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Stable 4*E*-Dipyrrinones

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Abstract. Dipyrrinones formed by DBU and *n*-Bu_3P-promoted condensation of 5-*p*-toluenesulfonylpyrrolinones with pyrrole 2-aldehydes, gave high yields of product with predominantly the *E*-configuration when the aldehyde had a 5-carboethoxy group. The 4*E*-dipyrrinones were readily purified by chromatography and were stable in solutions shielded from light.

Keywords: Pyrroles; stereoselection; stereoisomerism; hydrogen bonding

Introduction

The dipyrrinone chromophore (Fig. 1) is the major structural unit of bilirubin, a cytotoxic tetrapyrrole which is produced copiously in normal human metabolism of hemes and is the yellow pigment of jaundice.[1-3] Dipyrrinones give bilirubin its color and stereochemistry. Through rotations about a central CH_2, to which two *syn-Z*-dipyrrinones are conjoined, bilirubin adopts preferentially a shape that allows for considerable intramolecular hydrogen bonding with opposing propionic acids.[4-7] Such intramolecular hydrogen bonding controls the conformation of bilirubin in the crystal and in solution and dominates its solution properties, *e.g.*, its considerable hydrophobicity.[5] Typical dipyrrinones are bright yellow compounds with an intense UV-vis absorption near 400 nm (ϵ ~35,000 $L \cdot mole^{-1} \cdot cm^{-1}$) associated with the long axis polarized $\pi \rightarrow \pi^*$ excitation of the 14π-electron conjugated chromophore.[8,9] The parent unsubstituted *Z*- and *E*-dipyrrinones (Fig. 1) are essentially equi-energetic, according to molecular mechanics calculations;[8] whereas, *ab initio* molecular orbital calculations place the *syn-Z* ~2.4 kcal/mole more stable than the *anti-E*.[10] In contrast, the more common C-alkylated dipyrrinones are known from X-ray crystallography, NMR nuclear Overhauser effect (NOE) studies and molecular mechanics calculations to prefer clearly the *Z*-configuration when positions 3 and 7 are occupied by alkyl groups (by

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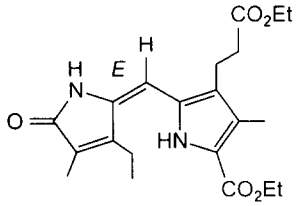
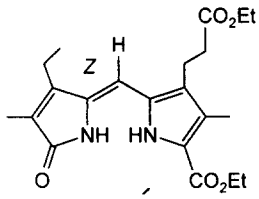
Table 3. UV-vis Data for Dipyrrinones (*E*)-**3** and (*Z*)-**3**.

				
Solvent	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)
$CHCl_3$	17,000 (377)	16,200 (278)^{sh} 20,600 (262)	24,200 (402) 30,300 (382)	23,700 (259) 22,900 (254)^{sh}
THF	13,800 (364)	18,600 (273) 21,600 (261)	23,500 (399) 30,000 (378)	23,600 (258) 21,200 (252)^{sh}
CH_3CO_2Et	14,400 (362)	18,000 (273)^{sh} 21,300 (260)	24,500 (396) 31,100 (376)	23,900 (258)
CH_3CN	14,500 (362)	17,900 (273) 21,100 (260)	21,900 (392)^{sh} 28,400 (374)	23,400 (257) 21,200 (251)^{sh}
CH_3OH	15,000 (370)	19,500 (276) 22,100 (262)	27,500 (400) 32,400 (380)	25,000 (258) 22,200 (251)^{sh}
$(CH_3)_2SO$	14,200 (367)	18,600 (276) 21,000 (263)	29,300 (405) 33,500 (383)	22,600 (261)

Concluding Comments

E-Dipyrrinones are typically unstable with respect to their *Z*-isomers; yet, synthesis of dipyrrinones with electron-withdrawing groups at C(9), *e.g.*, carboethoxy, appear to afford unusual stability to the *E*-diastereomers. The dipyrrinone-forming Wittig-type condensation reactions of this work give the *E*-diastereomer as the isolable kinetic product, which only slowly converts to (*Z*). On the other hand, when the electron-withdrawing C(9)-carboethoxy group is replaced by methyl or hydrogen, only *Z*-isomers are isolated in dipyrrinone-forming reactions. The current studies suggest that *E*-isomers of 10-oxo-bilirubin, a proposed metabolite formed in alternate pathways of bilirubin elimination, should be more stable than *E*-isomers of bilirubin. Bilirubin, which is composed of two dipyrrinones connected to a 10-CH_2, forms *E*-isomers photochemically and during neonatal phototherapy, but they are known to be unstable and readily revert to *Z*.

