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Intramolecular hydrogen bonding between remote termini

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Abstract—[10]-Semirubin (**1**) and [20]-semirubin (**2**), with dipyrrinones covalently linked to C_{10} and C_{20} fatty acid chains, were synthesized following Friedel–Crafts acylation of the parent 9-H dipyrrinone, (4*Z*)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one, with the diacid chlorides of decanedioic acid and eicosanedioic acid, respectively. Both of these bright yellow pigments are monomeric in $CHCl_3$ solvent: MW_{obs}=394±20 for **1** (formula weight 386), and 533±20 for **2** (formula weight 526) as determined by vapor pressure osmometry (VPO) measurements. In contrast, their methyl esters are dimeric in $CHCl_3$. $^1H\{^1H\}$-Nuclear Overhauser effects are found between the lactam NH and carboxylic acid OH of **1** and **2**, consistent with the type of intramolecular hydrogen bonding found in bilirubin (the yellow pigment of jaundice) and its analogs.

1. Introduction

Bilirubin (Fig. 1), the yellow pigment of jaundice and the end-product of heme metabolism in mammals is produced in large quantities (~300 mg) each day in adult humans.[1,2] It is composed of two dipyrrinone chromophores conjoined at and capable of independent rotations about a central CH_2 group. In its most stable conformation, bilirubin adopts a ridge–tile shape[3] with the propionic acid of one dipyrrinone engaged in intramolecular hydrogen bonding to the second dipyrrinone.[3–7] The intramolecular hydrogen bonding depicted in Fig. 1 has several consequences: it dictates the stereochemistry of the pigment;[3–8] it reduces the polarity of the molecule compared to analogs with propionic acids relocated away from C(8) and C(12);[8] and it makes the compound intrinsically unexcretable in vivo in mammals, except by conversion to glycosyl ester conjugates.[1,2,9]

Bilirubin analogs with but one dipyrrinone have long played an important role in understanding its chemical and metabolic properties and its photobiology.[10–16] Until recently, however, the known dipyrrinone analogs were structurally incapable of intramolecular hydrogen bonding.[17–20] Yet it became clear from close examination that dipyrrinones were avid participants in hydrogen bonding: if they could not find a carboxylic acid with which to engage in hydrogen bonding, they would form dipyrrinone to dipyrrinone hydrogen-bonded dimers (Fig. 2, top) in the crystal[7,20] as well as in solutions in nonpolar solvents.[22,23] The simplest known, intramolecularly hydrogen-bonded analog of bilirubin is [6]-semirubin (Fig. 2, bottom), with a pentamethylene chain linking C(9) of the dipyrrinone to the carboxylic

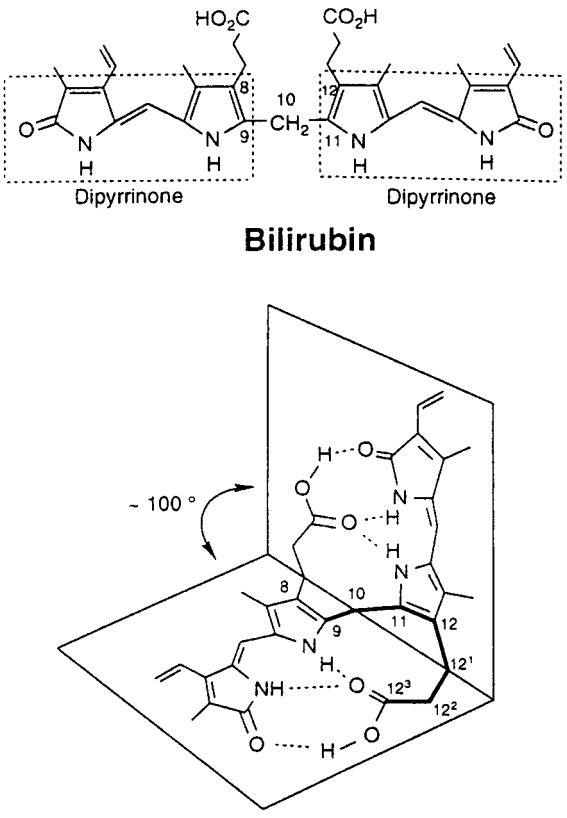

Figure 1. (Top) Constitutional structure of bilirubin. (Bottom) The most stable bilirubin conformation is shaped like a ridge–tile, with hydrogen bonds (shown by dashed lines) between the carboxylic acid groups and the opposing dipyrrinones. The bold lines show a typical six-carbon connectivity characteristic of intramolecular hydrogen bonding between the dipyrrinone and carboxylic acid.

Keywords: pyrroles; conformation; hydrogen bonding.

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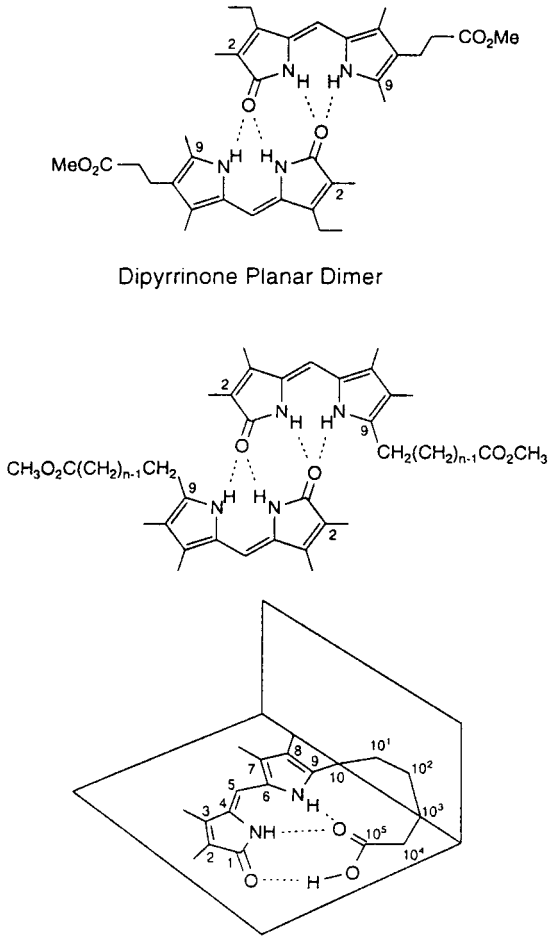
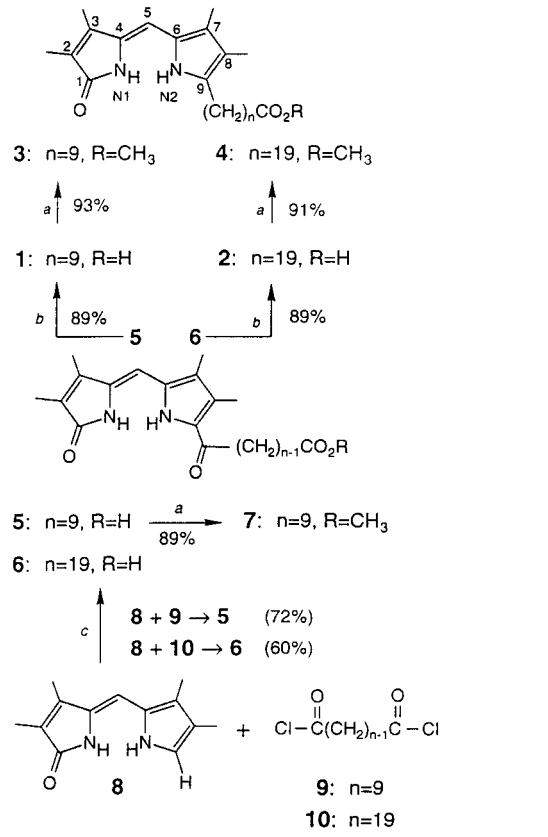


