM SYMMETRIC MESOBILIRUBIN ANALOGS

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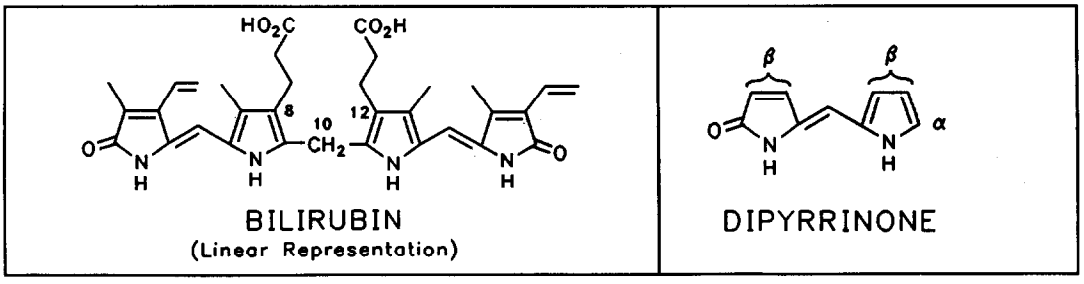
(*Received in USA* 19 *May* 1992)

Abstract: Symmetric analogs of mesobilirubin-XIIIα, with propionic acid groups shortened and lengthened, exhibit induced circular dichroism (ICD) in CH_2Cl_2 solvent with excess *S*-(-)-methyl-*p*-tolylsulfoxide. The dimethyl esters of mesobilirubins with acetic, propionic, butyric, valeric and caproic acid chains at C-8 and C-12 all give essentially the same bisignate ICD, with $\Delta\epsilon^{max}_{420} \simeq +13$, $\Delta\epsilon^{max}_{376} \simeq -10$. However, the bisignate ICD of the free acids varies from $\Delta\epsilon^{max}_{436} = -11$, $\Delta\epsilon^{max}_{393} = +6$ to $\Delta\epsilon^{max}_{425} = +14$, $\Delta\epsilon^{max}_{379} = -11$ according to the length of the alkanoic acid chains.

Bilirubin, the cytotoxic yellow pigment of jaundice, is composed of two dipyrrinone chromophores linked at their α-carbons by a $-CH_2-$ group. The ring β-positions of each dipyrrinone are substituted by vinyl, methyl and propionic acid groups. By varying the order of the β-substituents, a large array of bilirubin analogs becomes possible, although only one (bilirubin itself) is the major pigment produced and eliminated in mammals (at the rate of ~300 mg/day/individual — from the breakdown of $\sim 10^{11}$ red blood cells per day).[1-3] Only the location of the propionic acid groups has a profound influence on the spectroscopic, solution and metabolic properties of bilirubin.[1,4] When the propionic acid groups are moved away from their natural positions of C-8 and C-12, the resulting new pigments are much more polar, much less soluble in solvents such as chloroform or benzene (in which the UV-Vis λ_{max} are blue shifted), more soluble in weak base, and more excretable across the liver into bile.[4,5] On the other hand, when the vinyl groups are reduced to ethyl or replaced by methyl, these properties of the pigment remain relatively unchanged.



The unique role of the propionic acid groups at C-8 and C-12 is stabilization of a molecular conformation where the dipyrrinones are rotated about the C-10 -CH_2- so as to bring the CO_2H and the dipyrrinone pyrrole NH and lactam -NH-C=O groups into sufficiently close proximity for intramolecular hydrogen bonding (Fig. 1A).[6-8] Because the C-10 carbon is tetrahedrally hybridized, the molecule is bent across the middle to form two enantiomeric conformers shaped like ridge tiles[9a] (Fig. 1B). Equal numbers of the enantiomeric ridge-tile structures have been found in crystals of bilirubin and its dicarboxylate salts — to the exclusion of other conformations.[9] In the crystalline state bilirubin molecules can stretch and vibrate but are otherwise restrained. However, when dissolved in organic solvents, bilirubin is potentially more flexible. It might be expected to exhibit more conformational freedom, and it might form hydrogen bonds with solvent molecules, other bilirubin molecules, or intramolecularly as it does in the crystal.[10,11] Despite a multitude of conformational possibilities, it now seems clear that intramolecularly hydrogen-bonded structures like those of Figure 1 prevail in non-polar solvents such as chloroform, in polar solvents such as acetone and ethanol, and even in water at high pH (where bilirubin is present as the dicarboxylate dianion).[12]

