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Hydrogen Bonding and π-Stacking in Dipyrrinone Acid Dimers of Xanthobilirubic Acid and Chiral Analogs

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Abstract: Xanthobilirubic acid and its analogs self-associate strongly through intermolecular hydrogen bonding between their carboxylic acid and dipyrrinone components, forming π-stacked dimers. In contrast, their methyl esters form planar dimers conjoined by dipyrrinone to dipyrrinone intermolecular hydrogen bonding. When a stereogenic center is present in the propionic side acid chain, unusually large optical rotations and exciton coupling circular dichroism may be observed for the optically active acids: βS-methylxanthobilirubic acid (**1**) has $[\alpha]_D^{20} = -314°$ and $\Delta\epsilon_{434}^{max} = -10.9$, $\Delta\epsilon_{388}^{max} = +5.7$ ($CHCl_3$). In contrast, methyl esters show weaker rotations and vanishingly small CD: the methyl ester of (**1**) has $[\alpha]_D^{20}$ +62° and $\Delta\epsilon_{435} << 0.5$, $\Delta\epsilon_{390} << 0.5$.

INTRODUCTION

Bilirubin, the yellow pigment of jaundice[1,2] is a dicarboxylic acid composed of two dipyrrinone chromophores conjoined at a $-CH_2-$ group (Fig. 1A). In the most stable bilirubin conformation, each dipyrrinone engages a carboxylic acid group in a matrix of intramolecular hydrogen bonds that collectively act as a potent stabilizing force.[3] Even simple dipyrrinones participate avidly in hydrogen bonding.[4] Kryptopyrromethenone[5] and methyl xanthobilirubinate,[6] for example, form planar dimers (Fig. 1B) in nonpolar solvents ($K_{assoc} \simeq 25{,}000$ M, $CHCl_3$, 25°C)[4] or engage in hydrogen bonding to solvents such as DMSO.[4,7] The types of hydrogen bonding shown in Figs. 1A and 1B have been found in crystals of bilirubin[8] and dipyrrinones,[4,9] and they have been detected in solution by ^{1}H-NMR N-*H* (and CO_2H) chemical shifts and NOEs.[4,6,7,10,11]

Two fundamentally different intermolecularly hydrogen bonded dimers, each with four hydrogen bonds, can be drawn for dipyrrinone esters (Figs. 1B and 1C). The planar dimer (Fig. 1B) is the most common form in the crystal and in nonpolar solvents. In methyl xanthobilirubinate, for example, the methyl group at C(2)

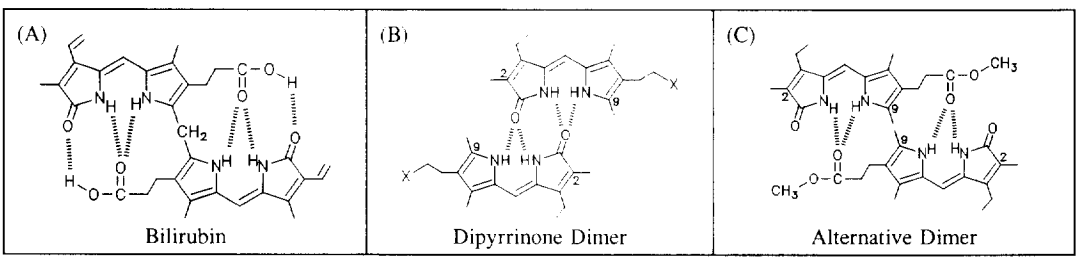


FIGURE 1. (A) Intramolecularly hydrogen bonded bilirubin with hydrogen bonding between carboxylic acids and dipyrrinones. (B) Intermolecularly hydrogen-bonded dipyrrinone dimer of kryptopyrromethenone (X=H) and methyl xanthobilirubinate (X=CO_2CH_3). (C) Alternative dimer representation for methyl xanthobilirubinate.

of one dipyrrinone lies close to the methyl group at C(9) of the other, and a significant NOE is found between them.[6] However, there is no evidence, either in solution or the crystal supporting the alternative dimer with ester-to-dipyrrinone hydrogen bonding (Fig. 1C).

Although there have been no reports on dipyrrinone acid dimers, it can be assumed that they would, at a minimum, adopt the typical dipyrrinone to dipyrrinone type (Fig. 2A). However, a pair of dipyrrinone acids might also adopt a dimeric form engaging six hydrogen bonds (Fig. 2B) and thus look like intramolecularly hydrogen bonded bilirubin (Fig. 1A). This alternative acid dimer (Fig. 2B) is more attractive than the alternative ester dimer (Fig. 1C), but both dimers would appear to suffer from destabilization by C(9) methyl-methyl nonbonded steric repulsion. Whether the capacity for two additional hydrogen bonds in the acid dimer is sufficient to overcome this drawback and whether the acid-dipyrrinone dimer of Fig. 2B is more stable than its planar dimer (Fig. 2A) is unclear. It was thus surprising and quite interesting to discover that whereas the N*H* ^{1}H-NMR chemical shifts of xanthobilirubic acid and its methyl ester were nearly identical in $(CD_3)_2SO$, they differed significantly in $CDCl_3$ solvent (Fig. 3). In order to confirm, explore and understand this behavior, we examined the ^{1}H-NMR of xanthobilirubic acid derivatives (**1**-**3**) and used molecular mechanics calculations and circular dichroism (CD) spectroscopy to show that dipyrrinone acids adopt a new and unexpected dimer type.

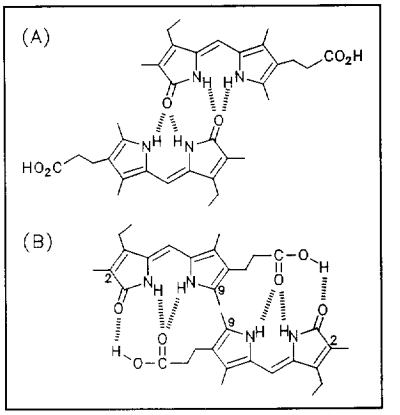


FIGURE 2. Xanthobilirubic acid dimers: (A) dipyrrinone to dipyrrinone and (B) dipyrrinone to acid.

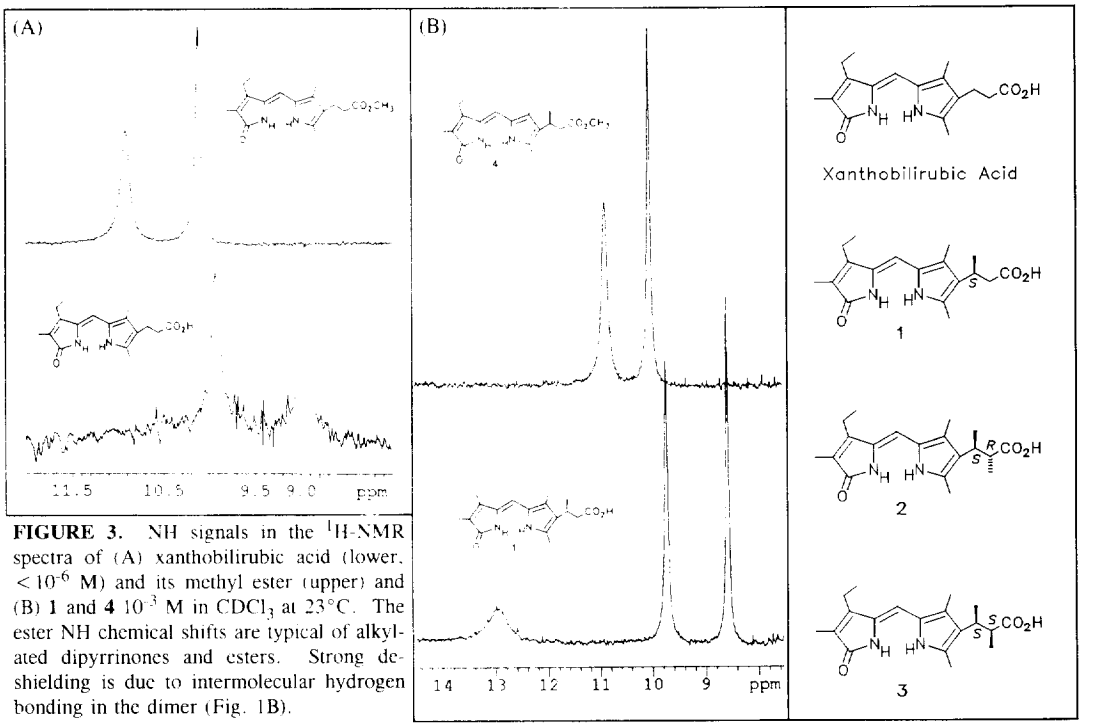
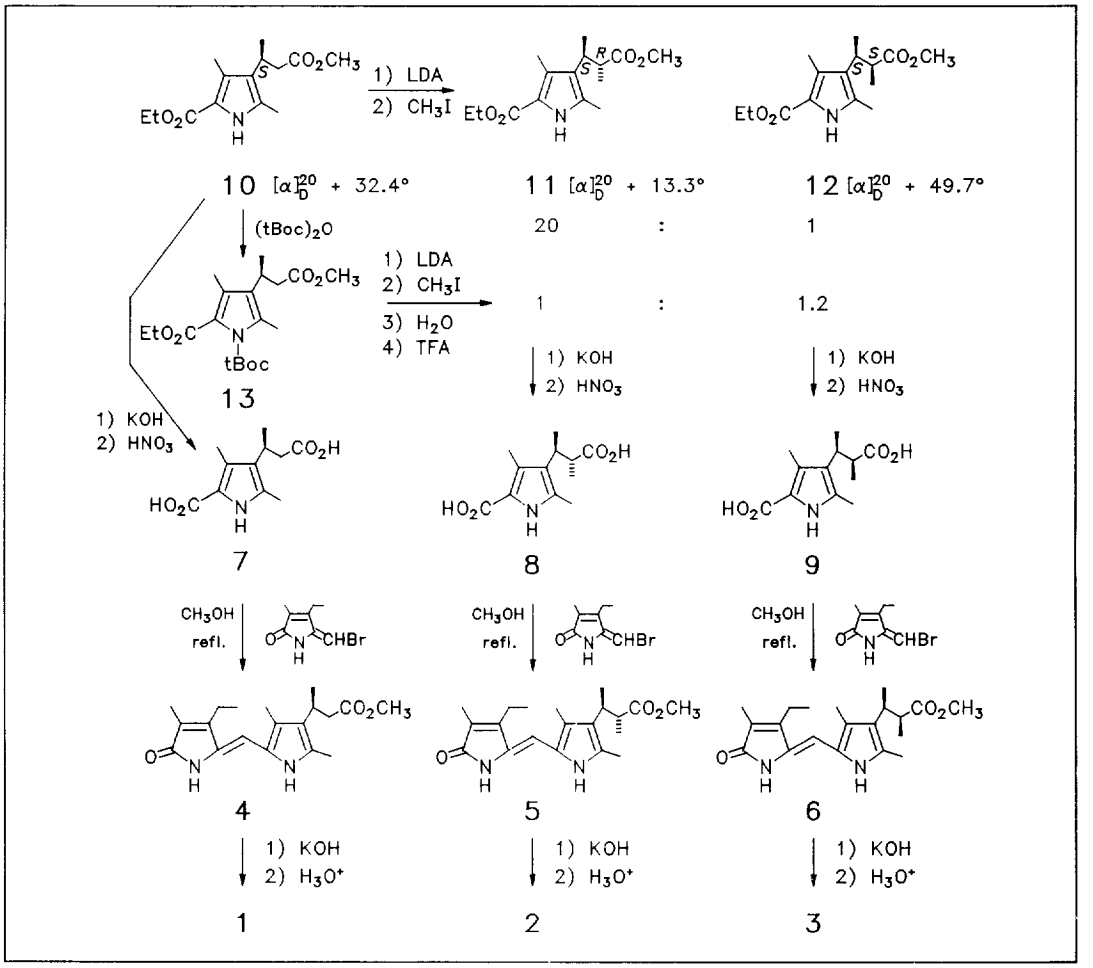