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TETRAHEDRON: *ASYMMETRY*

Synthesis of an optically active dipyrrinone sulfide and sulfoxide

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Abstract

Optically active dipyrrinone sulfide **2** and its sulfoxide **1** have been synthesized as potential precursors to tetrapyrrole analogs of bilirubin with sulfoxide groups replacing the natural carboxylic acids. Dipyrrinones **1** and **2** show weak exciton coupling in their circular dichroism spectra, with $\Delta\varepsilon_{427}^{max}$ −0.44, $\Delta\varepsilon_{398}^{max}$ +0.50 from **1**, and $\Delta\varepsilon_{442}^{max}$ –0.67, $\Delta\varepsilon_{404}^{max}$ +1.20 from **2**, but no evidence for inter- or intramolecular hydrogen bonding between the dipyrrinone NHs and the sulfoxide group of **1**.

1. Introduction

Dipyrrinones (Fig. 1A) are typically yellow chromophores with intense UV–visible absorption (ε ~30 000) near 400 nm.[1] They are the principal components of the important natural bile pigment bilirubin (Fig. 1B), the end product of heme metabolism in mammals and the colorful herald of hepatobiliary disease.[2,3] (4*Z*)-Dipyrrinones are avid hydrogen bonders and are strongly associated in solutions of nonpolar solvents.[4] In $CHCl_3$, for example, kryptopyrromethenone and methyl xanthobilirubinate show dimerization constants of 1700 M^{-1} (37°C)[5] and 25 000 M^{-1} (22°C)[4] measured by vapor pressure osmometry and ^{1}H NMR spectroscopy, respectively. The dimers are clamped together by four intermolecular hydrogen bonds, with a molecular mechanics-computed stabilization enthalpy of 20–30 kcal/mol.[6,7]

The type of dipyrrinone to dipyrrinone dimer shown in Fig. 1C is thought to be the most common type of hydrogen-bonded dipyrrinone dimer and is found even in bilirubin dimethyl ester.[1,8,9] However, in bilirubin and its analogs with propionic acids at C(8) and C(12), the component dipyrrinones participate in a unique type of hydrogen bonding involving the carboxylic acids (Fig. 1B), as found in the crystal by X-ray crystallography,[10–14] in solution by $^{13}C\{^1H\}$ heteronuclear Overhauser effects[15,16] and ^{1}H NMR,[8,9] and by molecular orbital and molecular dynamics computations.[17–20] Until recently,[6,21] it represented the only well-established example of carboxylic acid to amide hydrogen bonding. The potential for such hydrogen bonding is present in dipyrrinone acids, such as xanthobilirubic acid, but

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3. Concluding comments

Optically active dipyrrinones with sulfoxide **1** and sulfide **2** fragments exhibit weak bisignate CD Cotton effects in nonpolar solvents such as CCl_4. While these data suggest the presence of π-stacked dimers, ^{1}H NMR evidence suggests that the presence of such dimers is probably small.