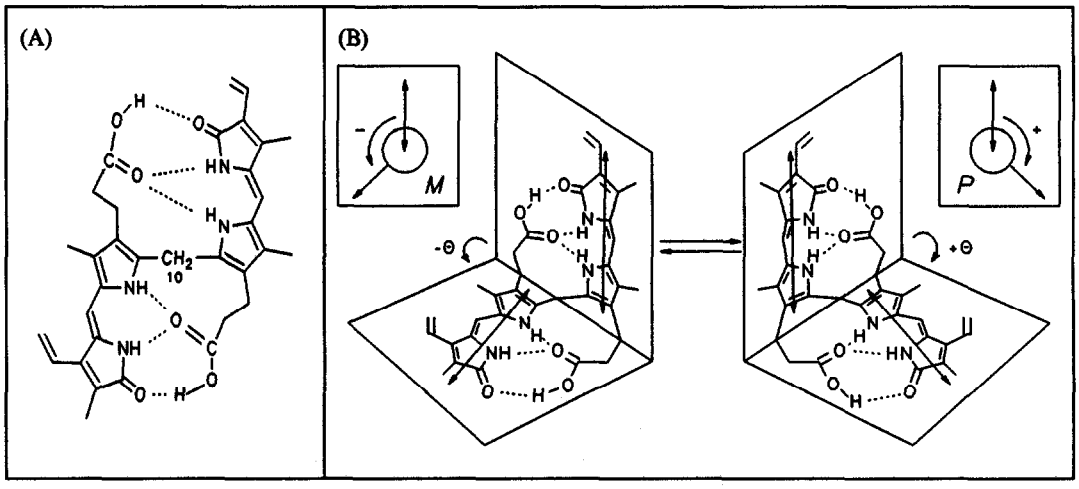


FIGURE 1. (A) Planar representation of bilirubin with dipyrrinone groups rotated about C-10 so as to enable effective intramolecular hydrogen bonding between the propionic acid CO_2H groups and the pyrrole NH and lactam -NH-C=O groups. (B) Interconverting intramolecularly hydrogen-bonded enantiomeric conformers of bilirubin-IXα. The double headed arrows represent the dipyrrinone long wavelength electric transition moment vectors (dipoles) associated with the UV-Visible spectrum of the pigment. The relative helicities (*M*, minus or *P*, plus) of the vectors are shown (inset) for each enantiomer Theta (θ) is the fold angle or the dihedral angle at the intersection of the planes containing each of the two dipyrrinones.

In contrast, dimethylsulfoxide, a polar solvent in which bilirubin has its highest known solubility, appears to be uniquely able to compete effectively with the -CO_2H groups for hydrogen bonding to dipyrrinones.[9,13] The change in hydrogen bonded partners, from that of Figure 2(A) to that of Figure 2(B), would appear to break the ties which stabilize the ridge-tile conformation, thereby allowing a multiplicity of new conformations. Resonance Raman spectroscopy indicates that the bilirubin conformation differs in chloroform and dimethylsulfoxide,[14] and a detailed analysis of ^{13}C-NMR spin lattice relaxation times of bilirubin in dimethylsulfoxide indicates that the propionic acid chains are immobilized by internal hydrogen bonds involving solvent participation.[13] However, the conformation of pigment remains unclear.