Figure 2. (Top) A typical planar, intermolecularly hydrogen-bonded dipyrrinone dimer: methyl xanthobilirubinate. (Middle) Intermolecularly hydrogen bonded dimeric structure of the methyl esters of [10]-semirubin (**3**, n=9) and [20]-semirubin (**4**, n=19) and [6]-semirubin (n=5). (Bottom) [6]-Semirubin in its favored intramolecularly hydrogen-bonded conformation. The shape of [6]-semirubin is similar to that of one-half of bilirubin (see Fig. 1). Hydrogen bonds are represented by dashed lines.



Scheme 1. *a*: CH_3OH/H_2SO_4; *b*: $NaBH_4/(CH_3)_2CHOH$ refl.; *c*: $SnCl_4/CH_2Cl_2$.

acid terminus. This compound was observed to be monomeric in $CHCl_3$ solution by vapor pressure osmometry (VPO) and found to be intramolecularly hydrogen-bonded by $^1H\{^1H\}$-nuclear Overhauser effect (NOE) spectroscopy.[17] In contrast, its methyl ester is dimeric in $CHCl_3$ (as in Fig. 2, top), with an NOE seen between the methyl attached to C(2) and the methylene group attached to C(9).

In order to explore the propensity for dipyrrinones to form intramolecular hydrogen bonds to well-separated carboxylic acid groups, we prepared two new semirubins: [10]-semirubin (**1**) and [20]-semirubin (**2**), with long chain fatty acids, decanoic acid and eicosanoic acid, respectively. In the following, we discuss their syntheses, characterization and intramolecular hydrogen bonding.

2. Results and discussion

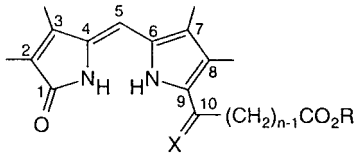
2.1. Synthesis

As with the preparation of [6]-semirubin, the syntheses of **1** and **2** (Scheme 1) were designed around the acylation of the known 9-H dipyrrinone (**8**).[20,24,25] Thus, when a cold solution of **8** in dichloromethane was treated with the diacid chloride of decanedioic acid (**9**) in the presence of anhydrous $SnCl_4$, then quenched with ice–HCl, a 72% yield of keto-acid **5** was obtained after radial chromatography. Similar treatment of **8** with the diacid chloride of eicosanedioic acid (**10**) afforded a 60% yield of **6**, which was unexpectedly very insoluble in $CHCl_3$. Interestingly, the acylation proceeded unsatisfactorily with anhydrous $AlCl_3$ catalyst but worked nicely with $SnCl_4$. Although this differential effectiveness of $AlCl_3$ and $SnCl_4$ parallels our earlier observations in acylating an 8-H dipyrrinone with the diacid chloride of eicosanedioic acid,[26] when acylating **8** with the half-ester acid chloride of adipic acid, we found that $AlCl_3$ was much more effective than $SnCl_4$.[17] Reduction of the ketone carbonyl of **5** and **6** using $NaBH_4$ in refluxing isopropyl alcohol proceeded smoothly to afford [10]-semirubin (**1**) and [20]-semirubin (**2**) in 89% yield after radial chromatography and crystallization. Their methyl esters (**3** and **4**) were obtained in 93 and 91% yield by Fischer esterification.

2.2. Molecular structure

The constitutional structures of **1**–**7** (see Scheme 1) follow from the structure of the common, well-known dipyrrinone (**5**) starting material[24,25] and from the method of synthesis. They were confirmed by their ^{13}C NMR spectra, and all assignments were made by HMQC and HMBC experiments. Consistent with the postulated structures, [10]-semirubin (**1**), [20]-semirubin (**2**) and their methyl esters (**3** and **4**) show chemical shifts (Table 1) characteristic of the

Table 1. ^{13}C NMR chemical shifts of semirubins **1** (n=9, X=H_2, R=H), and **2** (n=19, X=H_2, R=H), their methyl esters **3** (n=9, X=H_2, R=CH_3) and **4** (n=19, X=H_2, R=CH_3), and oxo-[10]-semirubin **5** (n=9, X=O, R=H), its methyl ester **7** (n=9, X=O, R=CH_3)



