Tetrahedron 65 (2009) 77–82

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Carboxylic acid to thioamide hydrogen bonding

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ARTICLE INFO

Article history:
Received 21 August 2008
Received in revised form
24 September 2008
Accepted 26 September 2008
Available online 8 October 2008

Keywords:
Pyrroles
Dipyrrinthiones
NMR
VPO

ABSTRACT

The lactam groups of dipyrrinones avidly engage in amide–amide hydrogen bonding to form dimeric association complexes in non-polar solvents (in $CHCl_3$, K_D ~25,000 M^{-1} at 22 °C). The corresponding thioamides (dipyrrinthiones), prepared from dipyrrinones by reaction with Lawesson's reagent, also form intermolecularly hydrogen-bonded dimers in non-polar solvents, albeit with much weaker association constants (in $CHCl_3$, K_D ~200 M^{-1} at 22 °C). When a carboxylic acid group is tethered to C(9) of the dipyrrinone, as in the hexanoic acid of [6]-semirubin, tight intramolecular hydrogen bonding between the carboxylic acid group and the lactam moiety (intramolecular $K_{assoc} \gg 25{,}000$) is found in $CHCl_3$ with no evidence of dimers. In contrast, the analogous dipyrrinthione, [6]-thiosemirubin, eschews intramolecular hydrogen bonds, as determined using NMR spectroscopy and vapor pressure osmometry, preferring to form intermolecularly hydrogen-bonded dimers of the thioamide–thioamide type.

1. Introduction

Although not as well studied as amide–amide and carboxylic acid–carboxylic acid hydrogen bonding,[1] amides are known to form strong hydrogen bonds to carboxylic acids, as was first recognized in bilirubin (Fig. 1A),[2,3] the yellow pigment of jaundice.[4] There, nature designed a molecule whose lipophilic character and poor aqueous solubility (K_{sp} ~4×10^{-15} M at 37 °C)[5] may be understood by considering pigment's structure in which both propionic acids are tucked inward and firmly *intramolecularly* hydrogen-bonded to the opposing dipyrrinones,[2,3,6] the key factor in bilirubin's aqueous solubility and metabolism. In further illustration of this attraction, strong, selective *intermolecular* hydrogen bonding between a carboxylic acid and a pyridone lactam has also been reported,[7] to the exclusion of carboxylic acid–carboxylic acid and amide–amide hydrogen bonding. The unusual type of hydrogen bonding seen in bilirubin is probably facilitated by the adjacency of the pyrrole hydrogen and has been replicated in simpler analogs such as [6]-semirubin (Fig. 1B)[8] and related analogs where recent studies have shown that the dipyrrinone moiety[9] is an excellent receptor for a carboxylic acid group[10,11] and probably also a carboxylate anion.[3c,6b]

The essential components for the hydrogen bonding seen in bilirubin are an amide (lactam) of a *Z*-configuration dipyrrinone and a carboxylic acid chain of at least six carbons that is tethered at C(9). This complementary combination was designed into the synthetic pigment model for one-half of bilirubin, [6]-semirubin (**1**) (Fig. 1B),[8] whose dipyrrinones, like those in bilirubin, have the *syn-Z* configuration,[3,6,8] and which was shown to be a monomer in chloroform with its CO_2H group engaged tightly in intramolecular hydrogen bonding (Fig 1A,B).[8] In contrast, the ethyl ester (**2**) of **1** and simple dipyrrinones with an alkyl group at C(9) replacing the carboxylic acid chain, e.g., kryptopyrromethenone (**3**), were shown to form strongly intermolecularly hydrogen-bonded dimeric structures (Fig. 1C) in $CDCl_3$ with large association constants (K_D ~25,000 M^{-1} at 22 °C)[12] — surprisingly, much larger than those of simple amides, whose K_D varies from ~30 to 7000.[13] The observation that [6]-semirubin (**1**) eschews dipyrrinone to dipyrrinone dimer formation[8] is consistent with the dipyrrinone unit strongly favoring ($K_{assoc} \gg 25{,}000$) complexation to the carboxylic acid group over a second dipyrrinone molecule. As such, **1** is an excellent model for exploring amide to carboxylic hydrogen bonding.

Though less well studied, thioamides, like amides, are known to dimerize in non-polar solvents by forming intermolecular hydrogen bonds. The simple thiolactams, γ-butyrothiolactam and δ-valerothiolactam, were shown to exhibit dimerization equilibrium constants (K_D=278 and 438 M^{-1} in CCl_4 at 25 °C)[13a,b] similar to the parent lactams.[13a,b] But the thiolactam analogs of 2-pyridone were found to have variable, but always lower K_D values than the parent: 4100 M^{-1} versus 7100 M^{-1} in CCl_4,[13c] 28 versus 2200 M^{-1} in benzene,[13d] and $2.7\pm1.0\times10^3$ M^{-1} versus $2.5\pm1.0\times10^4$ M^{-1} in $CHCl_3$.[14] To the best of our knowledge, hydrogen bonding between a thioamide and a carboxylic acid remains unknown.