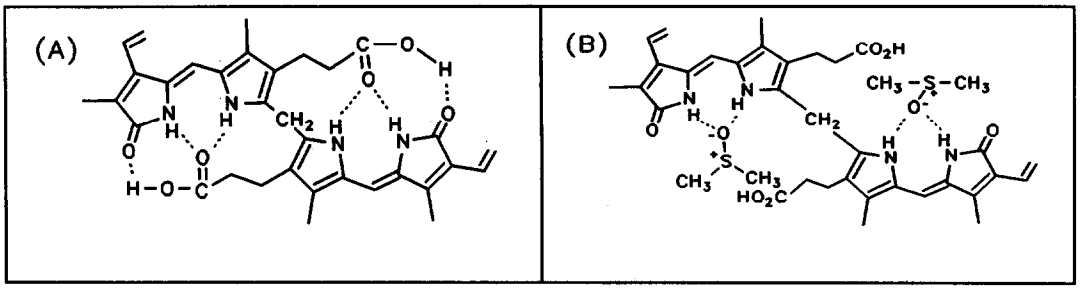
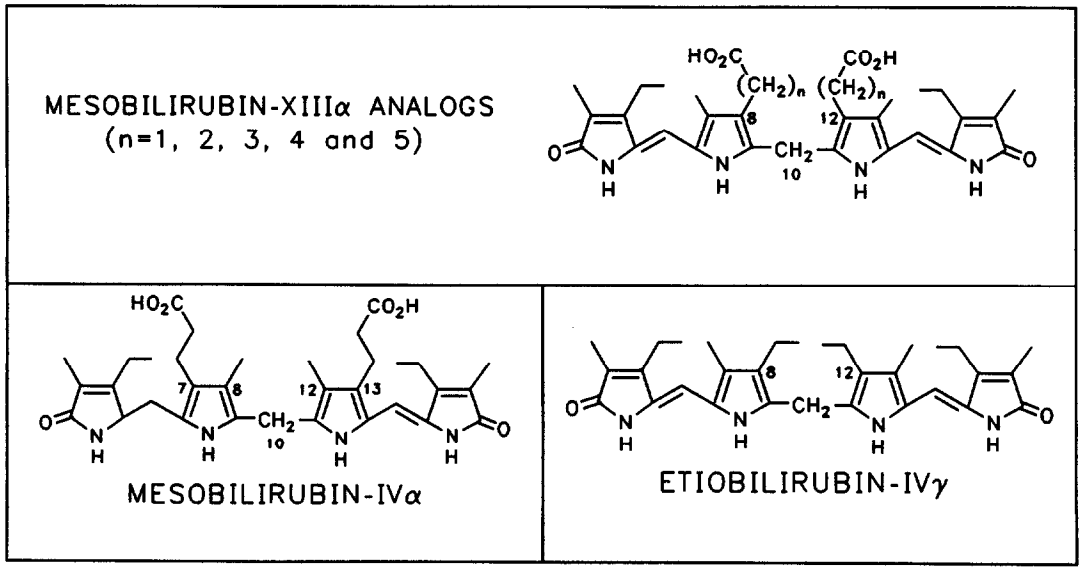


FIGURE 2. (A) Intramolecularly hydrogen-bonded bilirubin and (B) bilirubin intermolecularly hydrogen-bonded to dimethylsulfoxide.

Recently, we showed that bilirubin exhibits optical activity, as seen from induced circular dichroism (ICD), in optically active ethylmethylsulfoxide solvent or in dichloromethane solvent in the presence of a large excess of other optically active sulfoxides, such as methyl-*p*-tolylsulfoxide, benzylmethylsulfoxide and methyl-*n*-butylsulfoxide.[15] In the present work we examine the role of acid and ester residues at C-8 and C-12 in chiral recognition with *S*-(-) and *R*-(+)-methyl-*p*-tolylsulfoxide by measuring the ICDs of a series of symmetric mesobilirubin-XIIIα analogs with alkanoic acid chains varying in length from two to six carbons, as well as mesobilirubin-IVα, which has its propionic acid groups located at C-7 and C-13, and etiobilirubin-IVγ, a decarboxylated analog of (n=2) mesobilirubin-XIIIα. The work is important because it shows that propionic acid groups at C-8 and C-12 have a unique ability to determine the conformation of the pigment-sulfoxide complex.



EXPERIMENTAL

All circular dichroism spectra were recorded on a JASCO J-600 spectropolarimeter, and all UV-visible spectra were run on a Cary 219 spectrophotometer. The (n=1 to 5) mesobilirubin-XIIIα pigments reported in this work were prepared by total synthesis as described earlier.[16] Mesobilirubin-IVα and etiobilirubin-IVγ were also prepared by total synthesis.[5] *S*-(-)-Methyl-*p*-tolylsulfoxide, mp 76-77°C, $[\alpha]_D^{25}$ -145.7° (*c* 2.0, acetone), and *R*-(+)-methyl-*p*-tolylsulfoxide, mp 76-77°C, $[\alpha]_D^{25}$ +141.1° (*c* 2.1, acetone) were prepared by reaction of (+)-(1*S*)-menthyl (*R*)-toluene-4-sulfinate (Aldrich, $[\alpha]_D^{20}$ + 200° (*c* 2, acetone)) and (-)-(1*R*)-menthyl (*S*)-toluene-4-sulfinate (Aldrich, $[\alpha]_D^{20}$ - 195° (*c* 2, acetone)) respectively with methyl magnesium bromide, as described earlier.[17] The organic solvents used were spectral grade (Fisher).