Carbon	Dipyrrinone chemical shift in $(CD_3)_2SO$						Dipyrrinone chemical shift in $CDCl_3$					
	1	**2**	**3**	**4**	**5**	**7**	**1**	**2**	**3**	**4**	**5**	**7**
1	171.8	171.8	171.8	171.7	172.7	172.7	174.6	174.5	173.3	173.5	175.6	173.6
2	123.3	123.3	123.3	123.2	126.7	126.7	123.3	123.3	123.1	123.2	135.4	136.5
3	141.3	141.3	141.4	141.2	141.7	141.7	142.3	142.3	142.2	142.1	142.4	141.9
4	128.4	128.4	128.4	128.4	135.9	135.5	128.2	128.3	128.3	128.3	125.2	128.3
5	97.91	97.91	97.95	97.75	96.20	96.18	101.5	101.5	101.2	101.2	98.77	96.91
6	121.6	121.6	121.6	121.5	128.3	128.3	122.1	122.2	122.1	122.1	131.6	131.1
7	122.7	122.7	122.7	122.5	122.8	122.8	126.1	125.7	125.2	125.2	128.3	129.0
8	133.9	133.9	133.9	133.8	125.6	125.6	136.2	136.9	136.3	136.3	124.4	123.6
9	114.6	114.9	114.7	114.5	130.3	130.3	116.1	116.1	115.8	115.8	127.6	126.0
10	24.44	24.44	24.43	24.35	189.8	189.8	25.20	25.21	26.37	26.39	190.6	190.4
10^{n-1}	[a]	[b]	[c]	[d]	[e]	[f]	[g]	[h]	[i]	[j]	[k]	[l]
CO_2R	174.4	174.4	173.5	172.2	174.5	173.3	180.1	179.7	173.9	173.9	178.9	174.3
2-CH_3	8.29	8.29	8.34	8.14	8.39	8.36	8.21	8.26	8.64	8.62	8.39	8.60
3-CH_3	9.53	9.53	9.59	9.39	9.58	9.55	9.82	9.83	9.93	9.91	9.87	9.89
7-CH_3	9.38	9.38	9.44	9.24	9.11	9.08	9.69	9.69	9.73	9.72	9.34	9.47
8-CH_3	8.78	8.78	8.83	8.65	11.28	11.23	8.96	8.26	9.07	9.05	11.53	11.69

δ, ppm downfield from $(CH_3)_4Si$ for 10^2 M solutions.
[a] Carbons 10^1–10^9, in order: 25.79, 28.47, 28.69, 28.72, 28.74, 28.85, 29.71, 33.60 ppm.
[b] Carbons 10^1–10^{19} not assigned.
[c] Carbons 10^1–10^9, in order: 25.52, 28.43, 28.65, 28.73, 28.77, 28.56, 29.75, 33.24 ppm.
[d] Carbons 10^1–10^{18}, with some overlapping: 33.70, 33.16, 29.50, 28.81, 28.73, 28.66, 28.62, 28.55, 28.47, 28.43, 28.21, 25.40 24.29, 21.46.
[e] Carbons 10^1–10^9, in order: 33.65, 29.47, 28.91, 28.80, 28.72, 28.62, 28.55, 28.50 ppm.
[f] Carbons 10^1–10^9, in order: 39.43, 23.83, 28.82, 28.73, 28.60, 28.42, 28.42, 33.25 ppm.
[g] 34.12, 27.64, 27.44, 26.71, 26.12, 25.82, 23.41, 21.85.
[h] 34.98, 30.26, 29.68, 29.58, 28.27, 28.88, 28.64, 28.44, 28.39, 28.13, 28.09, 26.52.
[i] 34.10, 30.31, 29.48, 29.40, 29.29, 29.23, 29.13, 24.94.
[j] Carbons 10^1–10^{18}, with some overlapping: 34.74, 34.12, 30.34, 29.70, 29.47, 29.35, 29.27, 29.15, 25.05, 21.85.
[k] 39.28, 33.85, 27.51, 27.30, 26.87, 23.43, 23.37.
[l] 40.15, 34.08, 29.39, 29.32, 29.10, 24.92, 24.48.

dipyrrinone core and the fatty acid/ester fragment. The carbon resonances of acids **1**, **2** and **5** are scarcely distinguished from their corresponding esters in $(CD_3)_2SO$, except that the ester carbonyl is ~1 ppm higher field than the acid, and an OCH_3 resonance is present. Characteristically, C(9) of **1** and **2** (or **3** and **4**) is much more shielded than C(9) of the corresponding oxo analogs **5** (or **7**). In contrast, C(6) is more shielded in **1** and **2** (or **3** and **4**) than in **5** (or **7**), as are more remote carbons 2 and 4. Carbons 5 and 9, however, are more deshielded.

The carbon resonances of ring carbons 2, 4 and 6 and the methyls of **1**–**4** in $CDCl_3$ differ little from those in $(CD_3)_2SO$, while ring carbons 3 and 9 are more deshielded by ~1 ppm in $CDCl_3$. Larger differences appear at C(5), C(7) and C(8), which are ~3–4 ppm more deshielded in $CDCl_3$. Of particular interest are the lactam (C-1) and CO_2H carbonyl resonances of acids **1** and **2**, which are much more deshielded in $CDCl_3$ than in $(CD_3)_2SO$; yet the differences are only small in their esters, **3** and **4**. A similar behavior is found in contrasting **5** and **7**. As in earlier studies,[17] the contrasting behavior of **1**, **2** and **5** (vs **3**, **4** and **7**) suggest intramolecular hydrogen bonding in the acids.

2.3. Molecularity in solution

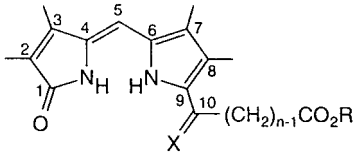
In order to assess whether **1**–**5** and **7** are monomeric in $CHCl_3$ solution, we determined their molecular weights by vapor pressure osmometry (VPO) over a molal concentration range 1.7–6.1×10^{-3} mol/kg. The calibration standard was benzil (MW_{calc}=210, MW_{obs}=220±15), and the molecular weights determined for the compounds of this work are summarized in Table 2. The data indicate that [10]-semirubin **1** and its oxo analog **5** are monomeric in $CHCl_3$ solution, as is [20]-semirubin **2**. In contrast, methyl esters **3** and **4** tend strongly toward dimerization. Dimer formation in these esters is not surprising in light of earlier observations that methyl xanthobilirubinate and related dipyrrinones are dimeric in nonpolar solvents,[22,27] as is [6]-semirubin methyl ester.[17] Surprisingly, but consistent with data for 10-oxo-[6]-semirubin ethyl ester,[17] oxo-semirubin methyl ester **7** is monomeric in $CHCl_3$ solution. Since the corresponding non-oxo esters **3** and **4** are dimeric, the differing behavior is apparently due to the presence and orientation of the oxo group: the C=O is probably oriented *anti* to the pyrrole NH,[17] leaving the alkyl chain oriented *syn* to the pyrrole NH and thus preventing intermolecular hydrogen bonding.