FIGURE 3. NH signals in the ^{1}H-NMR spectra of (A) xanthobilirubic acid (lower, $< 10^{-6}$ M) and its methyl ester (upper) and (B) **1** and **4** 10^{-3} M in $CDCl_3$ at 23°C. The ester NH chemical shifts are typical of alkylated dipyrrinones and esters. Strong deshielding is due to intermolecular hydrogen bonding in the dimer (Fig. 1B).

RESULTS AND DISCUSSION

Synthesis and Configuration. Xanthobilirubic acid and its analogs (**1-3**) were prepared by saponification of their methyl esters. Both methyl xanthobilirubinate[12] and its $\beta(S)$-methyl analog (**4**)[11a] had been prepared in earlier work. Ester **4** was prepared from optically active monopyrrole diacid **7** which was resolved as its mono-ester (carboethoxy at C(2)) with brucine. Its absolute configuration was determined by X-ray crystallography on the brucine salt.[11a] Diester **10** served as the starting point for the preparation of diastereomeric dipyrrinone acids **2** and **3** (Synthetic Scheme). α-Methylation of **10** was achieved on the lithium enolate formed by reaction with lithium diisopropylamide (LDA) to give a 20:1 mixture of diastereomers **11** and **12**. The stereochemistry of the major diastereomer (**11**), with $[\alpha]_D^{20}$ + 13.3 (*c* 1.9, $CHCl_3$), was assigned $\alpha R,\beta S$ based on steric approach control during methylation of the lithium enolate of **10**. It was confirmed as *erythro* by X-ray crystallography. The minor diastereomer (**12**), which is assigned the $\alpha S,\beta S$ configuration, has a

Synthetic Scheme



larger rotation ($[\alpha]_D^{20}$ + 49.7 (*c* 3.7, $CHCl_3$)) that is nearly the same as that of its aromatic analog ($\alpha S,\beta S$)-dimethyl-β-phenylpropionic acid ($[\alpha]_D$ + 53.1).[13]

Various attempts were made to invert or decrease the product ratio **11**:**12**. It was not significantly affected when the alkylation was carried out at higher temperatures (−10°, 0° or 25°C), or in the presence of HMPA (23% by vol). In the latter, the reaction products were predominantly N-alkylated **10** and α-methylated ester. However, alkylation of the t-BOC derivative (**13**) of **10** gave a slightly inverted product ratio (**11**:**12** = 1:1.2), and the purified diastereomeric esters could be obtained in 23% and 30% isolated yields by radial chromatography.

In the crystal, as seen by X-ray crystallography, two unrelated molecules of **11** form a dimer (Fig. 4A) by hydrogen bonding, from the pyrrole N-H of each molecule to the ethyl ester carbonyl O of the other. The monomers have assumed different conformations to produce a dimer with *pseudo* two-fold symmetry and strong H bonds; N···O distances are 2.83 and 2.88 Å and N-H···O angles are 162 and 164° for N12 to O37 and N32 to O17, respectively. In Fig. 4B the view down the α,β bond shows that both molecules have the $\alpha R,\beta S$ configuration shown in the Synthetic Scheme.

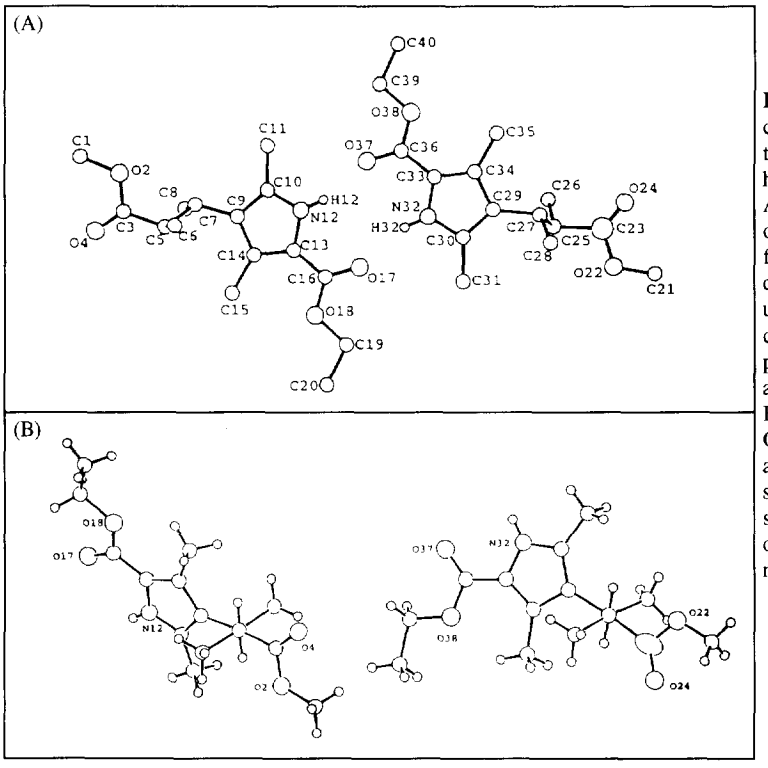


FIGURE 4. (A) View of the crystal structure of **11** showing the numbering scheme and the hydrogen bonding in the dimer. Atoms are represented by spheres of arbitrary size; H atoms (except for N-H) have been omitted for clarity. (B) Each of the two unique molecules of **11** in the crystal is viewed in Newman projection as in Fig. 5A. Only N and O atoms are labelled (see Fig. 4A); ellipsoids for C, N and O enclose 50% probability. H atoms are represented by small spheres. The atom numbering system is arbitrary. Molecule 2, on the right, is numbered like molecule 1, modulo 20.

The ^{1}H-NMR spectra of **11** and **12** are very similar, being nearly superimposable except between δ 0.9 - 1.3 ppm. In **11** the two methyl doublets (corresponding to the methyls at the stereogenic centers) are well-separated and centered at 0.94 and 1.19 ppm. In **12**, they are close together and centered at 1.23 and 1.24 ppm. The greater shielding in **11** is consistent with the $\alpha R,\beta S$ stereochemistry, in which the α-methyl lies over the face of the pyrrole ring (Fig. 5) — an orientation less favored sterically in the $\alpha S,\beta S$ stereochemistry.