RESULTS AND DISCUSSION

That sulfoxides can act as chiral recognition agents may be seen (Fig. 3) from the induced circular dichroism (ICD) when *S*-(-)-methyl-*p*-tolylsulfoxide is added in a large molar excess to a solution of (n=2) mesobilirubin-XIIIα in CH_2Cl_2 solvent. The ICD intensity reaches a maximum at a sulfoxide:pigment mole ratio of ~7000:1, and the characteristic bisignate shape of the ICD curve is due to exciton splitting of the pigment's long wavelength UV-Vis absorption band near 430 nm. As expected, addition of *R*-(+)-methyl-*p*-tolylsulfoxide gives a mirror image ICD. However, when the pigment is esterified as its dimethyl ester, or when the carboxyl groups are removed, as in etiobilirubin-IVγ, or when the propionic acid groups are transposed with the adjacent methyl groups, as in mesobilirubin-IVα, the ICD Cotton effect signs also become inverted (Fig. 4). It would seem, therefore, that the location and presence of CO_2H groups plays an important sign-determining role in the ICD of these pigments — implying a special involvement of the C-8 and C-12 propionic acid groups in selecting the chirality of the conformation. But does this behavior persist for other alkanoic acids at C-8 and C-12?

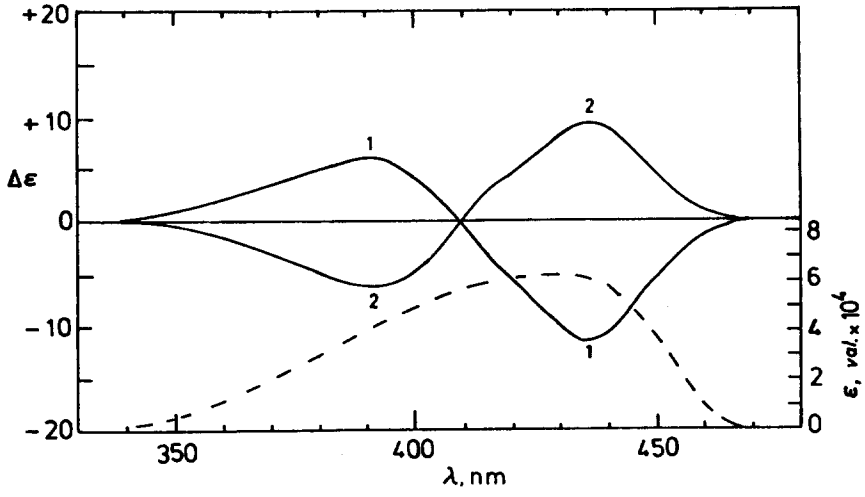


FIGURE 3. Induced circular dichroism (——) and UV-Vis spectra (— — —) for 2.4 x 10^{-4} *M* (n=2) mesobilirubin in CH_2Cl_2 with 2 *M* *S*-(-)-methyl-*p*-tolylsulfoxide (1) and *R*-(+)-methyl-*p*-tolylsulfoxide (2) at 22°C. The $\Delta\epsilon$=0 line is from the CD spectra in the presence of racemic sulfoxide.