Table 2. Molecular weights of semirubins and oxo-semirubins determined by vapor pressure osmometry at 45°C in $CHCl_3$ solution

Dipyrrinone	Molecular weight		Concentration range (mol/kg)
	Calculated	Measured by VPO	
1	386	394±20	$1.7–5.7\times10^{-3}$
2	526	533±20	$1.6–4.1\times10^{-3}$
3	400	691±25	$2.2–5.2\times10^{-3}$
4	540	902±30	$1.5–4.1\times10^{-3}$
5	400	411±10	$1.6–5.7\times10^{-3}$
7	414	455±25	$2.0–5.0\times10^{-3}$
[6]-Semirubin	330	337±20[a]	$2.1–6.6\times10^{-3}$

Calibrated with benzil (FW=210, measured MW=220±15, molecular weights in g/mol).
[a] From Ref. 17.

Table 3. Comparison of NH ^{1}H NMR chemical shifts of semirubins and oxo-semirubins in $CDCl_3$ and $(CD_3)_2SO$ solvents



Dipyrrinone	δ (ppm) in $CDCl_3$[a]			δ (ppm) in $(CD_3)_2SO$[a]		
	Lactam	Pyrrole	CO_2H	Lactam	Pyrrole	CO_2H
1 (n=9, X=H_2, R=H)	10.83	8.83	13.52	9.78	10.09	11.88
2 (n=19, X=H_2, R=H)	10.75	8.95	13.22	9.78	10.10	11.84
3 (n=9, X=H_2, R=CH_3)	11.34	10.18	–	9.81	10.10	–
4 (n=19, X=H_2, R=CH_3	11.17	10.06	–	9.79	10.09	–
5 (n=9, X=O, R=H)	10.40	9.22	12.03	10.35	10.74	11.95
7 (n=9, X=O, R=CH_3)	9.28	8.48	–	10.34	10.73	–

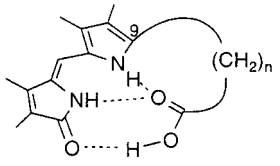
δ, Downfield from Me_4Si.
[a] Run as 10^2 M $(CD_3)_2SO$ and $\sim5\times10^3$ M $CDCl_3$ solutions at 25°C.

2.4. ^{1}H NMR and hydrogen bonding

Dipyrrinones are known to be avid participants in hydrogen bonding.[17–23,28] Diagnostic of this behavior and typical of the hydrogen bonding pattern found in the planar dimer motif (Fig. 2, top), the intrinsic N–H ^{1}H NMR chemical shifts of the lactam and pyrrole hydrogens of the monomer (δ ~8 ppm)[22] become strongly deshielded to, approximately, 11 and 10 ppm, respectively, in nonpolar solvents such as $CDCl_3$.[22,23,27] However, when the dipyrrinones engage in hydrogen bonding to CO_2H groups, whether intermolecularly[28] or intramolecularly[17] (Fig. 2, bottom), the NH chemical shifts are relatively more shielded, especially the pyrrole NH (~9 ppm), and to a lesser degree the lactam NH (~10.5).[17,28] Similar chemical shifts are also found in tetrapyrroles such as bilirubin[4,5,23] (Fig. 1) and its tripyrrolic analog.[19] Significantly, the NH chemical shifts of semirubins **1** and **2**, especially the shielded pyrrole NH near 9 ppm (Table 3), are similar to those of [6]-semirubin; whereas, those of the methyl esters (**3** and **4**) are more like those found in [6]-semirubin methyl ester and ordinary dipyrrinones, such as methyl xanthobilirubinate (Fig. 2, top). These data are consistent with intramolecular hydrogen bonding between dipyrrinone and the remote carboxylic acid groups both in **1** and **2** (Fig. 3), and intermolecular dipyrrinone-to-dipyrrinone hydrogen bonding in **3** and **4** (as in Fig. 2, middle). Although we cannot strictly rule out the possibility that one or more H_2O molecules might intervene between the dipyrrinone moiety and the remote carboxylic acid group, special care was taken to exclude traces of water from the samples and $CDCl_3$ solvent. In the absence of such procedures, the OH and NH resonances were somewhat broadened.

We rule out intermolecular hydrogen bonding between dipyrrinones and CO_2H groups, as has been reported for xanthobilirubic acid (acid of Fig. 2, top) and its alkanoic acid homologs (even to eicosanoic acid)[28] because VPO studies indicate that **1** and **2** are monomeric in $CHCl_3$. In contrast, in $(CD_3)_2SO$ solvent, the NH chemical shifts of **1**–**4** are all very similar, indicative of dipyrrinone hydrogen bonding to the solvent.

Similarly, for oxo-semirubin **5**, the dipyrrinone NH chemical shifts in $CDCl_3$ at ~10.5 and 9.2 for the lactam and pyrrole NHs are indicative of intramolecular hydrogen



1: n=9 **2**: n=19

Figure 3. [10]-Semirubin (**1**) and [20]-semirubin (**2**) with intramolecular hydrogen bonding between the dipyrrinone and carboxylic acid termini shown by dashed lines.

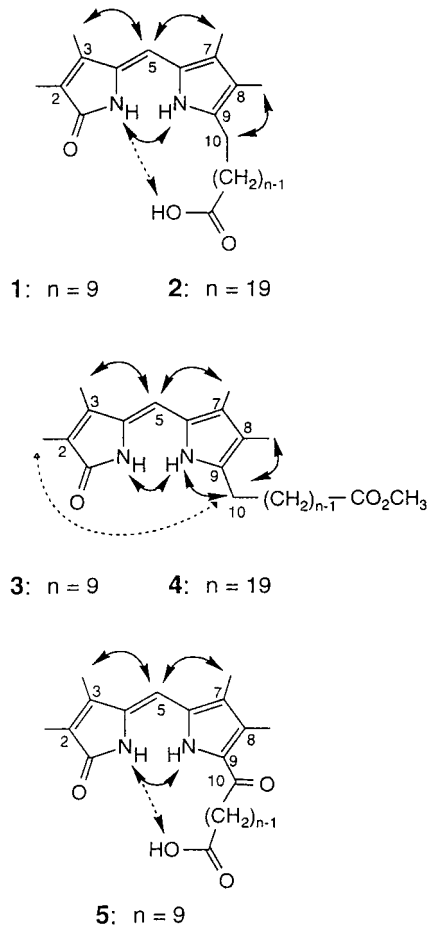


Figure 4. Selected $^{1}H\{^{1}H\}$–NOEs found in semirubins **1**–**5** in $CDCl_3$ solvent are indicated by curved double-headed arrows. The dotted arrows signify weak NOEs.