4. Experimental

4.1. General

Nuclear magnetic resonance spectra were obtained on GE GN-300 or Varian Unity Plus spectrometers operating at ^{1}H frequency of 300 or 500 MHz, respectively. $CDCl_3$ solvent (unless otherwise specified) was used throughout and chemical shifts are reported in δ ppm referenced to residual $CHCl_3$ ^{1}H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.00 ppm. *J*-modulated spin–echo experiment (Attached Proton Test) was used to obtain the ^{13}C NMR assignments. Optical rotations were measured on a Perkin–Elmer model 141 polarimeter and circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument. All ultraviolet–visible spectra were recorded on a Perkin–Elmer Lambda-12 spectrophotometer. Vapor pressure osmometry measurements were performed on an OSMOMAT 070-SA instrument (Gonotec GmbH, Berlin, Germany) in chloroform at 45°C. Gas chromatography–mass spectrometry analyses were carried out on a Hewlett–Packard 5890A capillary gas chromatograph (30 m DB-1 column) equipped with a Hewlett–Packard 5970 mass selective detector. Analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Radial chromatography was carried out on Merck Silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2 or 4 mm thick rotors. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. The spectral data were obtained in spectral grade solvents (Aldrich or Fischer). HPLC grade solvents were dried and purified following standard procedures.[26]

The starting compounds (+)-(*S*)-3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butanoic acid **9**,[23] 5-bromomethylene-4-ethyl-3-methyl-2-oxo-1*H*-pyrrole **8**,[22] and (+)-(*S*)-3-(2,4-dimethyl-5-ethoxycarbonyl-1*H*-pyrrol-3-yl)butyl iodide **7**[6] were synthesized as described previously.

4.2. (+)-(S)-3-(2,4-Dimethyl-5-ethoxycarbonyl-1H-pyrrol-3-yl)butyl methylsulfide 4

Sodium (1.38 g, 60 mg atoms) was added slowly under nitrogen to 75 mL of anhydrous ethanol over 30 min. After all the sodium had reacted, the solution was cooled with ice bath and methanethiol (**Caution!** Highly toxic, stench) was slowly bubbled through the mixture at 0°C for 30 min (until a yellow precipitate appeared in the 15 cm long trap filled with saturated aqueous $Pb(OAc)_2$ and attached to the condenser effluent end). A solution of 6.98 g (20 mmol) of iodide **7** in 100 mL of dry ethanol was added dropwise over 20 min and the mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum to ~40 mL, diluted with 200 mL of $CHCl_3$ and washed with water till neutral (4×200 mL). The organic extract was dried over anh. Na_2SO_4 and filtered, and the solvent was evaporated under vacuum. The residue was purified by radial chromatography on silica gel and recrystallization (EtOAc/hexane) to afford 5.17 g (96%) of sulfide **4**. It had an mp of 75–76°C (racemate mp 81–82°C); $[\alpha]_D^{20}$ +40.0 (*c* 1.0, EtOH); ^{1}H NMR: δ 1.24 (3H, d, *J*=7.2 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.87 (2H, m), 2.06 (3H, s), 2.24 (3H, s), 2.32 (3H, s), 2.36 (2H, m), 2.86 (1H, m), 4.28 (2H, q, *J*=7.1 Hz), 8.58 (1H, br.s) ppm; ^{13}C

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On the Molecularity of Bilirubins and their Esters and Anions in Chloroform Solution

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Summary. Bilirubins with propionic acids at C-8 and C-12 engage in intramolecular hydrogen bonding and are thought to be monomeric in solution, although the latter is unproven. In contrast, their dimethyl esters and etiobilirubin analogs (with the C-8 and C-12 propionic acids replaced by alkyl residues) favor intermolecular hydrogen bonding and are thought to be dimeric in nonpolar solvents. There is little information on the molecularity of the bilirubin dianion in solution. In this work, vapor pressure osmometry studies of chloroform solutions of bilirubins, their dimethyl esters, and etio-analogs clearly indicate that the diacids and dianions are monomeric, whereas the diesters and dialkyls are dimeric. However, the presence of a C-10 *gem*-dimethyl group causes the ester and the etiobilirubin to become monomeric.

Keywords. Bile pigments; Solution molecular weight; Aggregation; Vapor pressure osmometry.

Introduction

Bilirubin (Fig. 1) is a festuscine-colored tetrapyrrole discarboxylic acid that is produced in vertebrates, including humans, principally from the breakdown of red blood cells [1, 2]. Although intrinsically unexcretable, it is efficiently eliminated by the liver following uptake and enzymic conversion to water-soluble glucuronides that are promptly secreted into bile. Impaired excretion of the glucuronides occurs in many types of hepatobiliary disease, but retention of native bilirubin is observed principally in newborn babies [1–3]. Accumulation of either native bilirubin or its glucuronides in the body is manifested by jaundice.