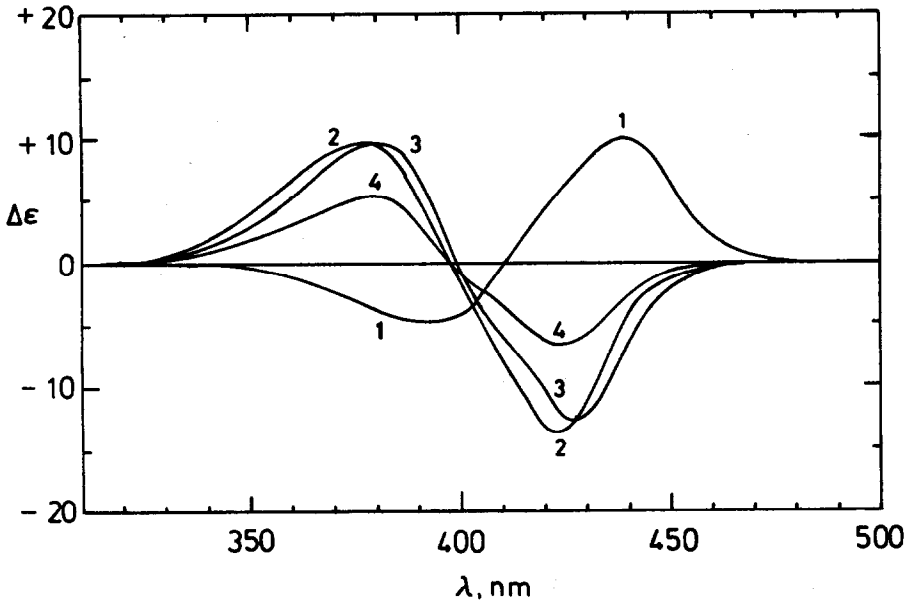


FIGURE 4. Induced circular dichroism of 2.1-2.4 x10^{-4} *M* (n=2) mesobilirubin (1), its dimethyl ester (2), etiobilirubin-IVγ (3) and mesobilirubin-IVα (4) in CH_2Cl_2 with 2 *M* *R*-(+)-methyl-*p*-tolylsulfoxide at 21°C. The $\Delta\epsilon$=0 line is from the CD spectra run in the presence of racemic sulfoxide.

TABLE 1. Induced Circular Dichroism and UV-Vis Spectral Data[a] for the Dimethyl Esters of (n=1) to (n=5) Mesobilirubins-XIIIα in the Presence of 2 *M* *S*-(-)-Methyl-*p*-tolylsulfoxide at 22°C in CH_2Cl_2 Solvent (A) and 15% CH_3OH -85% CH_2Cl_2 Solvent (B).[b]

Pigment[c]	(A) CD		(A) UV-Vis	(B) CD		(B) UV-Vis
	$\Delta\epsilon^{max}$ (λ)	λ at $\Delta\epsilon$=0	ϵ^{max} (λ)	ϵ^{max} (λ)	λ at $\Delta\epsilon$=0	ϵ^{max} (λ)
(n=1)	+11.0 (419) - 8.1 (378)	392	55,400 (412) 52,900 (390)^{sh}	+3.1 (426) - 2.7 (386)	405	56,200 (412) 52,400 (390)^{sh}
(n=2)	+14.5 (423) -16.3 (379)	397	40,900 (420)^{sh} 47,200 (384)	+ 8.9 (424) -10.2 (378)	399	44,900 (424) 42,400 (391)^{sh}
(n=3)	+14.2 (423) -11.2 (377)	395	34,800 (420)^{sh} 48,600 (385)	+10.1 (424) - 7.7 (378)	397	37,800 (420)^{sh} 42,000 (390)
(n=4)	+15.8 (425) -11.6 (379)	396	34,000 (425)^{sh} 40,800 (387)	+10.4 (426) - 8.0 (379)	397	36,400 (425)^{sh} 36,800 (390)
(n=5)	+17.0 (425) -13.0 (381)	396	40,800 (425)^{sh} 49,400 (387)	+10.7 (428) - 8.1 (379)	398	43,200 (430) 42,300 (392)^{sh}

[a] $\Delta\epsilon$ and ϵ in M^{-1} cm^{-1}; λ in nm; [b] vol/vol; [c] 2.4-2.8 x 10^{-4} *M* pigment.

As reference data, the ICD spectral data of the dimethyl esters of the (n=1) to (n=5) mesobilirubins are given in Table 1. It may be noted that in CH_2Cl_2 solvent the signed order of the ICD Cotton effects remains invariant, and the magnitudes are essentially the same for the entire set of alkanoic esters, ranging from acetate to caproate. The long wavelength UV-Vis band is also split by exciton coupling,[7,8,12,18,19] although the splitting is much more noticeable in the ICD spectra. Dilution with CH_3OH, which can participate in hydrogen bonding to both the pigment and the sulfoxide and might therefore disrupt or otherwise interact with the chiral pigment-sulfoxide complex, causes the ICD magnitudes to drop somewhat. The largest drop is found for the (n=1) pigment, with the decrease in magnitude being only about 30% in the (n=2) to (n=5) mesobilirubins. Thus, in 15% CH_3OH-85% CH_2Cl_2 solvent all of these pigments, except (n=1), exhibit nearly identical ICDs. On the basis of the data of Table 1, it would appear that the CO_2CH_3 groups play little or no role in stabilizing a pigment-sulfoxide complex, which favors a conformation where the orientation of the transition moment electric dipole vectors associated with the ~400 nm absorption are oriented in a *P*-chirality.[7,8,12,18,19] This conformation could have a folded shape (as in Fig. 1), but there is little evidence to bear on the exact shape of the pigment in the complex, except possibly from the UV-Vis spectral data.