bonding. Although the presence of the C(10) carbonyl group might be expected to cause some differences in NH chemical shifts in **5** relative to those of **1**, the shielding of the pyrrole NH in **5** is typical of a dipyrrinone hydrogen-bonded to a carboxylic acid—as suggested for **1**. Thus, on the basis of the ^{1}H NMR NH chemical shifts it seems probable that semirubins **1** and **2**, as well as the 10-oxo analog **5** (**6** was too insoluble in $CDCl_3$ to obtain NMR data) are strapped into the conformation shown in Fig. 3. In contrast, methyl esters **3** and **4** are intermolecularly hydrogen-bonded (Fig. 2).

The NH chemical shifts of oxo-methyl ester **7** in $CDCl_3$ is unusual. The pyrrole and lactam NH chemical shifts lie at 9.3 and 8.5 ppm, respectively; whereas, in methyl esters **3** and **4**, the corresponding chemical shifts lie at 11.2 and 10.2 ppm. While the data for **3** and **4** are consistent with an intermolecularly hydrogen-bonded dimer, the data for **7** indicate a monomer, which is unusual in dipyrrinone esters. In particular, the 8.5 ppm chemical shift of the pyrrole NH is indicative of an *anti* orientation of the C(10) carbonyl relative to the pyrrole NH. One may find a parallel for the dependence of the NH chemical shift on the orientation of the ketone carbonyl group in certain pyrryl ketones. For example, when the carbonyl is *anti* to the pyrrole NH, as in *tert*-butyl 2-(3,4-dimethyl pyrryl) ketone, the NH

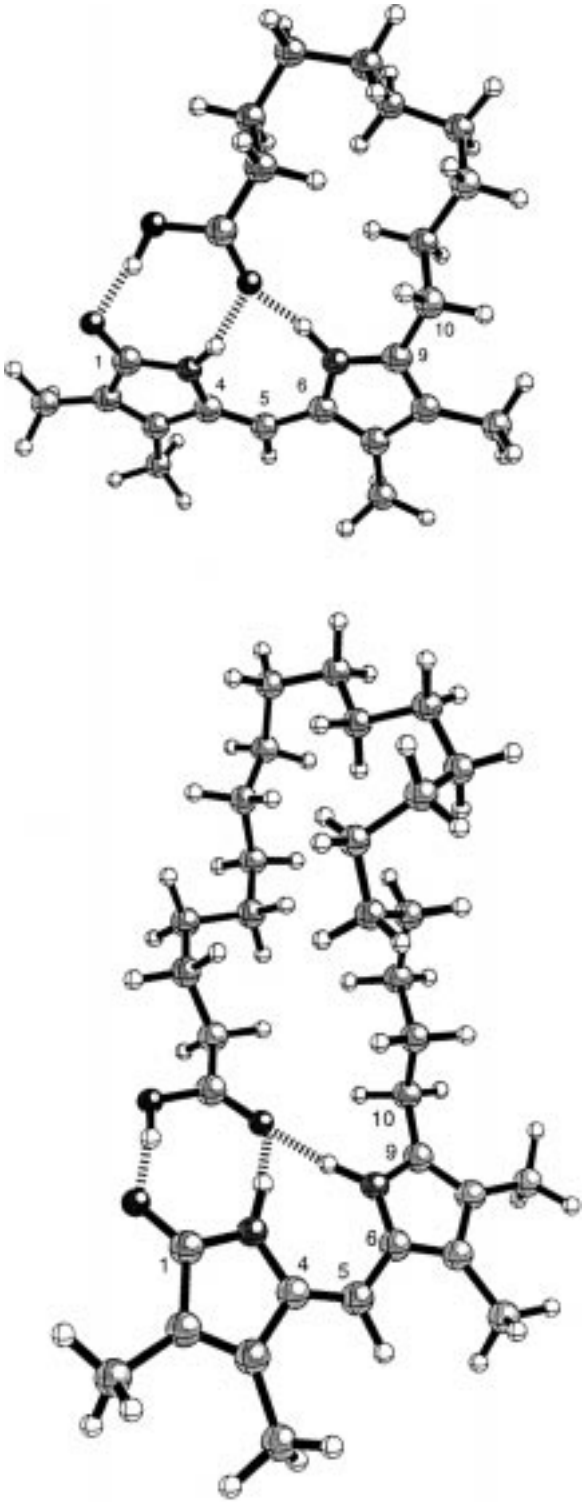


Figure 5. Ball and Stick models of the energy-minimized, intramolecularly hydrogen-bonded conformations of [10]-semirubin (**1**) (upper) and [20]-semirubin (**2**) (lower). Hydrogen bonds are shown by dashed lines.

chemical shift is 8.6 ppm, but when the carbonyl group is *syn*, as in *tert*-butyl 2-pyrryl ketone, it lies at 9.5 ppm.[29]

2.5. Conformation and NOE

The geometric structural assignment, particularly the *syn*-*Z*-configuration of the C(4) exocyclic double bond of the

Table 4. Solvent dependence of UV–visible data for semirubins **1** and **2**, their methyl esters (**3** and **4**) and 10-oxo-analogs (**5** and **7**)

Solvent	ϵ[a]	λ_{max} (ϵ_{max})[b] for					
		1	**2**	**3**	**4**	**5**	**7**
C_6H_6	2.3	427(29,800)	426(28,700)	410(35,500)	411(33,800)	422(19,800) 399(21,600)	419(17,500) 397(22,600)
$CHCl_3$	4.7	425(31,100)	426(32,000)	406(29,400)	406(30,100)	422(26,300) 399(28,500)	419(21,600) 398(24,200)
CH_3OH	32.6	415(37,000)	414(36,200)	414(35,700)	412(34,200)	416(24,300) 393(28,400)	418(25,100) 393(27,900)
CH_3CN	36.2	412(28,400)	411(29,100)	415(36,200)	415(36,200)	409(18,300) 387(23,400)	409(19,800) 386(25,600)
$(CD_3)_2SO$	49.0	413(29,800)	411(28,700)	412(31,400)	413(32,800)	412(19,800) 400(21,700)	414(17,700) 396(23,900)