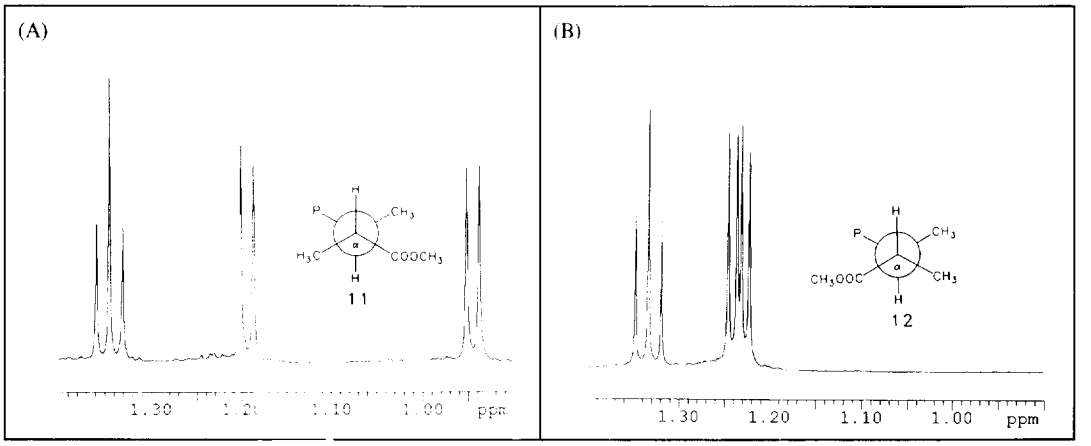


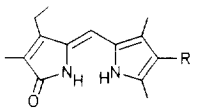
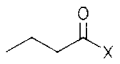
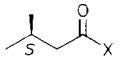
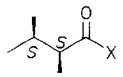
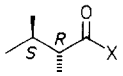
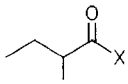
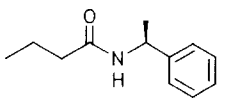
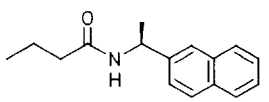
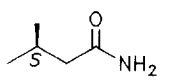
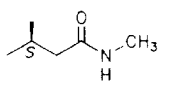
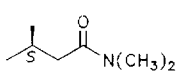
FIGURE 5. High field methyl region of the ^{1}H-NMR spectra of (A) **11** and (B) **12** in $CDCl_3$ solvent at 22°C. The unusual shielding (A) of the $\alpha(R)$-methyl is due to the (diamagnetic anisotropic) influence of the pyrrole ring (P) as shown in the Newman projection for the most stable rotamer. In the most stable rotamer of **12**, the $\alpha(S)$-methyl group lies away from the pyrrole ring. The antiperiplanar conformation of the α and β methine hydrogens in both **11** and **12** follow from the large vicinal $J = 11.1$ and 10.3 Hz, respectively. The triplet near 1.35 δ is for the CH_3 of the ethyl ester.

Conversion of **11** and **12** to dipyrrinone esters **5** and **6** proceeded smoothly. As outlined in the Synthetic Scheme, complete saponification to the diacid followed by careful, low temperature neutralization with nitric acid afforded diacids **8** and **9**, which were decarboxylated *in situ* in refluxing methanol and coupled with the known bromomethylenepyrrolinone. Under the reaction conditions (which liberate HBr) the propionic acid groups become esterified. The dipyrrinone esters (**4**, **5** and **6**) were easily saponified to afford the desired acids (**1**, **2** and **3**).

^{1}H-NMR and Hydrogen Bonding. Dipyrrinones are acquisitive hydrogen bonders.[4] Consistent with this behavior and typical of hydrogen bonding, the intrinsic N-*H* ^{1}H-NMR chemical shifts ($\delta \simeq 8$)[6] of esters such as methyl xanthobilirubinate become strongly *deshielded* in nonpolar solvents, to 10 and 11 ppm for the pyrrole and lactam hydrogens, respectively (Fig. 3A, B). Similar chemical shifts, characteristic of the traditional dipyrrinone-to-dipyrrinone dimer (Fig. 1B),[4-7,9] are found in a wide variety of dipyrrinones with hydrocarbon, ester and amide substituents (Table 1). Remarkably, the pyrrole and lactam N-*H*'s of dipyrrinone acids are *shielded* relative to their esters (Fig. 3A, B) in $CDCl_3$. The strong shielding found in xanthobilirubic acid is seen even in dipyrrinones with longer acid chains. It appears to be characteristic of dipyrrinone acids; yet, it is difficult to reconcile with either the traditional or alternative planar dimer structures shown in Fig. 2. The large N-*H* shieldings suggest either an implausible weakening of the dimer's intermolecular hydrogen bonding, or more likely, an arrangement where its N-*H*'s lie above or below the neighboring pyrrole or dipyrrinone π-system, as in a nonplanar dimer geometry where the dipyrrinones are stacked. This can be accomplished by the dimer of Fig. 2B simply by folding one dipyrrinone above or below the other while maintaining hydrogen bonding. The stacked arrangement removes a destabilizing C(9) methyl-methyl steric interaction while maintaining a complement of six hydrogen bonds. Apparently at least six hydrogen bonds are required for a stacked dimer; otherwise, dipyrrinone esters might adopt the stacked dimer configuration, which they do not. (They prefer the planar dimer of Fig. 1B.)[6] The stacked dimer is favored only with carboxylic acids.

^{1}H-NMR data provide no support for stacked dimers in primary and secondary amides of xanthobilirubic acid (Table 1), which have the potential for six hydrogen bonds.

TABLE 1. Comparison of Pyrrole and Lactam N-*H* ^{1}H-NMR Chemical Shifts[a] in $CDCl_3$ at 22°C.

 R =	Ester Chemical Shift (X = OCH_3)		Acid (X = OH) or Amide Chemical Shift		Chemical Shift Difference (Ester minus Acid or Amide)	
	Lactam N-H	Pyrrole N-H	Lactam N-H	Pyrrole N-H	Lactam N-H	Pyrrole N-H
	10.92	10.13	9.90	8.84	1.02	1.29
	10.89	10.03	9.70	8.54	1.19	1.49
	10.89	10.00	9.59	8.41	1.30	1.59
	10.94	10.09	10.71	9.05	0.23	1.04
	11.00	10.18	10.05	8.83	0.95	1.35
	—	—	11.02	10.14	-0.10	-0.01
	—	—	10.96	10.03	-0.04	0.10
	—	—	10.86	10.05	0.03	-0.02
	—	—	10.92	10.08	−0.03	-0.05
	—	—	10.93	10.06	-0.04	0.03

[a] δ, ppm downfield from $(CH_3)_4Si$ at 500 MHz. Solutions are all 1 x 10^{-3} M ± 10%.

Dipyrrinones, which are nearly planar, may be represented schematically (Fig. 6A) in forming hydrogen-bonded dimers of two types: planar and stacked. The emerging picture of the dipyrrinone dimer structure is one where the traditional planar dimer (Fig. 6B) is favored in most instances — except when the

dipyrrinone has an alkanoic acid tethered at C(8). Then the dipyrrinones stack above and below each other, held lock and key fashion by alkanoic acid straps and a network of six hydrogen bonds (Figs. 6C and D).