Bilirubin, one of the most interesting natural product members of the linear tetrapyrrole class [4], is a conformationally mobile bichromophore with characteristics of a molecular propeller. Rotation of its two dipyrrinone chromophores about the central CH_2 unit generates a large number of conformational isomers, of which only the ridge-tile shaped, folded conformations have their non-bonded steric interactions minimized [5]. The ridge-tile conformation brings the pigment's propionic acid groups into close proximity with the dipyrrinone NH and C=O groups where they easily embrace to form a network of six intramolecular hydrogen bonds (Fig. 1). This inward tucking of the CO_2H groups and their tethering to

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Conformational control by remote stereogenic centers: linear tetrapyrroles

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Abstract—A novel, optically-active N_{21}–N_{22}, N_{23}–N_{24} bis-carbonyl-bridged bilirubin congener **1** with propionic acids replaced by *sec*-butyls exhibits a strong negative exciton chirality circular dichroism spectrum from the (*S*,*S*)-enantiomer. Molecular dynamics calculations favor the ***M***-helical diastereomer by 0.4 kJ/mol over the ***P***. The dipyrrinone model **2** of one half of **1** exhibits an almost undetectable circular dichroism. Unlike **1**, which is only very weakly fluorescent, **2** is strongly fluorescent, with quantum yield $\phi_F \sim 0.70$.

1. Introduction

Conversion of dipyrrinones, such as kryptopyrromethenone (Fig. 1A), which are not fluorescent, to intensely fluorescent *N*,*N*-carbonyl-bridged derivatives (e.g., kryptoglow, Fig. 1A) has been accomplished in high yield by reaction with 1,1′-carbonyldiimidazole (CDI) in the presence of a non-nucleophilic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2.[1,2] Dipyrrinones form strongly intermolecularly hydrogen-bonded dimers in CH_2Cl_2 (Fig. 1A);[3,4] the *N*,*N*-carbonyl-bridged analogues cannot. From such dimers, weak exciton coupling occurs, as evidenced by the weak bisignate circular dichroism (CD) spectra seen from solutions of optically active dipyrrinones in CH_2Cl_2.[5] Optically active *N*,*N*-carbonyl-bridged dipyrrinones should not be able to form dipyrrinone dimers and thus not exhibit exciton CD, yet two covalently-linked bridged dipyrrinones might. Solutions of the carbonyl-bridged dipyrrinones should be intensely fluorescent, while those of the latter should be only weakly fluorescent due to energy-transfer fluorescence quenching. In order to examine these hypotheses, we synthesized a new, optically active *N*,*N*-carbonyl-bridged bis-dipyrrinone **1** and dipyrrinone **2** (Fig. 1B).

2. Results and discussion

2.1. Synthesis

Reaction of dipyrrinones with CDI, catalyzed by DBU in CH_2Cl_2 typically led smoothly and in high yield to the *N*,*N*-carbonyl-bridged dipyrrinones. Conversion of the known dipyrrinone **4**[6] to **2** (in 89% yield) proved no exception. Whether both dipyrrinones of a bis-dipyrrinone, such as the previously reported bilirubin analogue,[6] could be bridged similarly was previously unknown. Although lactam to lactam bridging or pyrrole to pyrrole bridging might be viewed as possible alternatives, an 86% yield of **1** was achieved.

2.2. Characterization

The starting dipyrrinone **4** and bis-dipyrrinone **3** are known, including the absolute stereochemistry, from previous studies.[6] Two characteristic changes in the NMR spectra distinguish products from reactants: the presence of a new carbonyl group, imide type near 143 ppm in the ^{13}C NMR spectrum and the absence of pyrrole and lactam NH resonances in the ^{1}H NMR (Table 1). Unlike the 'carbonylation' reactions of **4** (to **2**), there is an alternate bis-*N*,*N*-bridged structure to **1**: one involving a carbonyl bridge between the two pyrrole rings and a second carbonyl bridge between the two lactam rings. Since the two new carbonyls of such a structure are predicted to exhibit different carbonyl signals in the ^{13}C NMR spectrum, whereas only