Data obtained at 22°C on 2–4×10^{-5} M solutions.
[a] Dielectric constants from Ref. 33.
[b] λ_{max} in nm, ϵ_{max} in L M^{-1} cm^{-1}.

dipyrrinone moiety in **1**–**5** and **7** was confirmed by the observation of strong nuclear Overhauser effects (NOEs) in $CDCl_3$ between the lactam and pyrrole NHs, and moderate NOEs between the C(5)-H and the C(3) and C(7) methyls (Fig. 4). Since we were interested in evidence of hydrogen bonding, the relative orientation of the alkanoic acid group and the dipyrrinone terminus was of considerable interest to us. Their close proximity in **1**, **2** and **5** was confirmed by NOEs observed between the carboxylic acid hydrogens and the lactam NHs, as seen in bilirubin[6,27,30] (Fig. 1) and its models,[17–20] where similar carboxylic acid to dipyrrinone hydrogen bonding is present. Supporting intermolecular hydrogen bonding in **3** and **4**, an NOE was detected between the C(10) hydrogens and the C(2) methyl, as is expected[22] from a planar dimer (Fig. 2, middle). These data indicate: (i) a proximal spatial relationship between the carboxylic acid and lactam groups in **1**, **2** and **5** that is consistent with the intramolecular hydrogen bonding motif shown in the structural representation of Figs. 2 and 3, and (ii) planar, intermolecularly hydrogen-bonded dimers in **3** and **4**. Taken collectively, the NOE data are consistent with the VPO data which show that **1**, **2** and **5** (and probably **6**) are monomeric in $CDCl_3$, while **3** and **4** are dimeric.

2.6. Molecular dynamics calculations

In support of the conclusions reached (above) by NMR spectroscopic analysis, molecular dynamics calculations[31] of [10]-semirubin (**1**) and [20]-semirubin (**2**) show that these compounds prefer intramolecularly hydrogen-bonded conformations (Fig. 5), which are computed to lie some 11.4–12.6 kcal/mol lower in energy than the non-hydrogen-bonded forms. The intramolecularly hydrogen-bonded conformations shown in Fig. 5 have computed molecular parameters similar to those found in the dipyrrinones of bilirubin and mesobilirubin.[4,30,32] The dipyrrinone moiety in **1** and **2** is only slightly twisted, with C(4)–C(5)–C(6)–N torsion angles of ~11 and ~22°, respectively.

2.7. Optical spectra

The UV–visible spectral data for **1**–**5** and **7** in solvents with a wide range of polarity are shown in Table 4. The long wavelength bands of the semirubins (**1**–**2**) and their methyl esters (**3** and **4**) have nearly the same λ_{max} in polar solvents, but λ_{max} of **1** and **2** is strongly bathochromically shifted from that of **3** and **4** in nonpolar solvents, solvents likely to promote hydrogen bonding. Smaller wavelength shifts attend the spectra of the oxo-semirubin (**5**) and its methyl ester (**7**) over the range of solvents used. While the spectral shifts do not unambiguously confirm an intramolecularly hydrogen-bonded structure for **1**, **2** and **5**, they lend support to this conclusion, based on NMR spectral analysis and VPO studies, and they are consistent with the ability of the semirubin acids of this study to adopt a unique conformational structure in nonpolar solvents. The UV–visible spectral data for ester **7** is less solvent dependent than those of esters **3** and **4**, consistent with the indications that **3** and **4** tend toward dimeric in nonpolar solvents and **7** does not.

3. Conclusions

Remarkably and despite the remoteness of the two hydrogen bonding groups (dipyrrinone and acid) in semirubins **1** and **2**, these distal termini prefer intramolecular hydrogen bonding over intermolecular—as determined by ^{1}H NMR and VPO measurements. In contrast, their methyl esters are dimeric, with dipyrrinone to dipyrrinone intermolecular hydrogen bonding. The presence of an oxo group does little to thwart intramolecular hydrogen bonding in the 10-oxo-semirubin acids, but it appears to inhibit dimer formation is the corresponding methyl esters.

4. Experimental

4.1. General procedures

All UV–visible spectra were recorded on a Perkin–Elmer λ-12 spectrophotometer, and vapor pressure osmometry (VPO) measurements were performed using an Osmomat 070 (Gonotec, Berlin, Germany) in $CHCl_3$ at 45°C with benzil used for calibration. Nuclear magnetic resonance (NMR) spectra were obtained on a GE QE-300 spectrometer operating at 300 MHz, or on a Varian Unity Plus 500 MHz spectrometer in $CDCl_3$ solvent (unless otherwise specified). Chemical shifts were reported in δ ppm referenced to the residual $CHC1_3$ ^{1}H signal at 7.26 ppm and ^{13}C signal at 77.0 ppm. To ensure anhydrous samples and solvent in the

^{1}H NMR experiments, the samples were dried under vacuum in a drying pistol at refluxing toluene temperature and using P_2O_5 desiccant. The $CDCl_3$ solvent was stored over CaH_2 after having been passed through a column of Woelm basic Al_2O_3 (super Act 1). Heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) spectra were used to assign ^{13}C NMR spectra. Melting points were taken on a MelTemp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Fast atom bombardment high resolution mass spectra (FAB–HRMS) were obtained from the University of Minnesota Mass Spectrometry Facility. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μ layers). Flash column chromatography was carried out using Woelm silica gel F, thin layer chromatography grade. 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). Eicosanedioc acid was from TCI America and sebacoyl chloride was from Aldrich. Dichloromethane, methanol, tetrahydrofuran, hexane, and 2-propanol were from Fisher, and sodium borohydride and stannic chloride were from Acros.

Eicosanedioyl dichloride was prepared from by standard methods from eicosanedioic acid. 2,3,7,8-Tetramethyl-(10*H*)-dipyrrin-1-one (**8**)[25] was prepared according to literature procedures.