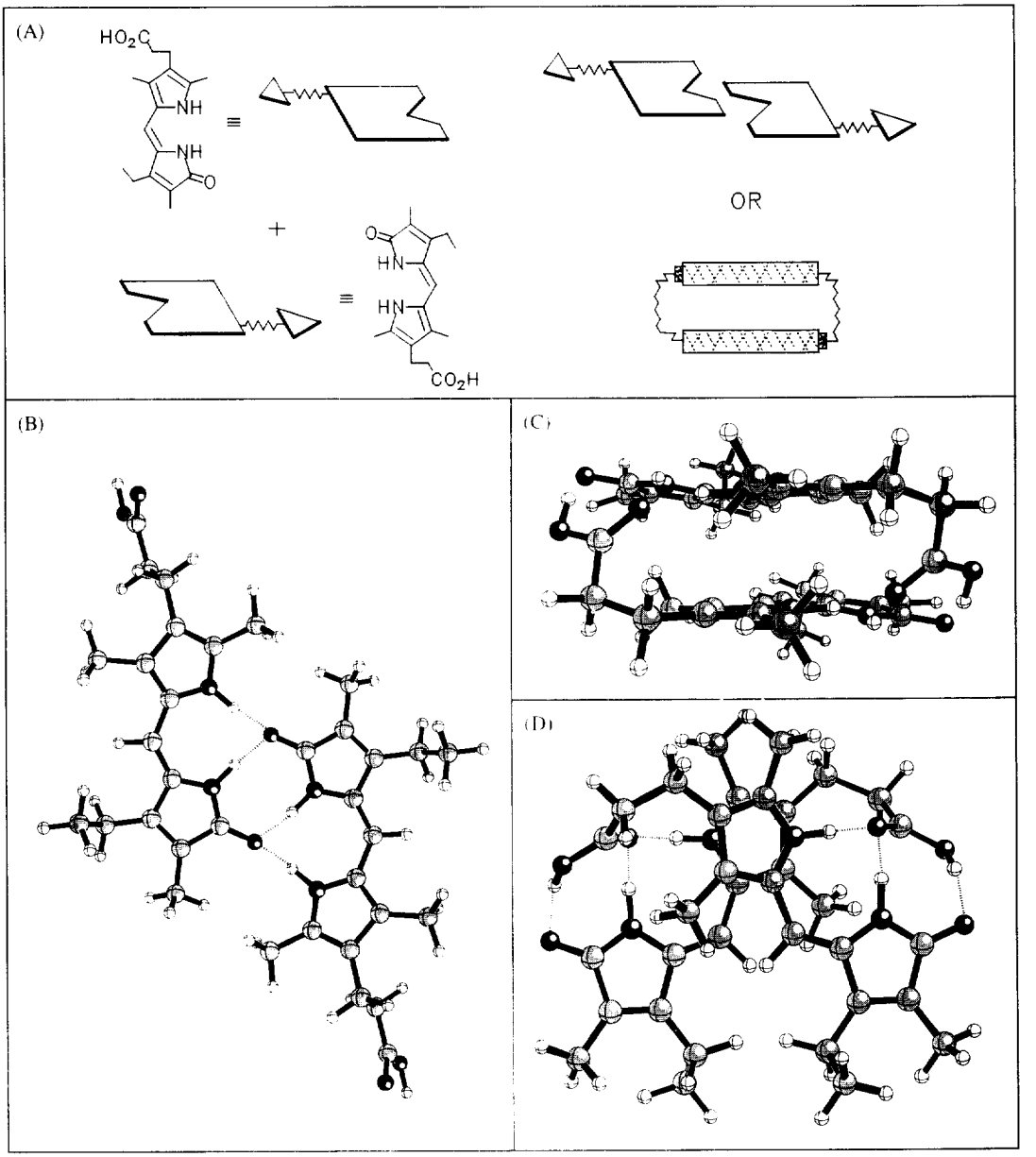
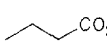
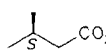
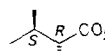
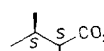
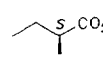


FIGURE 6. (A) Schematic representation for a planar dipyrrinone and its appended carboxylic acid. Two dipyrrinones are held together "in plane" through dipyrrinone to dipyrrinone hydrogen bonding or in a stacked arrangement through dipyrrinone to carboxylic acid hydrogen bonding. (B) Ball and stick planar dimer model of xanthobilirubic acid. (C) Ball and stick stacked model of xanthobilirubic acid dimer shown in edge-view representation and in (D) top view representation.

Molecular dynamics calculations[14] support this picture and predict that the π-stacked dimer of xanthobilirubic acid (Fig. 6C and D) will be ~12 kcal/mole more stable than the planar dimer (Fig. 6B). The planar dimer is predicted to be ~27 kcal/mole more stable than two isolated monomeric dipyrrinones (Table 2). The methylated analogs (**1-3**) of xanthobilirubic acid also prefer the stacked dimer stereochemistry. Interestingly, the presence of a β-methyl group is predicted to increase the stabilization of the stacked dimer relative to its planar dimer yet have relatively little influence on the stability relative to the separated monomers. And the "methylated" planar dimers are comparably less stable relative to two well-separated monomers when compared with the parent, xanthobilirubic acid (Table 2).

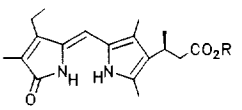
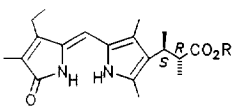
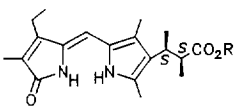
TABLE 2. Relative Energies of Stacked[a] and Planar Dimers[b] of Xanthobilirubic Acid and Its Methylated Analogs **1-3**.

R =	Relative Heat of Formation ($\Delta\Delta H_f$, kcal/mole)				
	ΔH_f (stacked[a]) — ΔH_f (planar[b])		ΔH_f (stacked[a]) — ΔH_f (2 monomers)		ΔH_f (planar[b]) — ΔH_f (2 monomers)
	M[c]	***P***[c]	***M***[c]	***P***[c]	
	-11.9	-11.9	-39.1	-39.1	-27.2
	-16.4	-10.8	-37.0	-31.4	-20.6
	-7.72	-7.49	-31.9	-31.6	-24.1
	-15.4	-3.08	-39.6	-27.3	-24.3
	-11.0	-5.7	-35.2	-30.0	-24.3

[a] As in Figure 6C and D. [b] As in Figure 6B. ***M*** = minus helicity, ***P*** = plus helicity of the stacked dimer. As in Fig. 8 two enantiomeric stacking arrangements are possible.

Optical Activity. Methylation in the propionic chain of xanthobilirubic acid introduces stereogenic centers in **1-3**, and these dipyrrinones are capable of exhibiting optical activity and circular dichroism (CD). As one might expect from the stacked dimer geometry, **1-3** exhibit unusual chiroptical data compared with their methyl esters (**4-6**). Dipyrrinones **1-3** were prepared from optically active monopyrrole **10** with the βS-configuration (Synthetic Scheme). The propionic acid analog of **10** had been prepared previously and resolved to 100% enantiomeric excess by crystallizing its brucine salt.[11a] Its absolute configuration was determined by X-ray crystallography.[11a] Optical rotations of the dipyrrinone methyl esters **4-6** are unexceptional at 589 nm: all are positive, with rotations ranging from 4 to 111 in chloroform and acetonitrile. In contrast, rotations of the corresponding dipyrrinone acids (**1-3**) are large and variable in chloroform but uniformly much weaker in acetonitrile (Table 3). This behavior would not be expected if both acids and esters formed the same type of dimer, and it confirms that: (i) dipyrrinone esters and acids adopt different dimer structures and (ii) the stability of the dimer is greatest in nonpolar solvents and is decreased substantially in more polar solvents such as acetonitrile. These distinctive differences in dimer structure are even more clearly evident from CD spectroscopy.

TABLE 3. Optical Rotations, $[\alpha]_D^{20}$, of Dipyrrinone Acids (**1-3**) and Their Methyl Esters (**4-6**) in $CHCl_3$ and CH_3CN.[a]

Solvent	$[\alpha]_D^{20}$ (°)					
						
	1: R=H	4: R=CH_3	2: R=H	5: R=CH_3	3: R=H	6: R=CH_3
$CHCl_3$	-314	+62	+182	+10	-900	+111
CH_3CN	- 36	+44	+30[b]	+4	+60[b]	+64

[a] Concentrations ~0.33-0.03 g/100 mL. [b] Containing 10% CH_3OH.

Circular Dichroism and Dimer Stereochemistry. Since dipyrrinones **1-6** are optically active, one can expect them to exhibit CD associated with the various electronic transitions in the chromophore. The dipyrrinones all have an intense ($\epsilon^{max} \simeq 30{,}000$) long wavelength and long axis polarized[5] UV-vis absorption near 400 nm.[4] This transition can be expected to exhibit at least a weak CD band from perturbation of the dipyrrinone chromophore by the neighboring stereogenic center(s).[3] To a first approximation, an isolated acid and its corresponding ester would be expected to exhibit very similar, but rather weak CD spectra with $|\Delta\epsilon_{\sim 400}^{max}| < 1$. Such very weak CD is seen for both esters and acids in polar solvents where monomers predominate. Even in nonpolar solvents where dipyrrinone esters form traditional dimers (Fig. 6B), only very weak CD is observed. In clear contrast, however, dipyrrinone acids in nonpolar solvents give moderately intense bisignate CD Cotton effects. Such bisignate Cotton effects cannot arise from perturbation of the dipyrrinone through dissymmetric vicinal action but must come about by an entirely different mechanism: exciton coupling between two dissymmetrically oriented proximal chromophores,[15] as seen in the CD of bilirubins.[3,11]

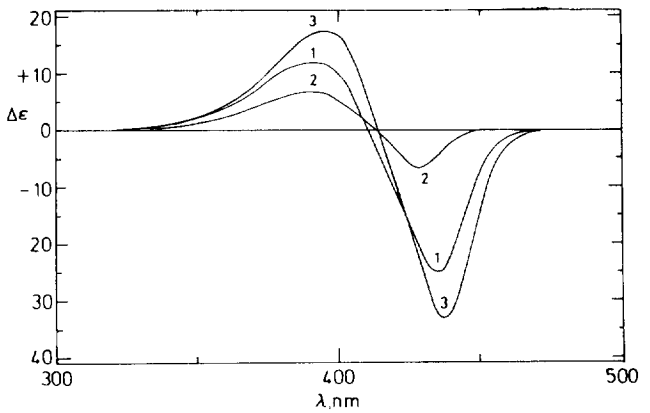
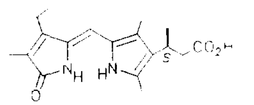
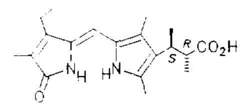
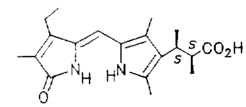


FIGURE 7. Circular dichroism spectra of 1 x 10^{-5} M dipyrrinone acids **1**, **2** and **3** in CCl_4. The CD spectra of **1-3** in CH_3OH lie on the $\Delta\epsilon=0$ line. The CD curves of the corresponding methyl esters (**4-6**) in CCl_4 and CH_3OH are extremely weak and also lie on the $\Delta\epsilon=0$ baseline.