In order to explore and evaluate the potential for such hydrogen bonding, we took advantage of the special ability of dipyrrinones to sequester a carboxylic acid group. Using [6]-semirubin (**1**) as

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0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.09.082

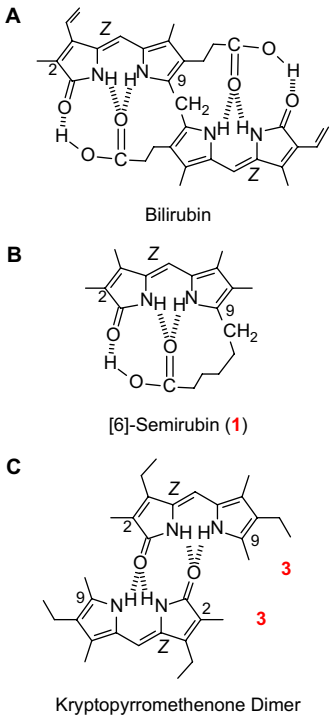


Figure 1. (A) Bilirubin, (B) its intramolecularly hydrogen-bonded dipyrrinone analog [6]-semirubin (**1**), and (C) intermolecularly hydrogen-bonded kryptopyrromethenone (**3**).

a model, we perturbed the dipyrrinone by converting its lactam moiety to thiolactam to give the dipyrrinthione, [6]-thiosemirubin (**4**). For comparison and evaluation of thiolactam–thiolactam association involving hydrogen bonding, we prepared the dipyrrinthiones, methyl thioxanthobilirubinate (**5**),[15] and kryptopyrromethenethione (**6**)[15] (Fig. 2), from which we could further evaluate the thioamide–thioamide hydrogen bonding and whose K_D values might serve as a reference value to be exceeded if intramolecular hydrogen bonding prevails in **4**. In the following, we describe the syntheses of **4**, its methyl ester (**8**), and dipyrrinthiones **5** and **6** (Fig. 2), and we analyze their ability to engage in hydrogen bonding in terms of inter- and intramolecular hydrogen-bonded structures.

2. Results and discussion

2.1. Synthesis

The syntheses of **4**–**6** and **8** involve thionation of the lactam units of the corresponding dipyrrinones using Lawesson's reagent.[16] We had previously converted kryptopyrromethenone **3** to its thioamide analog (**6**) in 82% yield[15] by treatment in dry THF with

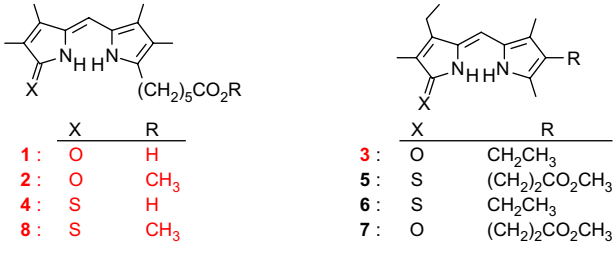
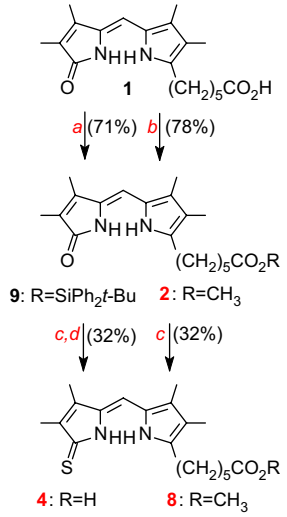


Figure 2. The thiolactam analogs (**4**–**6** and **8**) of [6]-semirubin (**1**) and its methyl ester (**2**), methyl xanthobilirubinate (**7**), and kryptopyrromethenone (**3**).

1 equiv of Lawesson's reagent for 2 h. Under similar reaction conditions, the known methyl xanthobilirubinate (**7**)[17] was converted smoothly to the thioamide analog (**5**) in 83% yield. Synthesis of **4** and **8** (Scheme 1) required the known [6]-semirubin (**1**)[7] and its methyl ester (**7**),[7] both obtained following Friedel–Crafts acylation at carbon-9 of 2,3,7,8-tetramethyl-10*H*-dipyrrinone.[8] Unlike the formation of thiolactam **5** from **7**, conversion of the amide of [6]-semirubin methyl ester (**2**) to its thioamide (**8**) with Lawesson's reagent proceeded inefficiently (32% yield). The reason for this is unclear and, disappointingly, methyl ester **8** resisted conversion to the parent free acid (**4**). Numerous attempts at converting **8** to **4** led to decomposition, as did direct thionation of dipyrrinone acid **1** to **4**. In order to circumvent these problems, especially the difficulties encountered in the methyl ester hydrolysis step (**8**→**4**), [6]-semirubin (**1**) was converted to its more easily deprotected *tert*-butyldiphenylsilyl ester (**9**) in good yield. Successful thionation of **9** using Lawesson's reagent, followed by fluoride ion deprotection of the silyl ester group, afforded the desired [6]-thiosemirubin (**4**) in 32% isolated yield from **9**.



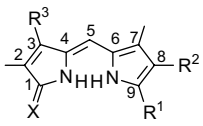
Scheme 1. [a]*t*-BuPh$_2$SiCl+imidazole/dry THF, rt, 4 days; [b]CH$_3$OH/H$_2$SO$_4$; [c]Lawesson's reagent/dry THF, rt, 36 h; [d](n-Bu)$_4$NF/THF to 5% H$_2$O, 12 h, rt.

2.2. Constitutional structures from NMR

The constitutional structures of **4** and **8** follow from the structures of their precursors (**1** and **2** of Fig. 1 and Scheme 1) and from their ^{13}C NMR spectra (Table 1). Thus, evidence for the loss of the lactam C=O at ~174 ppm and the appearance of the C=S carbon at ~187 ppm correlates with the C=S chemical shifts of dipyrrinthiones **5** and **6**[15] and the expectation of a more strongly deshielded carbon. Likewise, C(2) is deshielded to ~132 ppm in **4** and **8** (and **5** and **6**) relative to the lactam parents' ~123 ppm. Similar, but smaller deshieldings at C(4) and C(5) are found in **4** and **8** (**5** and **6**) relative to their parent dipyrrinones. Interestingly, the usual small (0.1 ppm) deshielding of C(5) in the acid relative to the ester (**1** vs **2**) is much smaller than the (~0.6 ppm) shielding in thiosemirubins **4** and **8**.