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3. Conclusions

An enantiomerically pure bilirubin congener lacking carboxylic acids is smoothly converted into an N_{21}–N_{22}, N_{23}–N_{24} bis-carbonyl-bridged bis-dipyrrinone by reaction with excess CDI in the presence of DBU. The new bichromophore rubin exhibits intense negative exciton chirality CD that originates from a monomeric species (as determined by VPO) that cannot engage in hydrogen bonding. The pigment's preferred conformation is governed by the absolute configuration of remote stereogenic centers, as confirmed by molecular mechanics calculations. In contrast to the mono-dipyrrinone fluorophore **2** (quantum yield $\phi_F = 0.83$ in cyclohexane), the bis-dipyrrinone fluorophore **1** has a much lower quantum yield ($\phi_F = 0.19$ in cyclohexane), presumably lowered by intramolecular quenching.

4. Experimental

4.1. General procedures

Nuclear magnetic resonance spectra were obtained on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating at ^{1}H frequency of 500 MHz and ^{13}C frequency of 125 MHz. $CDCl_3$ solvent was used throughout with chemical shifts reported in δ ppm referenced to residual $CHCl_3$ ^{1}H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.00 ppm. *J*-Modulated spin-echo (Attached Proton Test) and gHMBC experiments were used to obtain the ^{13}C NMR assignments. All UV–vis spectra were recorded on a Perkin–Elmer Lambda 12 spectrophotometer, fluorescence spectra were measured on a Jobin Yvon FluoroMax 3 instrument, and the circular dichroism spectra were recorded on a JASCO J-600 dichrograph. Vapor pressure osmometry measurements were performed on an OSMOMAT 070-SA instrument (Gonotec, GmbH) in acid free $CHCl_3$ at 45 °C. Radial chromatography was carried out on Merck silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2, or 4 mm thick rotors and analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. The combustion analyses were carried out by Desert Analytics, Tucson, AZ.

4.2. General procedure for the cyclization to 1 and 2

A mixture of 1 mmol of pigment **3**[6] or **4**,[6] 1.62 g (10 mmol) of 1,1′-carbonyldiimidazole (5 mmol for **4**), 3.0 mL (10 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (5 mmol for **4**) and 350 mL of anhydrous CH_2Cl_2 (100 mL for **4**) was heated under N_2 at reflux for 3 h (16 h for **4**). After cooling, the mixture was washed with 1% aq HCl (2 × 50 mL), then with water (3 × 50 mL) and the solution dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent under vacuum, the residue was purified by radial chromatography on silica gel and recrystallized from ethyl acetate–hexane to afford bright yellow tricyclic pigments.

4.2.1. (+)-(8[1]*S*)-1-Ethyl-8-(1-methylpropyl)-2,7,9-trimethyl-3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3,5-dione 2. Compound **2** was isolated in 89% yield; mp 97–98 °C; ^{1}H NMR: δ 0.82 (3H, t, $J = 7.4$ Hz), 1.21 (3H, t, $J = 7.7$ Hz), 1.23 (3H, d, $J = 7.2$ Hz), 1.63 (2H, m), 1.95 (3H, s), 2.16 (3H, s), 2.53 (2H, q, $J = 7.7$ Hz), 2.66 (3H, s), 2.70 (1H, m), 6.39 (1H, s) ppm; $[\alpha]_D^{20} = +25.4$ (*c* 0.22, $CHCl_3$). UV–vis: ε^{max} (λ) 18,500 (432 nm), 10,600 (279 nm) ($CHCl_3$); 18,400 (429 nm), 11,200 (278 nm) (CH_3OH). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.29; H, 7.55; N, 9.06.