As the folded conformation of Figure 1 closes (in book-like fashion)[20] toward the porphyrin shape (Fig. 5), the intensity of the *long wavelength* UV-Vis exciton component can be expected to decrease toward zero, leaving a more symmetric, blue-shifted band.[7,8,21] Alternatively, as the folded conformation opens toward the linear (extended) shape, the intensity of *short wavelength* UV-Vis exciton component should decrease toward zero, leaving a more symmetric, red-shifted band. Since we see both exciton components in the UV-Vis spectra of Table 1, and both are of comparable intensity, the angle between the two transition dipole moments should be ~90°,[18] and the pigment conformation is probably not very different from that represented in Figure 1.

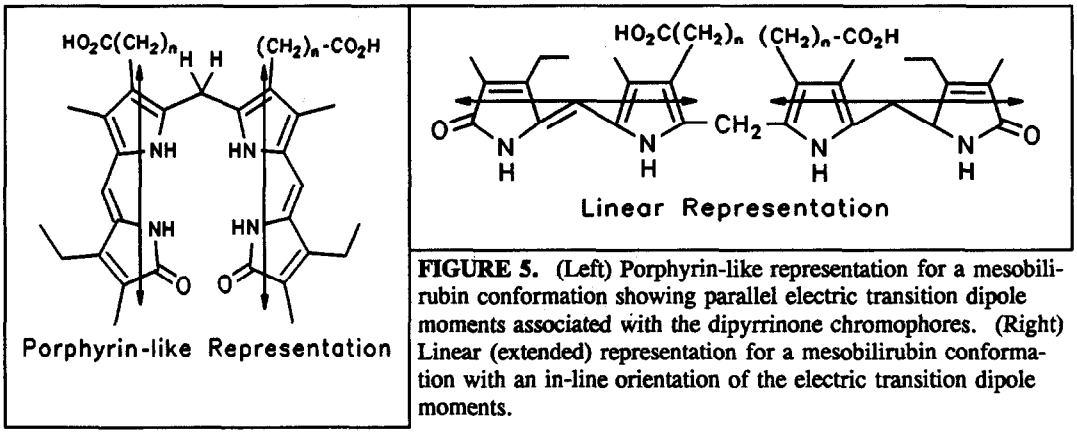


FIGURE 5. (Left) Porphyrin-like representation for a mesobilirubin conformation showing parallel electric transition dipole moments associated with the dipyrrinone chromophores. (Right) Linear (extended) representation for a mesobilirubin conformation with an in-line orientation of the electric transition dipole moments.

TABLE 2. Induced Circular Dichroism and UV-Vis Spectral Data[a] for (n=1) to (n=5) Mesobilirubins-XIIIα in the Presence of 2 *M* *S*-(-)-Methyl-*p*-tolylsulfoxide at 21°C in CH_2Cl_2 Solvent (A) and 15% CH_3OH -85% CH_2Cl_2 Solvent (B).[b]

Pigment[c]	(A) CD		(A) UV-vis	(B) CD		(B) UV-Vis
	$\Delta\epsilon^{max}$ (λ)	λ ($\Delta\epsilon$=0)	ϵ^{max} (λ)	ϵ^{max} (λ)	λ (Δ=0)	ϵ^{max} (λ)
(n=1)	+ 6.2 (418) - 3.2 (379)	390	41,900 (415) 37,900 (390)^{sh}	- 8.9 (424)[d] + 5.0 (373)[d]	397[d]	45,000 (421) 39,600 (400)^{sh}
(n=2)	-11.4 (436) + 6.1 (393)	408	63,000 (433)	-12.0 (437) + 7.0 (390)	409	58,500 (432)
(n=3)[e]	+ 1.6 (424) - 1.7 (378)	396	54,000 (440)	+ 2.2 (422) - 2.3 (380)	403	48,700 (438)
(n=4)	+16.0 (425) -13.5 (379)	399	44,500 (420)^{sh} 50,400 (390)	+10.3 (428) - 9.7 (381)	401	45,400 (424)^{sh} 46,800 (395)
(n=5)	+14.0 (425) -11.0 (379)	398	42,000 (425)^{sh} 48,000 (390)	+ 8.8 (429) - 8.2 (380)	400	43,800 (428) 43,400 (396)^{sh}

[a] $\Delta\epsilon$ and ϵ in M^{-1} cm^{-1}; λ in nm; [b] vol/vol; [c] 2.1-2.6 x 10^{-4} *M* pigment, except (n=1) 1.1-1.2 x 10^{-4} *M*; [d] In 4% CH_3OH, the values are nearly the same: $\Delta\epsilon^{max}_{423}$ = -7.6, $\Delta\epsilon^{max}_{382}$ = +5.7, $\Delta\epsilon$=0 at λ = 398 nm. [e] In the presence of 8.5 *M* sulfoxide, $\Delta\epsilon^{max}_{420}$ + 18.9, $\Delta\epsilon^{max}_{381}$ - 12.7, $\Delta\epsilon$=0 at λ = 396 in CH_2Cl_2.