The 4*Z*-configuration of dipyrrinones (Figs. 1 and 2, and Schemes), as well as bilirubin, has been long established:[2] in the solid by X-ray crystallography;[3,18,19] in solution by nuclear Overhauser effect (NOE) spectroscopy, where NOEs are found between C(5)–H and the C(3) and C(7) CH$_3$ groups, and between the two NHs.[2,18,20] Thus, it came as no surprise that NOE studies of **4**, **6**, and **8** indicated the favored *syn*-*Z* configuration (Fig. 3). *E*-Configuration dipyrrinones are accessible only by photoirradiation.[21]

Table 1
^{13}C NMR chemical shifts (δ)[a] and assignments of **1**–**8** in $CDCl_3$



	X	R^1	R^2	R^3
1	O	$(CH_2)_5CO_2H$	CH_3	CH_3
2	O	$(CH_2)_5CO_2CH_3$	CH_3	CH_2CH_3
3	O	CH_3	CH_2CH_3	CH_2CH_3
4	S	$(CH_2)_5CO_2H$	CH_3	CH_3
5	S	CH_3	$(CH_2)_2CO_2CH_3$	CH_2CH_3
6	S	CH_3	CH_2CH_3	CH_2CH_3
7	O	CH_3	$(CH_2)_2CO_2CH_3$	CH_2CH_3
8	S	$(CH_2)_5CO_2CH_3$	CH_3	CH_3

Carbon		**1**	**2**	**3**	**4**	**5**	**6**	**7**[b]	**8**
1	C=CX	174.7	173.9	174.1	186.8	186.7	185.9	174.1	186.7
2	=C–	123.6	123.2	122.2	132.2	131.5	131.0	122.4	133.5
2^1	CH_3	8.2	8.6	9.5	11.1	10.4	10.4	9.6	9.6
3	=C–	142.2	142.2	148.2	138.0	146.1	146.0	148.4	140.1
3^1	CH_2/CH_3	9.8	9.9	15.4	12.6	18.4	18.4	18.0	11.3
3^2	CH_3	—	—	17.5	—	15.1	17.3	15.0	—
4	=C–	128.7	128.3	127.0	131.4	132.3	132.0	127.2	133.2
5	=CH–	101.3	101.2	101.2	103.4	103.9	104.2	101.4	104.0
6	=C–	122.4	122.2	122.9	122.9	129.3	129.8	122.4	124.1
7	=C–	125.5	125.2	122.2	122.9	121.3	123.5	119.1	130.5
7^1	CH_3	9.7	9.7	11.5	12.3	11.9	11.9	11.5	11.0
8	=C–	135.8	135.8	124.6	138.0	123.6	123.5	124.6	140.6
8^1	CH_2/CH_3	8.8	9.1	18.0	12.0	19.7	18.0	19.9	10.6
8^2	CH_2/CH_3	—	—	15.1	—	34.7	15.1	35.2	—
8^3	CO_2R	—	—	—	—	173.5	—	174.1	—
9	=C–	116.7	115.9	131.1	117.0	136.1	136.0	131.6	118.8
9^1	CH_2/CH_3	23.0	25.7	8.5	26.1	9.8	9.7	8.5	26.7
9^2–9^5	CH_2	[c]	[d]	—	[e]	—	—	—	[f]
9^6	CO_2H/CO_2CH_3	180.8	174.2	—	178.7	—	—	—	174.2
	CO_2CH_3	—	51.4	—	—	51.7	—	51.2	52.4

[a] In parts per million downfield from $(CH_3)_4Si$ for 2×10^{-2} M solutions in $(CD_3)_2SO$ at 25 °C.
[b] Values taken from Ref. 15.
[c] R^1: 21.4 (9^2—CH_2), 26.2 (9^3—CH_2), 28.2 (9^4—CH_2), 32.6 (9^5—CH_2) ppm.
[d] R^1: 24.8 (9^2—CH_2), 28.7 (9^3—CH_2), 29.9 (9^4—CH_2), 34.0 (9^5—CH_2) ppm.
[e] R^1: 27.6 (9^2—CH_2), 30.3 (9^3—CH_2), 30.9 (9^4—CH_2), 35.9 (9^5—CH_2) ppm.
[f] R^1: 25.1 (9^2—CH_2), 29.2 (9^3—CH_2), 30.0 (9^4—CH_2), 24.5 (9^5—CH_2) ppm.

2.3. Hydrogen bonding

The NH chemical shifts of dipyrrinones have frequently been used in ^{1}H NMR to detect hydrogen bonding: intermolecular between two dipyrrinones[20] and between a dipyrrinone and a carboxylic acid.[6,8–10] It seemed reasonable to assume that this structure-distinguishing probe might carry over to dipyrrinthiones. Dipyrrinones that engage exclusively in intermolecular hydrogen bonding of the dipyrrinone to dipyrrinone type in $CDCl_3$, as in **2**, **3**, and **7** (Table 2), show lactam NH resonances near 11 ppm and pyrrole NHs near 10 ppm whereas, with the presence of a carboxylic acid group, as in [6]-semirubin, the pyrrole NH moves upfield by ~1 ppm (to ~9 ppm), and the lactam NH also moves upfield (to ~10.4 ppm). In $(CD_3)_2SO$ a leveling effect is exerted and the lactam NH signals of **1**–**3** and **7** are more shielded (to ~9.8 ppm) than the pyrrole NH (~10.2 ppm).