The CD spectra of **1-3** provide evidence supporting stacked, as opposed to planar dimers. Thus, in nonpolar solvents such as CCl_4, $CHCl_3$ and benzene, dipyrrinone acids **1-3** give moderately strong bisignate Cotton effects (Table 4). As might be expected from a monomer-dimer equilibrium where the dimer is the major contributor to the CD, the Cotton effect intensity is concentration sensitive. The larger CD magnitudes

are found with the higher concentrations; with high dilution the magnitude decreases substantially (Table 5). In contrast, in polar solvents such as CH_3OH or $(CH_3)_2SO$, which do not promote dimer formation, the Cotton effects are very weak and monosignate (Fig. 7 and Table 4). Esters **4-6** give very weak to vanishingly small Cotton effects in dimer-promoting nonpolar solvents as well as in polar solvents. Clearly, the acids and their esters cannot both adopt the planar dimer structure (Figs. 1B and 6B). Although the ester CDs are in complete accord with the planar dimer, the acid CDs exclude it. Rather, the two dipyrrinones of the acid dimer must be held in a dissymmetric orientation in order to exhibit the exciton CD couplets observed.

TABLE 4. Solvent Dependence of Circular Dichroism and UV-Visible Spectral Data for Dipyrrinone Acids **1-3**.[a]

Solvent	ϵ[b]	 1		 2		 3	
		$\Delta\epsilon^{max}$ (λ_1) $\Delta\epsilon$=0 at λ $\Delta\epsilon^{max}$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon^{max}$ (λ_1) $\Delta\epsilon$=0 at λ $\Delta\epsilon^{max}$ (λ_2)	ϵ^{max} (λ^{max})	$\Delta\epsilon^{max}$ (λ_1) $\Delta\epsilon$=0 at λ $\Delta\epsilon^{max}$ (λ_2)	ϵ^{max} (λ^{max})
CCl_4	2.2	-25.0(435) 411 +12.0(392)	28,800(430)[sh] 30,400 (415)	-6.70 (428) 413 +6.8 (392)	32,700 (426) 33,100 (415)[sh]	-33.0 (437) 414 +17.3 (396)	30,800 (422)
C_6H_6	2.3	-18.6 (434) 412 +11.6 (391)	29,800 (413)	-4.9 (428) 413 +5.4 (390)	30,900 (420)	-17.3 (440) 421 +12.1 (401)	31,100 (424)
$CHCl_3$	4.7	-10.9 (434) 410 +5.7 (388)	30,000 (416)	-2.0 (428) 413 +2.7 (385)	31,800 (410)	-22.5 (436) 413 +13.1 (393)	29,900 (419)
THF	7.3	0.0	32,200 (403)	0.0	31,900 (405)	+0.5 (410)	31,400 (407)
CH_3OH	32.6	+0.4 (388)	36,100 (412)	0.0	35,500 (413)	+0.55 (394)	37,900 (415)
CH_3CN	36.2	-0.7 (380)	32,400 (398)	0.0	31,100 (400)	-0.66 (433) 416 +1.03 (381)	33,300 (401)
$(CH_3)_2SO$	49	0.0	34,400 (409)	0.0	33,400 (409)	+0.58 (408)	36,400 (412)

[a] Concentrations of **1**: 4.10 x 10^{-5} M, **2**: 4.08 x 10^{-5} M, **3**: 4.24 x 10^{-5} M. [b] Solvent dielectric constant.

Bisignate Cotton effects, such as those seen for **1-3** (Table 4 and Fig. 7) are characteristic of exciton coupling between (the relevant electric dipole transition moments of) *two proximal chromophores held in a dissymmetric orientation*.[15] This dissymmetry is evident in Fig. 6D, where it is clear that the long axes of the two dipyrrinones are arranged in a positive (***P***) helical orientation. The mirror image dimer (not shown) would have a negative (***M***) helicity and is enantiomeric and isoenergetic. The stacked dimer of xanthobilirubic acid can thus be viewed as a racemate consisting of equally populated ***P*** and ***M*** helical forms. According to exciton chirality theory,[15] coupling of the long axis-polarized transition moments is expected to give bisignate CD Cotton effects of oppositely-signed sequences centered near the dipyrrinone ~400 nm UV-vis transition. For the ***P***-helicity dimer a long wavelength positive, short wavelength negative CD couplet is predicted.[16] For the ***M***-helicity dimer a long wavelength negative, short wavelength positive CD coupled is pre-

dicted. On the other hand, planar dimers (Figs. 1B and 6B) are expected to give no exciton CD bands[15,16] because the chromophores and their transition moments lie in the same plane.

TABLE 5. Concentration Dependence on the CD Long Wavelength Cotton Effects of Dipyrrinone Acid **3**.[a]

Dipyrrinone Concentration (M)	Circular Dichroism		
	$\Delta\epsilon^{max}$ (λ_1)	λ at $\Delta\epsilon=0$	$\Delta\epsilon^{max}$ (λ_2)
2.01×10^{-3}	-28.4 (436)	413	+15.9 (393)
1.00×10^{-4}	-23.5 (436)	413	+13.4 (392)
4.01×10^{-5}	-21.4 (436)	413	+12.0 (394)
8.02×10^{-6}	-16.3 (436)	413	+9.1 (393)
2.01×10^{-6}	-8.7 (436)	413	+4.8 (393)
3.70×10^{-5}[b]	-1.5 (435)	417	+1.4 (393)

[a] In $CHCl_3$ at 23°C. [b] $CHCl_3$ - 2% vol CH_3OH solvent.

Optically active xanthobilirubic acid analogs **1-3** are also expected to stack in ***P*** and ***M***-helicity dimers, as in the parent, xanthobilirubic acid (Fig. 6D). However, unlike the parent, since **1-3** have stereogenic centers, their ***P*** and ***M*** helicity dimers are diastereomeric and thus not isoenergetic. As illustrated in Fig. 8 and indicated by the *negative* exciton chirality CD (Fig. 7 and Table 4), the ***M***-helical dimer is apparently preferred. In the ***M*** helical dimer of **3** the αS and βS methyl groups at the stereogenic centers are located in sterically less crowded environments than in the ***P*** helical dimer (Fig. 8). Thus, the (αS,βS)-dimethyl dipyrrinone **3** should give a net *negative* exciton chirality, which is observed (Table 4). However, in **2** the βS methyl favors the ***M***-helicity dimer, but the αR methyl favors the ***P*** (Fig. 7). Apparently, the β-methyl exerts a stronger effect on the choice of stacked dimer helicity, as **2** exhibits a weak but negative exciton chirality (Table 4).

Dimer Stereochemistry from Molecular Mechanics Calculations. The computed relative stabilities of the ***M*** and ***P*** helicity dimers of dipyrrinone acids **1-3** (Table 6) offer qualitative support to the conclusions reached from the CD data (Table 4). Thus, the ***M***-helical dimers of **1-3** are predicted to be more stable than the ***P***, with the greater difference in stability predicted for **3**. In **2** the ***M*** and ***P*** helical dimers are predicted to be essentially isoenergetic. These data suggest that **3** should exhibit the most intense (negative exciton chirality) Cotton effects, and **2** should exhibit the weakest Cotton effects – as is observed (Table 6). αS-Methylxanthobilirubic acid is also predicted to prefer the ***M***-helicity dimer (Table 6), but the synthesis of this analog has not been accomplished. Even optically active amides of xanthobilirubic acid with *S*-α-phenethylamine and *S*-α-naphthylethylamine are predicted to adopt a stacked dimeric arrangement, with the preferred helicity of the dimer determined by the *R*/*S* stereochemistry of the amide. The ***M***-helical dimer is predicted to be formed with the *S*-stereochemistry, and weak negative CD Cotton effects are observed.