The situation is different for the (n=1) to (n=5) mesobilirubins with free carboxylic acid groups, as may be seen from the ICD data of Table 2. Only the spectra of the mesobilirubins with longer alkanoic acid chains (n=4) and (n=5) remain quite similar to those of their dimethyl esters (*cf* Table 1). In marked contrast, the ICD Cotton effects signs are inverted for the (n=2) pigment and substantially reduced for the (n=3) pigment. With an increased ratio of sulfoxide:pigment (~4 times), the Cotton effect magnitudes are increased by an order of magnitude for the (n=3) mesobilirubin, but the data for the other pigments remain essentially unchanged. The data confirm that the presence of a CO_2H at the end of a chain of the right length (3 carbons) can have a profound influence on the ICD spectra and thus the pigment conformation from which they are derived.

We believe that these phenomena can be understood in terms of a model whereby the *S*-(-)-methyl-*p*-tolylsulfoxide enters into intermolecular hydrogen bonding with the dipyrrinone components of the pigments (Fig. 6), thus displacing any intramolecular hydrogen bonding from the CO_2H groups. In this simple picture there would be two diastereomeric complexes derived from the two enantiomeric conformers of Figure 1. The conformational equilibrium is displaced toward one diastereomer (*P*-chirality, when n=1, 3, 4 or 5), although it would have been difficult to predict *a priori* which diastereomer is more stable. As little as a 5% shift from a 50:50 equilibrium could account for the observed ICD.[19] The displaced CO_2H groups might coordinate with excess sulfoxide, but they are apparently unable to coordinate with the sulfoxides engaged in hydrogen bonding to the dipyrrinones. An exception is the (n=2) pigment, where the propionic acid chain length is apparently optimum for hydrogen bonding between the CO_2H and the bound sulfoxide,[13] and the ICD Cotton effects are opposite to those seen when (n=1), (n=3), (n=4) and (n=5). The oppositely signed Cotton effects may be explained as follows. Molecular models show that when the fold angle (θ, Figs. 1 and 6) is opened, the pigment conformation begins to extend (Fig. 5) and the CO_2H groups become able to

hydrogen bond to sulfoxide molecules already engaged in hydrogen bonding to the dipyrrinones (O=C—O—H ··· S^+—O^-). This additional hydrogen bonding interaction presumably involves the carboxyl *hydrogen*, as its attributed effects were not seen in the ICD of the dimethyl esters (*cf* Table 1). Opening the folded conformation causes the relative orientation of the dipyrrinone induced electric transition vectors moments to invert ($|\omega| > 180°$), with the result that the ICD Cotton effect signs become inverted even though the absolute configuration of the pigment remains unchanged ($|\theta| < 180°$).[8] Inversion of helicity of the transition dipoles without an accompanying change in molecular chirality has been reported previously for dipyrrinone esters of cyclohexane-1,2-diols[22] and merocyanine derivatives of 1,2-diaminocyclohexane.[23] Further evidence for a more open conformation in (n=2) mesobilirubin may be found in the UV-Vis spectra: The 433 nm band (n=2, Table 2) is narrower than that of the dimethyl ester (n=2, Table 1) and also red shifted.

When CH_3OH is added to the solutions (Table 2), the ICD magnitudes decline by about the same factor for the (n=4) and (n=5) mesobilirubins as for their dimethyl esters. There is essentially no change for the (n=3) and (n=2) acids, but, surprisingly, Cotton effect signs of the (n=1) acid become inverted, with the pigment now exhibiting an ICD very similar to that of the (n=2) mesobilirubin. The change in ICD of the (n=1) mesobilirubin with added CH_3OH can also be interpreted, as above, in terms of an inversion of helicity of the dipyrrinone electric transition dipoles, with the OH of CH_3OH acting as a bridge between the acetic acid CO_2H and the sulfoxide (O=C—O—H ··· O—H ··· S^+—O^-).