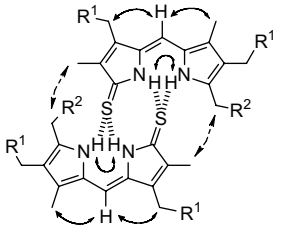


Figure 3. Key NOEs observed for **4** (R^1=H, R^2=$CH_2CH_2CH_2CH_2CO_2H$), **8** (R^1=H, R^2=$CH_2CH_2CH_2CH_2CO_2CH_3$), and **6** (R^1=CH_3, R^2=H) in $CDCl_3$ are shown by double-headed arrows. The dashed arrows indicate weak NOEs. No NOEs were observed between the CO_2H and the lactam or pyrrole NH.

Table 2
Comparison of the pyrrole, lactam, and carboxylic acid ^{1}H NMR chemical shifts[a] of **1**–**8** in $CDCl_3$ and $(CD_3)_2SO$[b]

Compound	Lactam NH	Pyrrole NH	CO_2H
1	10.42[c]	8.98[c]	13.22[c]
	9.81	*10.12*	*11.95*
2	11.17[c]	10.11[c]	—
	9.81	*10.12*	—
3	11.10	10.05	—
	9.83	*10.33*	—
4	11.05[d]	9.55[d]	13.06[d]
	11.92	*10.98*	*12.62*
5	11.47	9.95	—
	11.44	*10.94*	—
6	11.41[e]	9.94[e]	—
	11.43	*10.91*	
7	11.15	10.25	—
	9.72	*10.26*	—
8	11.26[f]	9.71[f]	—
	11.59	*10.91*	—

[a] δ ppm downfield from $(CH_3)_4Si$ for 3×10^{-3} M solutions in $CDCl_3$ and $(CD_3)_2SO$ at 25 °C.
[b] The data from $(CD_3)_2SO$ are shown in italics, concentration=4×10^{-2} M.
[c] Concentration=1×10^{-3} M.
[d] Concentration=8×10^{-3} M at 3×10^{-2} M, δ_{lactam}=11.77 and $\delta_{pyrrole}$=9.88 ppm.
[e] Concentration=1.33×10^{-2} M; at 3.09×10^{-3} M, δ_{lactam}=10.27 and $\delta_{pyrrole}$=9.06 ppm.
[f] Concentration=1×10^{-2} M.

With dipyrrinthiones **5** and **6** as reference standards for investigating the pyrrole and lactam NH chemical shift, we note that in $CDCl_3$, consistent with those of the parent dipyrrinones (**7** and **3**), the lactam NH (~11.5 ppm) is more deshielded than the pyrrole NH (~10 ppm). And in fact the thiolactam and pyrrole NH chemical shifts (11.47 and 11.41, and 9.95 and 9.94 ppm) of **5** and **6** are not very different from the lactam (11.15 and 11.10 ppm) and pyrrole (10.02 and 10.05 ppm) NH chemical shifts of **3** and **7**. Remarkably, the thiolactam NH chemical shifts of **5** and **6** are nearly identical in $CDCl_3$ and $(CD_3)_2SO$, which is not seen in the parent lactams, **3** and **7**, yet the pyrrole NH chemical shifts of **5** and **6** in $CDCl_3$ are shielded by ~1 ppm from those in $(CD_3)_2SO$—a much larger difference than that found in **3** and **7** (0.01–0.28 ppm). The reasons for this are unclear. Comparing **4** and **8** to **5** and **6**, we note that the NH chemical shifts of both **4** and **8** in $CDCl_3$ and $(CD_3)_2SO$ are similar to those of **5** and **6** in the corresponding solvent. These data suggest similar environments for the dipyrrinthiones in $(CD_3)_2SO$, as is typically found for this solvent. Unexpectedly, the data also suggest similar environments in $CDCl_3$—a solvent where intramolecular hydrogen bonding between carboxylic acid and dipyrrinthione might have been expected in **4**, and dipyrrinthione to dipyrrinthione hydrogen-bonded dimer formation expected only for **5**, **6**, and **8**—analogous to **1** versus **2**, **3**, and **7**. However, these data alone do not disprove dipyrrinthione to CO_2H hydrogen bonding in **4**.

2.4. NOE measurements

One indicator of dimer formation lies with NOE data from ^{1}H NMR spectroscopy in $CDCl_3$. Thus, when dipyrrinones form intermolecularly hydrogen-bonded dimers, an NOE is observed between the C(2^1) hydrogens and those at C(9^1), as has been noted for **3**, **7**, and even **1**. In contrast, when the dipyrrinone sequesters a CO_2H group through hydrogen bonds, an NOE is observed between the CO_2H hydrogen and the dipyrrinone lactam NH—as is seen in [6]-semirubin (**1**), bilirubin, etc. For dipyrrinthiones **5**, **6**, and **8**, we observe NOEs (Fig. 3) of the former type. For **4**, we also see the former type and not the latter. These data suggest

that all of the dipyrrinthiones of this study form predominantly *intermolecularly* hydrogen-bonded dimers in $CDCl_3$. Again, however, although the failure to find a CO_2H to dipyrrinthione NOE does not support carboxylic acid to dipyrrinthione hydrogen bonding, it does exclude its possibility.