4.1.1. 9-(9-Carboxynonanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (5). 2,3,7,8-Tetramethyl-(10*H*)-dipyrrinone (**8**) (0.180 g, 0.83 mmol) and 150 mL of dichloromethane were added to a 500 mL round-bottom flask equipped for magnetic stirring. The solution was cooled in an ice bath for 20 min with stirring; then a solution of sebacoyl dichloride (1.0 g, 4.2 mmol) and $SnCl_4$ (6.5 g) in 100 mL of dichloromethane was added in one portion. The reaction mixture was stirred for 6 h at room temperature then poured into a mixture of conc. HCl (200 mL) and 100 g of ice and stirred for 2 h. The organic layer was separated, and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with sat. aq. $NaHCO_3$ then with water, and dried over Na_2SO_4 (anhydr.). The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2–hexane to afford 0.24 g, 72% of **5**. It had mp 155–156°C; IR (KBr) ν 3317, 2925, 2853, 1695, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (m, 8H), 1.61 (m, 2H), 1.78 (m, 2H), 1.92 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (t, 7.5 Hz, 2H), 2.82 (t, 6.5 Hz, 2H), 6.02 (s, 1H), 9.27 (s, 1H), 10.36 (s, 1H), 12.14 (bs, 1H) ppm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.23 (m, 8H), 1.45 (m, 2H), 1.57 (m, 2H), 1.78 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.17 (t, 7.5 Hz, 2H), 2.21 (s, 3H), 2.79 (t, 6.5 Hz, 2H), 5.95 (s, 1H), 10.35 (s, 1H), 10.74 (s, 1H), 11.95 (s, 1H) ppm; ^{13}C NMR are in Table 1. UV–visible data are in Table 4. Anal. Calcd for $C_{23}H_{32}N_2O_4$ (400.2): C, 68.97; H, 8.05; N, 6.99. Found: C, 68.81; H, 8.02; N, 7.14.

4.1.2. 9-(9-Carbomethoxynonanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (7). Dipyrrinone (**5**) (75 mg, 0.19 mmol) and 50 mL of methanol were added to a 100 mL round-bottom flask equipped for magnetic stirring. Five milliliters of 10% aq. H_2SO_4 was added to the solution dropwise over 5 min, and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in dichloromethane, and washed with water and sat. aq. sodium bicarbonate solution. The organic extract was dried over Na_2SO_4 (anhydr.), and the solvent was removed (rotovap). The residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2–hexane to give **7** (71 mg) in 89% yield. It had mp 121–122°C; IR (KBr) ν 3340, 3118, 2923, 2855, 1741, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (m, 8H), 1.61 (m, 2H), 1.69 (m, 2H), 1.93 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.29 (t, 7.5 Hz, 2H), 2.30 (s, 3H), 2.78 (t, 7.5 Hz, 2H), 3.66 (s, 3H), 5.94 (s, 1H), 8.48 (s, 2H), 9.28 (s, 1H) ppm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.27 (m, 4H), 1.30 (m, 4H), 1.51 (m, 2H), 1.58 (m, 2H), 1.80 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 2.22 (s, 3H), 2.28 (t, 7.5 Hz, 2H), 2.80 (t, 7.5 Hz, 2H), 3.57 (s, 3H), 5.96 (s, 1H), 10.34 (s, 1H), 10.73 (s, 1H) ppm; ^{13}C NMR are in Table 1; UV–visible data are in Table 4. Anal. Calcd for $C_{24}H_{34}N_2O_4$(414.2): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.16; N, 7.05.

4.1.3. 9-(9-Carboxynonyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (1). Dipyrrinone (**5**) (110 mg, 0.28 mmol) and 50 mL of 2-propanol were placed in a 100 mL round-bottom flask equipped for magnetic stirring. Sodium borohydride (100 mg, 1.7 mmol) was added, and the reaction mixture was heated at reflux for 3 h. The hot reaction mixture was poured into 100 mL of ice water, and the solution was acidified with 10% aq. HCl. The suspension was extracted with dichloromethane, and the combined organic extracts were washed with water and dried over Na_2SO_4 (anhydr.). The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from methanol–water to give 0.106 g (89%) of **1**. Although the sample gave excellent ^{13}C NMR, it was difficult to remove water completely. It had mp 189–190°C; IR (KBr) ν 3345, 3114, 2931, 2848, 1745, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (m, 10H), 1.62 (m, 2H), 1.73 (m, 2H), 1.90 (s, 3H), 1.96 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.38 (t, 7.5 Hz, 2H), 2.64 (t, 8.0 Hz, 2H), 6.13 (s, 1H), 8.83 (s, 1H), 10.83 (s, 1H), 13.52 (bs, 1H) ppm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.24 (m, 10H), 1.49 (m, 4H), 1.77 (s, 3H), 1.85 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.17 (t, 7.5 Hz, 2H), 2.50 (t, 7.5 Hz, 2H), 5.92 (s, 1H), 9.78 (s, 1H), 10.09, (s, 1H), 11.88 (s, 1H) ppm; ^{13}C NMR are in Table 1; and UV–visible data are in Table 4; FAB-HRMS (3-NBA+PEG400): calcd for $C_{23}H_{34}N_2O_3$ [M^+] 386.2569; found 386.2581, error 3.0 ppm, Δ 0.8 mDa. Anal. Calcd for $C_{23}H_{34}N_2O_3$ (386.5): C, 71.47; H, 8.87; N, 7.25. Calcd for $C_{23}H_{34}N_2O_3{\cdot}0.5H_2O$ (395.5):C, 69.79; H, 8.92; N, 7.09. Found: C, 69.33; H, 8.48; N, 7.07.

4.1.4. 9-(9-Carbomethoxynonyl)-2,3,7,8-tetramethyl-dipyrrin-1-one (3). Dipyrrinone (**1**) (50 mg, 0.13 mmol) and 50 mL of methanol were added to a 100 mL round-bottom flask equipped for magnetic stirring. Five milliliters of 10% aq. H_2SO_4 was added to the solution dropwise over 5 min, and the reaction mixture was heated at reflux for 1 h.