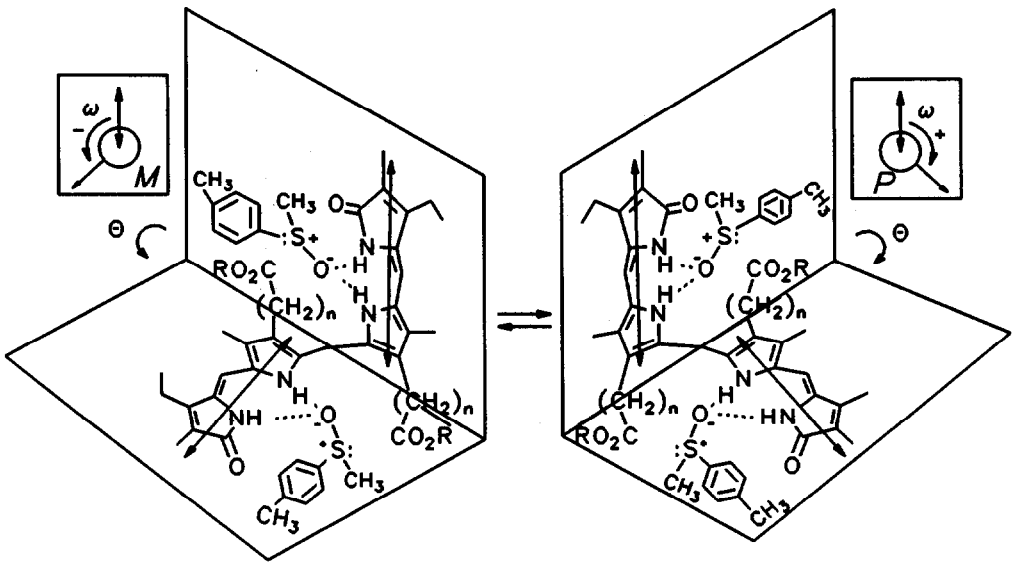


FIGURE 6. Interconverting intramolecularly hydrogen-bonded diastereomeric conformers of (n=1) to (n=5) mesobilirubin-XIIIα acids (R=H) and dimethyl esters ($R=CH_3$). The double headed arrows represent the dipyrrinone long wavelength electric transition moment vectors (dipoles). The relative helicities (*M*, minus or *P*, plus) of the vectors are shown (inset) for each enantiomer.

In the (n=3) mesobilirubin, the very small ICD (compared with its dimethyl ester), would appear to implicate the butyric acid CO_2H group in some residual hydrogen bonding to dipyrrinone-bound sulfoxide where the pigment also adopts a more open folded conformation, one close to (but not past) the cross-over conformation at which the relevant electric transition dipole moments invert their helicity.[7,8] Consistent with this rationale is the observation that the long wavelength UV-Vis absorption band at 440 nm (n=3, Table 2) is narrower than that of the dimethyl ester (n=3, Table 1) and red-shifted, as in (n=2) mesobilirubin.

CONCLUDING COMMENTS

Chiral recognition by optically active methyl-*p*-tolyl-sulfoxide has been demonstrated by CD spectroscopy for a series of symmetric (n=1) to (n=5) mesobilirubin-XIIIα analogs with alkanoic acid and ester groups ranging from acetic to caproic. The induced CD spectra of these pigments is interpreted in terms of sulfoxide effecting a first order asymmetric transformation[24] on a pair of interconverting mesobilirubin conformational enantiomers.[25] Sulfoxides are tethered to the dipyrrinones of the mesobilirubins by hydrogen bonding, which displaces the alkanoic acid CO_2H groups from intramolecular hydrogen bonding. Consequently, the signed order of the ICD Cotton effects is determined more by the absolute configuration of the sulfoxide than by the nature or location of the alkanoic acid groups. In CH_2Cl_2 solvent, *S*-(-)-methyl-*p*-tolyl-sulfoxide induces a *P*-chirality bisignate CD, with $\Delta\epsilon_{max} \simeq +15$, $\Delta\epsilon_{max} \simeq -12$ at λ_{max} near 425 and 380 nm, respectively. For certain chain lengths, and only for CO_2H groups, residual intramolecular hydrogen bonding (we assume from CO_2H to the bound sulfoxide) opens the folded conformation so as to cause an inversion (by propionic acid groups) or major reduction in magnitude (by butyric acid groups) of the Cotton effects. Consistent with earlier observations,[22] the inversion occurs through an inversion of the relative orientation of the dipyrrinone electric transition dipoles rather than from an inversion of pigment chirality.

Acknowledgement. We thank the National Institutes of Health (HD-17779) for generous support of this work and a NATO grant (No. 850382) which made this collaborative effort possible.

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