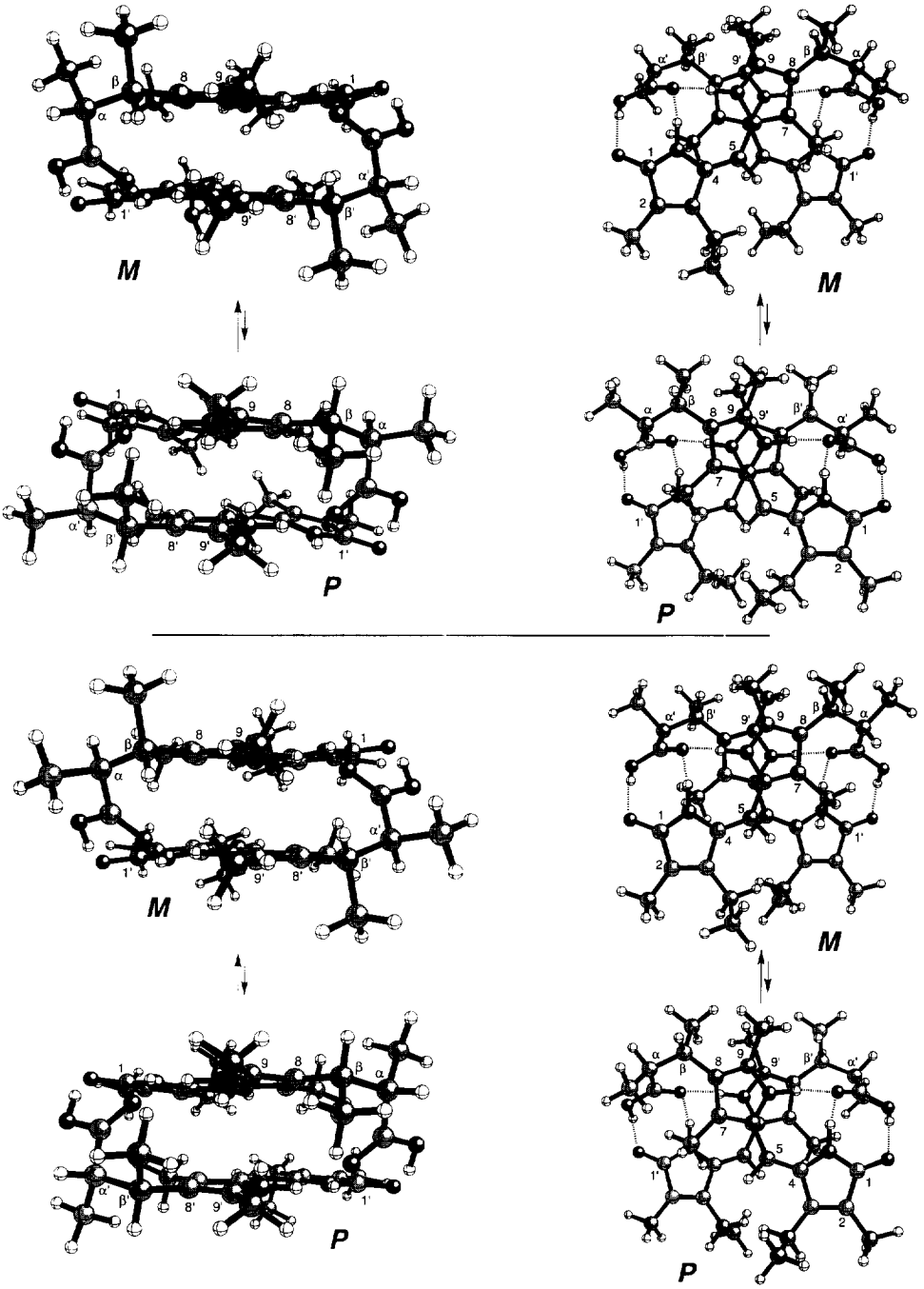
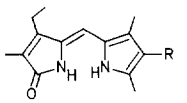
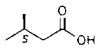
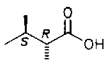
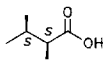
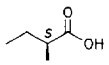
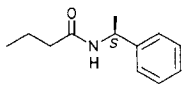
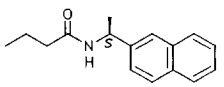


FIGURE 8. Ball and stick representations of the stacked dimers of dipyrrinone acids **2** (upper) and **3** (lower) as seen in edge (left) and face (right) views. The dipyrrinone components stack in either a left-handed (*M*) or right-handed (*P*) helicity.

TABLE 6. Computed Energy Differences ($\Delta\Delta H_f$) Between ***M*** and ***P***-Helicity Stacked Dimers of Dipyrrinone Acids **1-3** and the Observed Exciton Chirality CD Sign and Amplitude.

 R =	Computed Stacked Dimers		Exciton Chirality CD		
	$\Delta\Delta H_f = \Delta H_f(M) - \Delta H_f(P)$ (kcal/mole)	Predominant Dimer	Observed Amplitude in: CCl_4	$CHCl_3$	Predominant Dimer
 **1**	-5.6	***M***	-37	-17	***M***
 **2**	-0.3	***M***	-13	-5	***M***
 **3**	-12.0	***M***	-50	-36	***M***
	-5.3	***M***	NA	NA	—
	-0.9	***M***	NA	-4.4	***M***
	-1.0	***M***	NA	-7.2	***M***

SUMMARY

Dipyrrinones with propionic acid groups at C(8) form a hitherto unrecognized stacked dimer in nonpolar solvents. The stacked dimer is held together in a chiral orientation with six hydrogen bonds linking dipyrrinone and acid groups. This is distinctly different for dipyrrinone esters and other dipyrrinones without acid groups. They form planar dimers with four hydrogen bonds. Because dipyrrinone acids form stacked dipyrrinone dimers, they exhibit more shielded N*H* chemical shifts in their ^{1}H-NMR spectra than do dipyrrinone esters, for example. In the stacked dimers, the dipyrrinones are held in either of two enantiomeric helical arrangements, ***M*** or ***P***. This can be detected by circular dichroism spectroscopy of optically active dipyrrinone acids **1-3**, which prefer to adopt the ***M***-helicity stacking arrangement. Evidence for interchromophoric interaction in the dimer is found in their exciton coupling bisignate CD spectra (Fig. 6), from which the absolute configuration (***M***) of the preferred dimer can be determined. This new understanding of how dipyrrinones may form dimers offers an explanation for previously reported bisignate CD spectra of the amides of xanthobilirubic acid with *R* and *S*-α-phenethylamine and *R* and *S* α-naphthylethylamine.[17]

EXPERIMENTAL

General Methods. All UV-visible spectra were recorded on a Perkin Elmer model 3840 diode array or Cary 219 spectrophotometer, and all circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument. NMR spectra were obtained on a GE QE-300 or GN-300 spectrometer operating at 300 MHz or Varian Unity Plus spectrometer operating at 500 MHz. $CDCl_3$ solvent (unless otherwise noted) was used and chemical

shifts were reported in δ ppm referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and ^{13}C signal at 77.00 ppm. A J-modulated spin-echo experiment (*A*ttached *P*roton *T*est) was used to obtain ^{13}C-NMR spectra. Optical rotations were measured on a Perkin Elmer model 141 polarimeter. Gas chromatography-mass spectrometry (GCMS) analyses were carried out on Hewlett-Packard 5890A capillary gas chromatograph (30 m DB-1 column) equipped with Hewlett-Packard 5970 mass selective detector. Mass spectra (EI) were measured on Finnigan MAT SSQ 710 instrument. Radial chromatography was carried out on Merck silica gel PF_{254} with $CaSO_4$ preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA). Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ.

Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Methyl iodide, di-*tert*-butyl dicarbonate, diisopropylamine, triethylamine, trifluoroacetic acid, and 4-dimethylaminopyridine were from Aldrich. HPLC grade solvents (Fischer) were dried and distilled prior to use: tetrahydrofuran (THF) from $LiAlH_4$, methanol from magnesium methoxide and dichloromethane from P_2O_5.

(+)-(*S*)-3-(2,4-Dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butanoic acid was obtained as described previously via resolution of the racemate as 1:1 salt with brucine by fractional crystallization from acetone.[11a] It had $[\alpha]_D^{20}$ +30.5° (*c* 0.8, ethanol).

(+)-(*S*)-Methyl 3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butanoate (10). A solution of 7.6 g (30 mmol) of (+)-(*S*)-mono acid in 40 mL of dry tetrahydrofuran was treated at 5°C with ethereal diazomethane solution, prepared from 75 mmoles of N-methyl-N-nitrosourea.[18] After stirring for 1 h at room temperature, the solvents were removed under vacuum, and the residue was recrystallized from ethyl acetate-hexane to afford 7.63 g (95%) of methyl ester **10**. It had mp 72-73°C; $[\alpha]_D^{20}$ +38.7° (*c* 1.4, ethanol); $[\alpha]_D^{20}$ +32.4° (*c* 0.8, $CHCl_3$); ^1H-NMR: δ 1.25 (d, 3H, J=7.1 Hz), 1.32 (t, 3H, J=7.6 Hz), 2.24 (s, 3H), 2.32 (s, 3H), 2.59 (d, 2H, J=7.2 Hz), 3.28 (m, 1H), 3.59 (s, 3H), 4.28 (q, 2H, J=7.6 Hz), 9.12 (br.s, 1H) ppm; ^{13}C-NMR: δ 11.03, 12.40, 14.52, 20.23, 27.47, 41.02, 51.33, 59.57, 116.87, 124.2, 126.5, 129.3, 161.8, 173.1 ppm; MS, *m/z* (rel. intens.): 267 [$M^{+\bullet}$] (4%), 222 (4), 194 (34), 148 (100) amu.