2.5. Beer's law behavior

Further evidence for a monomer⇆dimer equilibrium may be found in the Beer's law plots (Fig. 4) of the dipyrrinthiones. The parent dipyrrinone, [6]-semirubin (**1**), was found to obey Beer's law, whereas its ester (**2**) diverges.[8] Just as dipyrrinones **2**, **3** and **7** (but not **1**) diverge from ideality with increasing concentration in $CHCl_3$,[7] so do their thiolactam analogs **5**, **6**, and **8**—as might be expected. What was not originally expected was that **4**, like **1**, would not diverge, yet, its Beer's law behavior, like that of **8**, is found to be consistent with dimer formation.

2.6. VPO studies of self-association

In order to establish the presence of dimers in non-polar solvents, we used vapor pressure osmometry (VPO) to analyze the molecular weights of **4**–**6** and **8** in $CHCl_3$ solution (Table 3). Previous studies showed that dipyrrinones such as **3** and **7** were dimeric, that [6]-semirubin ester (**2**) was also a dimer, but [6]-semirubin (**1**) itself was a monomer. The data were part of the argument in favor of an intramolecularly hydrogen-bonded structure for **1**.[8] When VPO was applied to dipyrrinthione esters **5**, **6**, and **8**, we found that these compounds were *dimers in CDCl*$_3$, consistent with the behavior of their dipyrrinone ester parents (**2**, **3**, and **7**), and showing that their sulfur analogs were capable of intermolecular hydrogen bonding. Just how strong this preference might be remained to be determined. Especially revealing was the

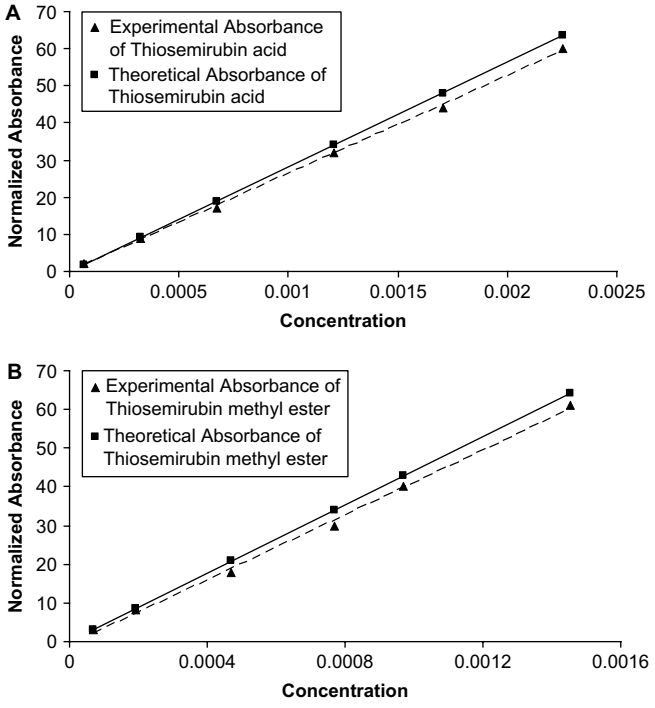


Figure 4. Beer's law plot for (A) thiosemirubin (**4**) and (B) its methyl ester (**8**) showing deviation from ideality. The actual absorbance measured for the highest concentration=2.0 (see Section 4). For the contrasting plots of **1**, which obeys Beer's law, and **2**, which does not, see Ref. 8.

Table 3
Molecular weights of dipyrrinthiones and dipyrrinones **1**–**8** determined by vapor pressure osmometry[a] at 45 °C in $CHCl_3$ solution

Dipyrrinthione	Formula weight (g/mol)	Molecular weight by VPO (g/mol)	Concentration range (mol/kg)
1	330	337 ± 20[b]	$2.1–6.6\times10^{-3}$
2	344	584 ± 30[b]	$1.7–6.1\times10^{-3}$
3	258	509± 20[c]	$2.0–12.8\times10^{-3}$
4	346	689 ± 7	$1.0–6.5\times10^{-3}$
5	384	654 ± 20	$0.72–2.2\times10^{-3}$
6	274	535 ± 12	$4–7\times10^{-3}$
6	274	416 ± 21	$4–7\times10^{-4}$
7	316	579 ± 25[c]	$1.5–6.5\times10^{-3}$
8	360	700 ± 30	$1.6–5.8\times10^{-3}$

[a] Calibrated with benzil (FW=210, measured MW=208±5).
[b] Data from Ref. 7.
[c] Data from Ref. 15.

unexpected observation that **4**, unlike **1**, also was a dimer in $CHCl_3$—at least at the concentrations of the VPO measurement.