4.2.2. (−)-(*S*,*S*)-Bis-[1-ethyl-8-(1-methylpropyl)-2,9-dimethyl-3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3,5-dione-7-yl]methane 1. Compound **1** was isolated in 86% yield; mp 168–169 °C; ^{1}H NMR: δ 0.66 (6H, t, $J = 7.4$ Hz), 1.03 (6H, d, $J = 7.1$ Hz), 1.21 (6H, t, $J = 7.7$ Hz), 1.43, 1.48 (2 × 2H, 2 × m), 1.94 (6H, s), 2.14 (6H, s), 2.42 (2H, m), 2.53 (4H, q, $J = 7.7$ Hz), 5.29 (2H, s), 6.40 (2H, s) ppm; $[\alpha]_D^{20} = -621.8$ (*c* 1.4×10^{-2}, $CHCl_3$). UV–vis: ε^{max} (λ) 33,500 (442 nm), 21,200 (278 nm) ($CHCl_3$); 31,900 (423 nm), 21,900 (278 nm) (CH_3OH). Anal. Calcd for $C_{37}H_{44}N_4O_4$: C, 73.00; H, 7.29; N, 9.20. Found: C, 72.66; H, 7.23; N, 9.21.

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Bright yellow N,N′-carbonyl-bridged dipyrrinones (substituted 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-diones) were synthesized by reaction of the parent dipyrrinone with carbonyldiimidazole. Their solutions in organic solvents fluoresced strongly, with fluorescent quantum yields (ϕ_F) 0.32-0.92.

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Dipyrrinones (Figure 1A) typically exhibit only weak fluorescence at room temperature, with fluorescence quantum yields (ϕ_F) of the order of 0.001 at room temperature [1]. The dipyrrinone excited state relaxes to a new ground state by rapid $Z \rightarrow E$ double bond isomerization (Figure 1A), but when this relaxation mode is inhibited by bridging the lactam and pyrrole nitrogens, strong fluorescence is observed [2-4]. One of the easiest bridges to build is the carbonyl, in a reaction discovered recently [5] to give 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-diones (Figures 1B and C) in high yield from the parent dipyrrinone by reaction with 1,1′-carbonyldiimidazole (CDI) in the presence of a non-nucleophilic amine base, *e.g.*, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Thus, xanthoglow (Figure 1C) is a highly-fluorescent, bridged dipyrrinone analog of the linear tetrapyrrole of jaundice, bilirubin [6], *e.g.*, xanthoglow methyl ester was found to exhibit $\phi_F = 0.80$ in cyclohexane [7]. In the following, we describe the syntheses and fluorescence properties of nine new "xanthoglow" derivatives (Figure 1E), with various substituents at C(8) of the dipyrrinone.

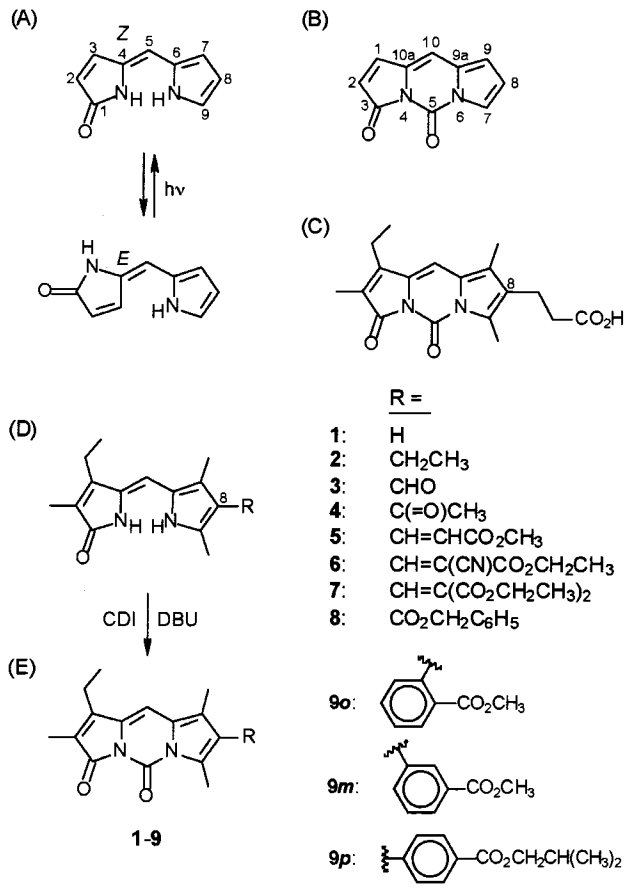

Figure 1. (A) $Z \rightarrow E$ Dipyrrinone photoisomerization. (B) The parent N,N'-carbonyldipyrrinone chromophore, 3*H*,5*H*-dipyrrolo[1,2-*c*:2',1'-*f*]-pyrimidine-3,5-dione. (C) Xanthoglow. (D) The dipyrrinone precursors to (E). (E) The xanthoglow target analogs (**1**-**9**) of this work. The latter are prepared from the former in high yield simply by reaction with carbonyldiimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU).