(+)-(2*R*,3*S*)-Methyl 3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)-2-methylbutanoate (11). To a solution of diisopropylamine (9.4 mL, 67 mmol) in 40 mL of dry THF was added 1.6 M *n*-butyl lithium in hexane (41.5 mL, 67 mmol) at -20°C over 10 min. After stirring 15 min, the mixture was cooled to -50°C, and solution of 7.17 g (26.8 mmol) of pyrrole **10** in 67 mL of dry tetrahydrofuran was added dropwise over 15 min. The mixture was stirred for 1 h while the temperature was slowly raised to −35°C. A solution of methyl iodide (4.0 mL, 64.3 mmol) in 13 mL of tetrahydrofuran was added dropwise, and the mixture was stirred at -30°C for 1 h. The reaction was quenched with 20 mL of water. The product was extracted with ether (3 x 50 mL), washed with brine (3 x 100 mL), dried over anhydr. $MgSO_4$, filtered, and evaporated to dryness. Recrystallization from minimum volume of CH_3OH (-25°C) afforded 7.11 g (94%) of pure diastereomer **11**. It had mp 109-110°C, $[\alpha]_D^{20}$ +11.7° (*c* 1.9, ethanol); GC: R_T 17.17 min; ^1H-NMR: δ 0.94 (d, 3H, J=6.8 Hz), 1.19 (d, 3H, J=7.0 Hz), 1.34 (t, 3H, J=7.1 Hz), 2.23 (s, 3H), 2.32 (s, 3H), (2.69, 2.73) (dq, 1H, J=11.1, 6.8 Hz), (2.90, 2.94) (dq, 1H, J=11.1, 7.0 Hz), 3.72 (s, 3H), 4.29 (q, 2H, J=7.1 Hz), 8.72 (br.s, 1H) ppm; ^{13}C-NMR: δ 11.23, 12.58, 14.57, 16.69, 19.02, 34.15, 45.09, 51.49, 59.66, 117.0, 123.1, 126.9, 129.4, 161.6, 177.4 ppm; MS, *m/z* (rel. intens.): 281 [$M^{+\bullet}$] (13%), 236 (7), 194 (85), 148 (100) amu. A crystal of **11**, suitable for X-ray analysis, was obtained by very slow crystallization from dilute methanol solution at 0°C.

Anal. Calcd. for $C_{15}H_{23}NO_4$ (281.3): C, 64.03; H, 8.24; N, 4.98
Found: C, 63.78; H, 8.29; N, 4.96

(+)-(*S*)-Methyl 3-(2, 4-Dimethyl-5-ethoxycarbonyl-1-*tert*-butoxycarbonylpyrrol-3-yl)butanoate (13). Di-*tert*-butyl dicarbonate (8.66 g, 39 mmol) was added portionwise over 15 min to a solution of pyrrole **10** (6.94 g, 26 mmol) in 40 mL of dry CH_2Cl_2 and 36.2 mL (260 mmol) of dry triethylamine plus 319 mg (2.6 mmol) 4-dimethylaminopyridine. The mixture was stirred for 17 h, after which CH_2Cl_2 (200 mL) was added, and the solution was washed with 2% aq. HCl (2 x 200 mL) then water (3 x 200 mL). The organic phase was dried over anhydr. Na_2SO_4 and filtered. The solvent was evaporated under vacuum to afford the crude product, which was purified by radial chromatography (10% ethylacetate in hexane) to yield 9.11 g (95%) of the N-t-Boc protected pyrrole (**13**) as a colorless oil. It had $[\alpha]_D^{20}$ +21.1° (*c* 1.2, $CHCl_3$). GC: R_T 19.24 min; ^{1}H-NMR: δ 1.25 (d, 3H, J=7.3 Hz), 1.34 (t, 3H, J=7.1 Hz), 1.55 (s, 9H), 2.23 (s, 3H), 2.31 (s, 3H), 2.59 (d, 2H, J=7.7 Hz), 3.31 (q, 1H, J=7.4 Hz), 3.63 (s, 3H), 4.28 (q, 2H, J=7.1 Hz) ppm; ^{13}C-NMR: δ 10.90, 11.70, 14.17, 19.83, 26.98, 27.36, 40.32, 51.23, 60.10, 83.95, 120.78, 124.8, 128.1, 131.1, 149.6, 161.5, 172.5 ppm. MS: *m/z* (rel. intens.): 367 [$M^{+\bullet}$] (4%), 294 (2), 267 (18), 222 (2), 194 (100), 148 (61), 91 (13), 57 (69) amu.

(+)-(2*S*,3*S*)-Methyl 3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)-2-methylbutanoate (12). A solution of N-t-Boc protected pyrrole (**13**) (8.92 g, 24 mmol) in 48 mL of dry tetrahydrofuran was added to a solution of lithium diisopropyl amide (48 mmol) in 115 mL of dry tetrahydrofuran at -30°C. After stirring 1 h at −30°, a solution of 6.0 mL (96 mmol) of methyl iodide in 24 mL of tetrahydrofuran was added, and the mixture was stirred 1 h at -30°C. The reaction was quenched with water and the product was extracted with ether (3 x 80 mL). The combined ether extracts were washed with brine until neutral, dried over anhydr. Na_2SO_4 and filtered. The solvent was removed under vacuum, and the crude product was treated with 25 mL of trifluoroacetic acid with stirring for 15 min. The mixture was diluted with water, carefully neutralized with sat. aq. $NaHCO_3$, and the product was extracted with CH_2Cl_2. After washing the organic extracts with water until neutral, drying over anhydr. Na_2SO_4 and filtering, the solvent was removed under vacuum. The crude product was divided into 10 portions and each was separated by radial chromatography (6-15% ethyl acetate in hexane) to afford 1.58 g (23%) of the less polar (2*R*,3*S*)-diastereomer (**11**) and 2.00 g (30%) of the more polar (2*S*,3*S*) diastereomer (**12**). Isomer **11** had mp 111-112°C; $[\alpha]_D^{20}$ +13.3° (*c* 1.6, $CHCl_3$) and GC: R_T 17.15 min. Its MS, ^{1}H-NMR and ^{13}C-NMR were identical to those reported above for **11**. Isomer **12** had mp 68-69°C: $[\alpha]_D^{20}$ +49.7° (*c* 3.7, $CHCl_3$); GC: R_T 16.45 min; ^{1}H-NMR: δ 1.21 (d, 3H, J=6.8 Hz), 1.22 (d, 3H, J=7.2 Hz), 1.32 (t, 3H, J=7.1 Hz), 2.22 (s, 3H), 2.30 (s, 3H), (2.73, 2.76) (dq, 1H, J=10.3, 6.8 Hz), (2.90, 2.93) (dq, 1H, J=10.3, 7.2 Hz), 3.42 (s, 3H), 4.26 (q, 2H, J=7.1 Hz), 8.92 (br.s, 1H); ^{13}C-NMR: δ 11.03, 12.53, 14.50, 15.74, 17.11, 33.87, 45.18, 51.14, 59.53, 116.6, 123.9, 126.8, 129.6, 161.8, 176.4 ppm. MS *m/z* (rel. intens.): 281 [$M^{+\bullet}$] (10%), 236 (4) 194 (80), 148 (100) amu.

Anal. Calcd. for $C_{15}H_{23}NO_4$ (281.3): C, 64.03; H, 8.24; N, 4.98
Found: C, 64.19; H, 8.36; N, 4.96

(+)-(*S*)-Methyl 3-(3-ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)butanoate (4) was synthesized from **7** and 5-bromomethylene-4-ethyl-3-methyl-2-oxo-1*H*-pyrrole as described previously,[11a] $[\alpha]_D^{20}$ +61.8° (*c* 0.8, $CHCl_3$).

(+)-(2*R*,3*S*)-Methyl 3-(3-ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)-2-methylbutanoate (5). To a solution of 1.40 g (5 mmol) of monopyrrole **11** in 10 mL of ethanol was added a solution of 1.0 g (25 mmol) of NaOH in 9 mL of H_2O, and the mixture was heated at reflux 4 h. The solvents were completely removed under vacuum (1 mm Hg, 60°C). To the residue was added 5-bromomethylene-4-ethyl-3-methyl-2-oxo-1H-pyrrole[12] (5 mmol) and 15 mL of dry CH_3OH. The mixture was cooled with ice bath and carefully acidified with conc. HNO_3. Then, the mixture was heated at reflux for 6 h followed by chilling overnight at −25°C. The precipitate was filtered, suspended in 30 mL of tetrahydrofuran-methanol 1:1 and treated with ethereal diazomethane (obtained from 15 mmoles of N-methyl-N-nitrosourea[18]). The solvents were removed under vacuum, and the crude product was dissolved in CH_2Cl_2, filtered from inorganic salts, and purified by radial chromatography (2-4% CH_3OH in CH_2Cl_2). The major yellow band was collected. After solvent evaporation and recrystallization from the minimum volume of $CHCl_3$ and CH_3OH (added portionwise), 871 mg (51%) of **5** was obtained. It had mp 211-213°C, $[\alpha]_D^{20}$ +9.7° (*c* 1.1, $CHCl_3$). ^{1}H-NMR: δ 0.99 (d, 3H, J=6.9 Hz), 1.18 (t, 3H, J=7.6 Hz), 1.22 (d, 3H, J=7.1 Hz), 1.95 (s, 3H), 2.17 (s, 3H), 2.45 (s, 3H), 2.56 (q, 2H, J=7.6 Hz), (2.72, 2.75) (dq, 1H, J=11.1, 6.9 Hz), (2.92, 2.96) (dq, 1H, J=1.11, 7.1 Hz), 3.74 (s, 3H), 6.15 (s, 1H), 10.34 (br.s, 1H), 11.32 (br.s, 1H) ppm; ^{13}C-NMR: δ 8.51, 10.46, 12.62, 15.00, 16.77, 17.92, 19.13, 34.34, 45.25, 51.43, 100.9, 122.1, 122.3, 122.4, 124.4, 127.1, 131.5, 148.4, 174.1, 177.6 ppm.