2.7. Dimeric association

In an earlier study of dimerization of **3** and **7**, we determined the dimeric association constant (K_D) in $CDCl_3$ from the concentration dependence of the ^{1}H NMR chemical shifts of the lactam and pyrrole NHs. The K_D values were large (K_D ~25,000 M at 25 °C). Using the same method, in order to compare the tightness of hydrogen bonding in dipyrrinones with their thiolactam analogs, we determined K_D for **5** and **6** in $CDCl_3$ and found the pyrrole and thiolactam NH chemical shifts to be more concentration-sensitive than the pyrrole and lactam NHs of the parent dipyrrinones, **3** and **7**. For example, the thiolactam (δ_L) and pyrrole (δ_P) chemical shifts were observed at 11.41 and 9.94 ppm, respectively, at 1.33×10^{-2} M concentration of **6**, and at 10.27 and 9.06 ppm, respectively, at 2.06×10^{-3} M—a difference ($\Delta\delta$) of 1.14 and 0.88 ppm, respectively. In contrast, δ_L and δ_P were observed at 11.15 and 10.25 ppm, respectively, for 1.41×10^{-2} M of **3** and at 10.84 and 10.04 ppm, respectively, at 2.10×10^{-3} M—a $\Delta\delta$ of 0.31 and 0.21 ppm, respectively. This was a tip-off that the K_D of **6**, for example, might be substantially lower than that of **3**. This was realized from the K_D determinations, using the method described previously for **3** and **7**,[10] where the upper plateau (Fig. 5, upper) and lower foot (Fig. 5, lower) of plots of NH chemical shifts versus pigment concentration give δ_D and δ_M for dimer and monomer, respectively, for both the thiolactam and pyrrole NHs. Using the equations developed earlier that relate K_D to δ_D, δ_M, $\delta_{observed}$, and initial concentration of pigment, [M_O], one extrapolates to K_D values that are a factor of 100 smaller than those of the dipyrrinones (Table 4)—a clear indication that the thiolactam unit, unlike the lactam, in cooperation with the pyrrole behaves more or less like an ordinary thiolactam. The relative failing in this regard of the dipyrrinthione may be due to the longer C=S (vs C=O) bond that (in the dimer) increases the pyrrole NH···S=C distance relative to the NH···O=C distance.

Although the ^{1}H NMR study of the concentration dependence of the pyrrole and lactam chemical shifts in $CDCl_3$, VPO measurements, and Beer's law plots of [6]-semirubin (**1**) differed uniquely from its methyl ester (**2**) as well as dipyrrinones **3** and **7**, we failed to detect a similar difference in its thiolactam derivative **4** relative to thiolactams **5**, **6**, and **8**. For **1**, VPO indicated monomers in $CHCl_3$; its NH chemical shifts were invariant over the concentration range and Beer's law was obeyed—all of which are consistent with an intramolecular hydrogen-bonded monomer: dipyrrinone to CO_2H. We expected **4** to behave like **1** in these studies, but its behavior was much more like its ester (**8**), **5** and **6**, which may be considered to be intermolecularly hydrogen-bonded dimers in chloroform.

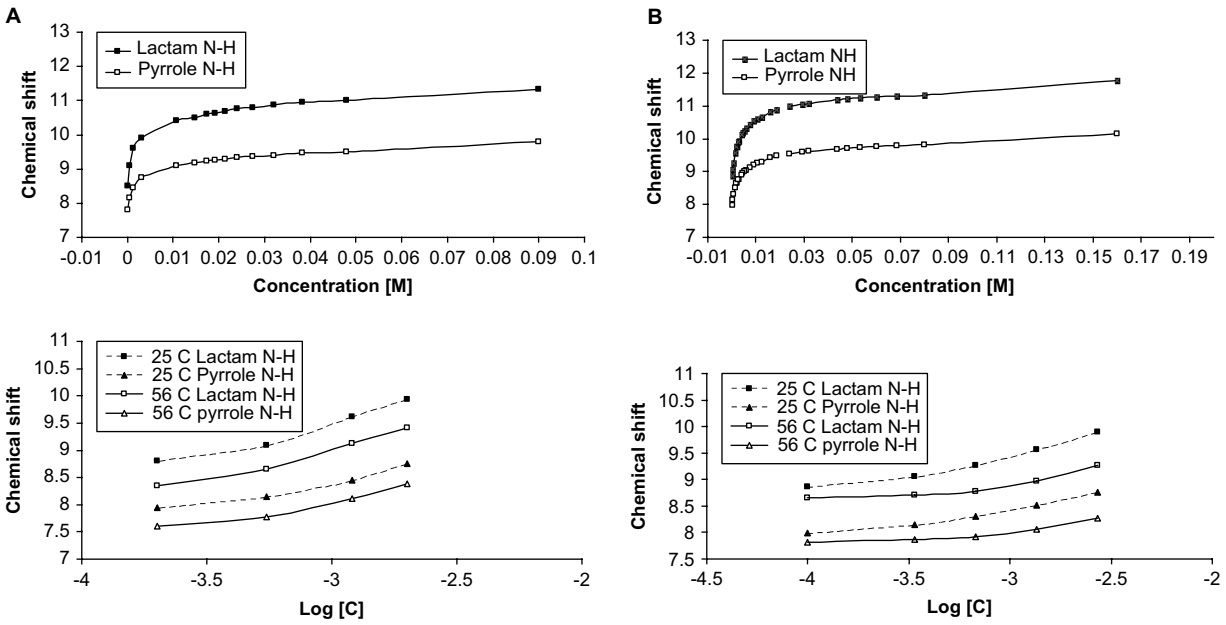


Figure 5. (A) Plots of pyrrole and lactam ^{1}H NMR chemical shifts versus concentration in $CDCl_3$ of thiosemirubin (**4**) (A, upper) and methyl thioxanthobilirubinate (**5**) (B, upper), and comparison of data from the low concentration of **4** (A, lower) and **8** (B, lower) plotted as NH chemical shift versus log concentration at 25 and 56 °C. Similar plots were found for **6** and **8**.

2.8. Solution properties and UV–vis spectra

Dipyrrinthiones (**4**–**6** and **8**) are red solids that form reddish solutions with long-wavelength UV–vis absorption bands centered near 490 nm. In contrast, the parent dipyrrinones are yellow with typical intense long-wavelength UV–vis absorption near 410 nm. Although bathochromically shifted, the absorption bands of the thiolactam analogs have molar absorptivity constants nearly unchanged from those of the parents, and their solutions are more noticeably solvatochromic (Table 5) than those of the parent dipyrrinones.