The reaction mixture was cooled to room temperature, taken up in dichloromethane, and washed with water and sat. aq. sodium bicarbonate solution. The organic extract was dried over Na_2SO_4 (anhydr.), and the solvent was removed (rotovap). The residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from abs ethanol to give **3** (48 mg) in 93% yield. It had mp 136–137°C; IR (KBr) ν 3348, 3152, 2861, 1736, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (m, 10H), 1.59 (m, 2H), 1.64 (m, 2H), 1.93 (s, 3H), 1.96 (s, 3H), 2.11 (s, 3H), 2.13 (s, 3H), 2.28 (t, 7.5 Hz, 2H), 2.74 (t, 7.5 Hz, 2H), 3.65 (s, 3H), 6.13 (s, 1H), 10.18 (s, 1H), 11.34 (s, 1H) ppm; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.23 (m, 10H), 1.48 (m, 4H), 1.75 (s, 3H), 1.84 (s, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.26 (t, 7.5 Hz, 2H), 4.50 (t, 7.5 Hz, 2H), 3.56 (s, 3H), 5.91 (s, 1H), 9.81 (s, 1H), 10.10 (s, 1H) ppm; ^{13}C NMR are in Table 1; and UV–visible data are in Table 4. Anal. Calcd for $C_{24}H_{36}N_2O_3$ (400.6): C, 71.96; H, 9.06; N, 6.99. Found: C, 71.90; H, 8.97; N, 7.20.

4.1.5. 9-(19-Carboxynonadecyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (2). (a) Eicosanedioic acid (0.50 g, 1.46 mmol) was heated at reflux in thionyl chloride (15 mL) for 1 h. Excess thionyl chloride was removed by distillation at water aspirator pressure, and 10 mL of dry CCl_4 was added to the crude acid chloride. The CCl_4 was removed by distillation at water aspirator pressure, and the process repeated. The residue was added to a solution of dipyrrinone **8** (79 mg, 0.37 mmol) in 150 mL in a 250 mL round-bottom flask. Anhydrous stannic chloride (5.0 g, 0.37 mmol) was added, and the mixture was stirred for 16 h at room temperature. The reaction mixture was then poured into a mixture of conc. HCl (200 mL) and 100 g of ice and stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with sat. aq. $NaHCO_3$, water, and dried over Na_2SO_4 (anhydr.). The solvent was removed (rotovap), and the crude product was purified to afford 9-(19-carboxynonadecanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrinone (**6**) (119 mg, 60%). The product **6** was unusually insoluble in nonpolar organic solvents and contained significant amounts of eicosanoic acid, which had similar solubility properties. Consequently, **6** was reduced directly to **2**. The spectral data relevant to **6** are: IR (KBr) ν 3316, 2927, 2850, 1695, 1675 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.27 (m, 24H), 1.29 (m, 4H), 1.46 (m, 2H), 1.57 (m, 2H), 1.79 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.18 (t, 7.5 Hz, 2H), 2.21 (s, 3H), 2.78 (t, 7.5 Hz, 2H), 5.95 (s, 1H), 10.34 (s, 1H), 10.72 (s, 1H), 11.92 (s, 1H) ppm.

(b) Dipyrrinone (**6**) (55 mg, 0.1 mmol) and 50 mL of 2-propanol were placed in a 100 mL round-bottom flask equipped for magnetic stirring. Sodium borohydride (100 mg, 1.7 mmol) was added, and the reaction mixture was heated at reflux for 3 h. The hot reaction mixture was poured into 100 mL of ice water, and the solution was acidified with 10% aq. HCl. The suspension was extracted with dichloromethane, and the combined organic extracts were washed with water and dried over Na_2SO_4 (anhydr.). The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2–hexane to give 48 mg (89%) of **2**. Although the sample gave excellent ^{13}C NMR, it was difficult to remove water and traces of eicosanedioic acid completely. It had mp 144–146°C; IR (KBr) ν 3347, 3229, 1707, 1654 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.22 (m, 28H), 1.48 (m, 4H), 1.76 (s, 3H), 1.84 (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 2.17 (t, 7.0 Hz, 2H), 2.49 (t, 7.0 Hz, 2H), 5.92 (s, 1H), 9.78 (s, 1H), 10.10 (s, 1H), 11.89 (s, 1H) ppm; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (m, 28H), 1.62 (m, 2H), 1.70 (m, 2H), 1.90 (s, 3H), 1.94 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.38 (t, 7.5 Hz, 2H), 2.64 (t, 7.5 Hz, 2H), 6.12 (s, 1H), 8.95 (s, 1H), 10.75 (s, 1H), 13.22 (s, 1H) ppm; ^{13}C NMR data are in Table 1; and UV–visible data are in Table 4; FAB-HRMS (3-NBA+PEG400): calcd for $C_{33}H_{54}N_2O_3$ [$M^{+\cdot}$] 526.4134; found 526.4132, error 0.5 ppm, Δ 0.8 mDa.

4.1.6. 9-(19-Carbomethoxynonadecyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (4). Dipyrrinone (**2**) (56 mg, 0.1 mmol) and 50 mL of methanol were added to a 100 mL round-bottom flask equipped for magnetic stirring. Five milliliters of 10% aq. H_2SO_4 was added to the solution dropwise over 5 min, and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in dichloromethane (50 mL), and washed with water and sat. aq. sodium bicarbonate solution. The organic extract was dried over Na_2SO_4 (anhydr.), and the solvent was removed (rotovap). The residue was purified by radial chromatography (97:3 by vol. CH_2Cl_2/MeOH) and recrystallized from methanol–water to give **4** (52 mg) in 91% yield. Although the sample gave excellent ^{13}C NMR, it was difficult to remove water completely. It had mp 147–148°C; IR (KBr) ν 3348, 3156, 2870, 1741, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (m, 30H), 1.61 (m, 4H), 1.93 (s, 3H), 1.95 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 2.24 (t, 7.5 Hz, 2H), 2.73 (t, 7.5 Hz, 2H), 3.66 (s, 3H), 6.12 (s, 1H), 10.06 (s, 1H), 11.17 (s, 1H) ppm; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.21 (m, 30H), 1.50 (m, 4H), 1.76 (s, 3H), 1.84 (s, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.21 (t, 7.5 Hz, 2H), 2.26 (t, 7.5 Hz, 2H), 3.56 (s, 3H), 5.91 (s, 1H), 9.79 (s, 1H), 10.09 (s, 1H) ppm; ^{13}C NMR data are in Table 1; and UV–visible data are in Table 4; FAB-HRMS (3-NBA+PEG400): calcd for $C_{34}H_{56}N_2O_3$ [$M^{+\cdot}$] 540.4291; found 544.4240, error 1.2 ppm, Δ 0.8 mDa.

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