Anal. Calcd. for $C_{20}H_{28}N_2O_3$ (344.4): C, 69.74; H, 8.19; N, 8.13
Found: C, 69.87; H, 8.05; N, 8.11

(+)-(2*S*,3*S*)-Methyl 3-(3-ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)-2-methylbutanoate (6) was synthesized as above from monopyrrole **12** in 35% yield. It had mp 220-222°C, $[\alpha]_D^{20}$ +111.4° (*c* 0.7, $CHCl_3$). ^{1}H-NMR: δ 1.17 (t, 3H, J=7.6 Hz), 1.24 (d, 3H, J=6.8 Hz), 1.26 (d, 3H, J=7.2 Hz), 1.94 (s, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 2.54 (q, 2H, J=7.6 Hz), (2.76, 2.79) (dq, 1H, J=10.0, 6.8 Hz), (2.95, 2.99) (dq, 1H, J=10.0, 7.2 Hz), 3.46 (s, 3H), 6.12 (s, 1H), 10.26 (br.s, 1H), 11.30 (br.s, 1H); ^{13}C-NMR: δ 8.54, 10.31, 12.68, 15.04, 15.69, 17.18, 17.94, 34.09, 45.33, 51.26, 101.2, 122.2, 122.2, 123.1, 124.6, 126.9, 131.5, 148.3, 174.1, 176.6 ppm.

Anal. Calcd. for $C_{20}H_{28}N_2O_3$ (344.4): C, 69.74; H, 8.19; N, 8.13
Found: C, 70.19; H, 8.11; N, 8.01

(-)-(*S*)-3-(3-Ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)butanoic acid (1). Methyl ester (**4**) (165 mg, 0.5 mmol) was heated at reflux for 7 h in 15 mL of 10% aq. NaOH. Then the mixture was cooled, diluted with 50 mL of H_2O, and acidified with 10% HCl. The precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by radial chromatography (5% CH_3OH/CH_2Cl_2) and recrystallized from $CHCl_3/CH_3OH$ to yield 141 mg (89%) of **1**. It had mp 262-264°C (decomp.), $[\alpha]_D^{20}$ −314° (*c* 0.07, $CHCl_3$), $[\alpha]_D^{20}$ −35.8° (*c* 0.02, CH_3CN); ^{1}H-NMR: δ 1.11 (3H, t, J=7.5 Hz), 1.34 (3H, d, J=7.2 Hz), 1.86 (3H, s), 1.97 (3H, s), 2.40 (3H, s), 2.50 (2H, q, J=7.5 Hz), 2.56 (1H, dd, J=7.7, 12.6 Hz), 2.76 (1H, dd, J=6.1, 12.6 Hz), 3.37 (1H, m), 5.87 (1H, s), 8.80 (1H, br.s), 10.06 (1H, br.s), 13.1 (1H, very br.s) ppm; ^{1}H-NMR (d_6-DMSO): δ 1.07 (3H, t, J=7.5 Hz), 1.16 (3H, d, J=7.1 Hz), 1.77 (3H, s), 2.06 (3H, s), 2.21 (3H, s), 2.47 and 2.49 (1H each, AB), 2.50 (2H, q, J=7.5 Hz), 3.13 (1H, m), 5.91 (1H, s), 9.77 (1H, s), 10.20 (1H, s), 11.94 (1H, br.s) ppm; ^{13}C-NMR (d_6-DMSO): δ 8.13, 10.03, 12.05, 14.95, 17.23, 20.55, 27.14, 41.04, 97.56, 121.7, 121.8, 122.7, 123.0, 127.4, 128.8, 147.3, 172.0, 173.6

ppm. Calcd. MW ($C_{18}H_{24}N_2O_3$) 316. Found by MS: *m/z* (relative intensity) 316 [$M^{+\bullet}$] (100), 257 (73) amu.

(+)-(2*R*,3*S*)-3-(3-Ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)-2-methylbutanoic acid (2). A mixture of 0.5 mmol of methyl ester **5**, 2.5 mmoles of KOH, 5 mL of ethanol, and 1 mL of water was heated at reflux for 4 h. Ethanol was removed under vacuum, and the residue was acidified with 10% aq. hydrochloric acid. The resulting precipitate was filtered, purified by radial chromatography on silica gel (5-8% CH_3OH in CH_2Cl_2), and recrystallized from CH_3OH to afford free acid **2** in 41% yield. It had mp 312-315°C (decomp.), $[\alpha]_D^{20}$ +182° (*c* 0.03, $CHCl_3$). ^{1}H-NMR: δ 1.06 (d, 3H, J=6.7 Hz), 1.18 (t, 3H, J=7.6 Hz), 1.32 (d, 3H, J=6.9 Hz), 1.94 (s, 3H), 2.21 (s, 3H), 2.50 (s, 3H), 2.55 (q, 2H, J=7.6 Hz), 2.86 (m, 1H), 3.03 (m, 1H), 6.16 (s, 1H), 9.05 (br.s, 1H), 10.75 (br.s, 1H), 14.2 (very br.s, 1H); ^{13}C-NMR ($(CD_3)_2SO$): δ 8.02, 10.11, 11.90, 14.78, 16.58, 17.12, 19.11, 33.53, 44.60, 97.40, 121.3, 121.7, 121.8, 122.7, 127.5, 129.1, 147.2, 171.9, 177.7 ppm; molec. wt. 330.4 ($C_{19}H_{26}N_2O_3$); MS: *m/z* (rel. intens.) 330 [$M^{+\bullet}$] (100%) 257 (51) amu.

(-)-(2*S*,3*S*)-3-(3-Ethyl-2,7,9-trimethyl-1-oxo-1,10-dihydrodipyrrin-8-yl)-2-methylbutanoic acid (3) was prepared as above from **6** in 54% yield. It had mp 244-246°C, $[\alpha]_D^{20}$ -900° (*c* 0.07, $CHCl_3$), $[\alpha]_D^{20}$ +59.5° (*c* 0.12, CH_3CN:MeOH 9:1 v/v). ^{1}H-NMR: δ 1.06 (t, 3H, J=7.6 Hz), 1.31 (d, 3H, J=7.2 Hz), 1.34 (d, 3H, J=6.7 Hz), 1.86 (s, 3H), 1.90 (s, 3H), (2.33, 2.44) (2xq, 2H, J=7.6, 14.7 Hz), 2.37 (s, 3H), (2.51, 2.55) (dq, 1H, J=6.7, 11.0 Hz), (2.94, 2.97) (dq, 1H, J=7.2, 11.0 Hz), 5.70 (s, 1H), 8.44 (br.s, 1H), 9.66 (br.s, 1H), 13.8 (very br.s, 1H); ^{13}C-NMR: δ 8.06, 9.03, 14.44, 14.99, 15.39, 17.29, 17.78, 34.60, 48.09, 101.4, 121.7, 121.8, 123.4, 125.6, 126.3, 131.2, 147.8, 173.9, 181.8 ppm. Molec. wt. 330.4 ($C_{19}H_{26}N_2O_3$); MS: *m/z* (rel. intens.) 330 [$M^{+\bullet}$] (100%), 257 (60) amu.

*Crystal Data for **11***: $C_{15}H_{23}NO_4$, M=281.35, monoclinic, space group $P2_1$, *a*=11.871(11), *b*=7.177(7), *c*=18.694(18) Å, β=103.11(3)°, U=1551.1(25) Å^3, μ (Mo K_α)=0.074 mm^{-1}, F(000)=608, Z=4, D_c= 1.205 g cm^{-3}, Picker (Crystal Logic) diffractometer, T=156 K, $\theta/2\theta$ scan, $2\theta_{max}$=50°, 3308 reflections measured, direct methods solution (SHELXS-86),[19] 2971 unique reflections used in refinement of 373 parameters on F^2 (SHELXL-93),[20] 1594 reflections with $F > 4\sigma(F)$ gave a final R1=0.078, wR2=0.189, GoF= 1.067. The structure possesses a near center of symmetry and can indeed be solved in $P2_1/a$, but that solution ignores many systematic-absence violations and does not refine below R1=0.20. Exhaustive search for missed symmetry was fruitless. Views of the structure are presented in Figures 4A and 4B.[21] Figure 4B shows clearly that the molecules have the same stereochemistry but are different. However, the large ellipsoids in the second molecule suggest some disorder, especially in the region near C23, C25 and C27, where the deviation from the *pseudo* 2-fold axis or center of symmetry is the greatest. Data collection and reduction, as well as other necessary calculations, were performed with the UCLA Crystallographic Package.[22]

The full listing of the crystallographic data collection details, data reduction and refinement procedures, bond lengths, bond angles, positional parameters, thermal parameters, tables of calculated and observed structure factors have been deposited at the Cambridge Crystallographic Data Centre.

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