Table 4
Extrapolated dimerization association constants (K_D, M) and dimer (δ_D, ppm) and monomer (δ_M, ppm) NH chemical shifts of dipyrrinthiones (**4**–**6** and **8**) at 25 °C compared with dipyrrinones **3**, **7**, and **8** at 25 °C

	3	**4**	**5**	**6**	**7**	**8**
K_D[a]	22,000	160	315	238	28,600	208
K_D[b]	23,000	103	292	198	24,800	162
δ_D[c] (HN–C=X)	11.42	11.78	11.78	11.83	11.39	11.52
δ_D[d] (pyrrole)	10.44	9.98	10.17	10.21	10.43	10.02
δ_M[c] (HN–C=X)	7.75	8.21	8.65	8.65	7.75	8.25
δ_M[d] (pyrrole)	8.10	7.61	7.81	7.73	8.10	7.52

[a] From thiolactam or lactam NH data.
[b] From pyrrole NH data.
[c] Thiolactam (X=S) or lactam (X=O) NH NMR chemical shift of monomer (δ_M) and dimer (δ_D).
[d] Pyrrole NH NMR chemical shift of monomer (δ_M) and dimer (δ_D).

Table 5
Comparison of UV–vis spectral data of **1**–**8**[a]

Pigment	ε^{max} (λ^{max}, nm)				
	C_6H_6	$CHCl_3$	CH_3CN	CH_3OH	$(CH_3)_2SO$
1	27,200 (426)	28,200 (421)	26,600 (411)	31,500 (416)	30,400 (413)
2	33,200 (411)	28,800 (407)	33,600 (413)	33,500 (415)	33,200 (411)
3	36,100 (412)	32,200 (408)	32,000 (406)	39,400 (417)	35,600 (415)
4	28,400 (492)	29,100 (495)	28,000 (490)	29,400 (490)	28,300 (493)
	26,200 (513)^{sh}	27,800 (515)^{sh}			
5	26,200 (484)	32,500 (489)	28,500 (480)	32,000 (481)	31,100 (482)
6	34,800 (484)	32,200 (493)	31,200 (484)	34,500 (485)	33,700 (484)
7	26,500 (412)	34,000 (408)	28,900 (400)	37,700 (411)	34,600 (410)
8	38,500 (487)	38,300 (492)	42,350 (485)	46,000 (488)	42,600 (494)

[a] Solutions were $\sim 1\times10^{-5}$ M at 22 °C; ε in L mol cm^{-1}.

3. Concluding comments

[6]-Thiosemirubin **4** is a dimer in $CHCl_3$, as measured by VPO. Its pyrrole and lactam NH chemical shifts are concentration-dependent and it fails to obey Beer's law. We conclude that the thiolactam unit of **4**, and indeed the entire dipyrrinthione, offers no special attraction to the carboxylic acid that the unique ability of a dipyrrinone to sequester a CO_2H group through hydrogen bonding is lost in dipyrrinthiones. Since the available evidence suggests a weaker K_D ($\sim$300 M) for the monomer$\leftrightarrows$dimer equilibrium in dipyrrinthiones relative to dipyrrinones ($K_D \sim$25,000 M), we predict that any hydrogen bonding between the dipyrrinthione and CO_2H units of **4** would have an intermolecular association constant (K_{assoc}) $<\sim$200–300 M.

4. Experimental section

4.1. General procedures

Nuclear magnetic resonance (NMR) spectra, NOEs, and T_1 measurements were obtained on a Varian Unity Plus 500 MHz spectrometer in $CDCl_3$ solvent (unless otherwise specified) at 25 °C. Chemical shifts were reported in δ ppm referenced to the residual $CHCl_3$ ^{1}H signal at 7.26 ppm and ^{13}C signal at 77.0 ppm. A combination of heteronuclear multiple bond correlation (HMBC) spectra and ^{1}H{^{1}H} NOE data were used to assign ^{1}H and ^{13}C NMR spectra. UV–vis spectra were recorded on a Perkin–Elmer Lambda-12 spectrophotometer. Melting points were taken on a Mel Temp capillary apparatus and are corrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. High resolution mass spectra were determined at the Nebraska Center for Mass Spectroscopy, University of Nebraska, Lincoln. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μm layers). Radial chromatography was carried out on Merck silica gel PF_{254} with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Palo Alto, CA). Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). THF used was distilled from Na/benzophenone. Deuterated chloroform and dimethylsulfoxide were from Cambridge Isotope Laboratories. 2,3,7,8-Tetramethyl-(10*H*)-dipyrrin-1-one,[8,10] [6]-semirubin (**1**),[8] [6]-semirubin methyl ester (**2**),[8] kryptopyrromethenone (**3**),[22] kryptopyrromethenethione

(**6**),[15] methyl xanthobilirubinate (**7**),[17] and methyl thioxanthobilirubinate (**5**)[15] were prepared as described in the literature.

Beer's law measurements were carried out as follows:[8] (1) measure a standard UV–vis spectrum and calculate ε^{max} at λ^{max}. (2) Using ε^{max} calculate the highest concentration possible for the shortest cell path length available, usually 0.5–1.0 mm, to give an absorbance=2. (3) Prepare a solution at the concentration determined in (2) and measure the spectrum. (4) Perform serial dilutions, e.g., 1:2, etc., until the lower limit of detection of the instrument is reached. (5) Normalize the absorbance data to a path length of 1 cm and plot. This procedure gave the plots of Figure 4.

4.2. 9-[5-Carbo(*tert*-butyldiphenylsilyl)pentyl]-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one ([6]-semirubin *tert*-butyldiphenylsilyl ester) (9)

[6]-Semirubin (**1**) (1 equiv, 100 mg, 0.303 mmol) and 3 equiv of imidazole (61.8 mg, 0.909 mmol) were mixed in dry THF (40 mL). Then 2 equiv of *tert*-butyldiphenylsilyl chloride (166.5 mg≡0.16 mL, 0.606 mmol) was added to the reaction mixture and stirred at room temperature. After 4 days, 15 mL of water was added and the reaction solution was extracted with CH_2Cl_2. The organic layer was removed and dried over anhyd Na_2SO_4, and the solvent was evaporated (rotovap) to give a yellow solid. This was purified by radial chromatography on silica gel using CH_3OH/CH_2Cl_2 (2:98). The isolated yellow solid (71% yield), mp 144–146 °C, was obtained after evaporation of CH_2Cl_2/CH_3OH solution and was treated directly with Lawesson's reagent. It had ^{1}H NMR δ: 1.37–1.42 (m, 2H), 1.42 (s, 9H), 1.65–1.72 (m, 4H), 1.91 (s, 3H), 1.95 (s, 3H), 2.11 (s, 6H), 2.45 (t, 2H, J=7.6 Hz), 2.75 (t, 2H, J=7.2 Hz), 5.92 (s, 1H), 6.13 (s, 1H), 7.36 (t, 4H), 7.41 (d, 2H), 7.65 (d, 4H, J=7.5 Hz), 10.15 (s, 1H), 11.30 (s, 1H) ppm; ^{13}C NMR δ: 9.3, 9.8, 10.4, 10.6, 19.4, 25.8, 26.9, 27.5 (×3), 29.5, 30.8, 36.8, 101.2, 116.6, 122.9, 123.8, 126.0, 128.0, 128.9, 130.7, 132.7, 136.0, 136.6, 142.9, 173.6, 174.6 ppm. Anal. Calcd for $C_{35}H_{44}N_2O_3Si$ (568.8): C, 73.90; H, 7.80; N, 4.92. Found: C, 73.48; H, 7.73; N, 5.32.

4.3. 9-(5-Carboxypentyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-thione ([6]-thiosemirubin) (4)

tert-Butyldiphenylsilyl ester (**9**, 1 equiv, 100 mg, 0.183 mmol) from above and 3 equiv of Lawesson's reagent (222.6 mg, 0.550 mmol) were mixed together in dry tetrahydrofuran (20 mL), and the reaction mixture was stirred at room temperature for 2 days under N_2 atmosphere. Then 2 mL (2.0 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF was added to deprotect the silyl ester, and the reaction mixture was stirred for 12 h. THF solvent was removed (rotovap), the residue was dissolved in CH_2Cl_2, and the solution was passed through a short column of silica gel (filtration chromatography), using CH_2Cl_2 as eluent. The product was further purified by radial chromatography using CH_2Cl_2 as eluent. The deep red-colored solid (**1**) (32% yield), mp 178–180 °C, was obtained after evaporation of CH_2Cl_2. It was stored in the dark under N_2 at 0 °C. It had ^{1}H NMR δ: 1.38–1.43 (m, 2H), 1.57–1.66 (m, 2H), 1.71–1.74 (m, 2H), 1.90 (s, 3H), 1.94 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.48 (t, 2H, J=7.2 Hz), 2.72 (t, 2H, J=7.2 Hz), 6.11 (s, 1H), 8.96 (s, 1H), 10.49 (s, 1H), 13.5 (br s, 1H) ppm; ^{13}C NMR data in Table 1; UV–vis spectral data are in Table 5; HRMS (FAB, glycerol); calcd for $[M+H^+]$ $C_{19}H_{27}N_2O_2S$: 347.1793; found: 347.1784.

4.4. 9-(5-Carbomethoxypentyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-thione ([6]-thiosemirubin methyl ester) (8)

[6]-Semirubin methyl ester (**2**, 1 equiv, 100 mg, 0.291 mmol) and 3 equiv of Lawesson's reagent (352 mg, 0.872 mmol) were mixed together in dry THF (40 mL), and the reaction mixture was stirred at room temperature for 36 h under N_2. THF solvent was removed (rotovap), the residue was dissolved in CH_2Cl_2, and the solution was passed through a short column of silica gel (filtration chromatography) using CH_2Cl_2 as eluent. The solution was evaporated and the residue was purified by radial chromatography on silica gel using CH_2Cl_2 as eluent. The deep red-colored solid (**4**) (32% yield), mp 215–217 °C, was obtained after evaporation of CH_2Cl_2. It was stored in the dark under N_2 at 0 °C. It had ^{1}H NMR δ: 1.22–1.28 (m, 2H), 1.49–1.54 (m, 4H), 1.86 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.24 (t, 2H, J=7.9 Hz), 2.67 (t, 2H, J=7.5 Hz), 3.59 (s, 3H), 6.19 (s, 1H), 9.48 (br s, 1H), 10.98 (br s, 1H) ppm; ^{13}C NMR data are in Table 1; UV–vis spectral data may be found in Table 5. Anal. Calcd for $C_{20}H_{28}N_2O_2S$ (360.5): C, 66.63; H, 7.83; N, 7.77. Found: C, 67.03; H, 7.88; N, 7.42.

Acknowledgements

This work was supported by the U.S. National Institutes of Health (HD17779). S.D. is an R.C. Fuson Graduate Fellow. We thank the U.S. National Science Foundation (CHE-0521191) for matching funds to acquire a 400 MHz NMR spectrophotometer and upgrade our 500 MHz NMR. We also thank Professor T.W. Bell for use of the vapor pressure osmometer.

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