All of the N,N′-carbonyl-bridged dipyrrinones of this work were prepared simply and directly from the parent dipyrrinones (Figure 1D $\rightarrow$ E) by reaction with 5 equivalents of CDI in refluxing dichloromethane for 16-18 hours in the presence of 5 equivalents of DBU. The product yields were invariably good to excellent (Table 1), and the products were much more soluble in organic solvents than the starting dipyrrinones, some of which (Figure 1D **1**, **2**, **9**) were available from previous studies [8-10]. The others (Figure 1D **3**-**7**) were prepared starting from the 8-H dipyrrinone (Figure 1D **1**) as outlined in Scheme 1. (Reactions designed to convert the N,N′-carbonyl-bridged 8-H dipyrrinone (Figure 1E **1**) directly into the substituted analogs **3** and **4** by ethyl orthoformate – trifluoroacetic acid (TFA) formylation and Friedel-Crafts acylation reactions, respectively, failed.) Dipyrrinone D-**3** served as the precursor to dipyrrinone D-**6**, but the N,N′-carbonyl-bridged products proved to exhibit very different stabilities under the reaction conditions. Whereas the acrylate ester (E-**5**) was stable and isolated in high yield, the cyano ester (**6**) was rather unstable and isolated in only 40% yield after carefully adjusting the reaction conditions by increasing the CDI to ten equivalents and decreasing the DBU to three equivalents and terminating the reaction after only 3 hours – or as soon as the starting dipyrrinone had disappeared. Difficulties were also encountered in the synthesis of D-**7** from D-**3**. Thus, treatment of dipyrrinone D-**3** with diethyl malonate under Knoevenagel conditions in the presence of piperidine gave only a modest yield of dipyrrinone D-**7**, of 85% purity. Insertion of the carbonyl bridge afforded yellow crystalline product E-**7**

N_{21},N_{22}-Carbonyl-bridged Biliverdin. Red-blue Color Change Effected by Conformation

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An N_{21},N_{22}-carbonyl-bridged mesobiliverdin, prepared in high yield by reaction of the unbridged parent (λ_{max} 639 nm, ε 15,700, chloroform) with 1,1'-carbonyldiimidazole and 1,8-diazabicyclo[5.4.0]undec-7-ene, gave magenta-colored solutions in chloroform that absorb strongly in the visible spectrum (λ_{max} 534 nm, ε 27,700) and shifted to bright blue (λ_{max} 669 nm, ε 35,300) upon addition of trifluoroacetic acid.

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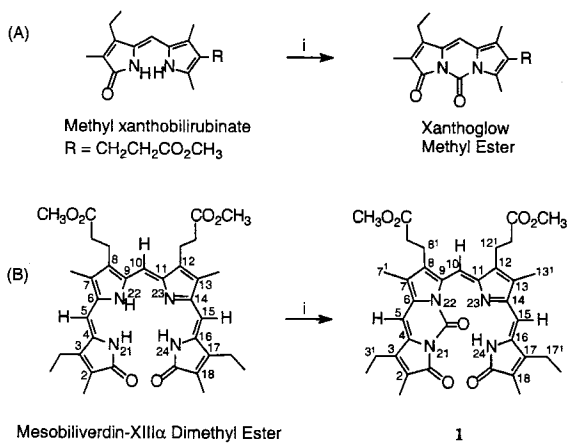
Reaction of dipyrrinones, such as methyl xanthobilirubinate (Scheme 1A) with 1,1'-carbonyldiimidazole (*CDI*) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (*DBU*) has been shown to give the N,N'-carbonyl-bridged dipyrrinones in excellent yield [1]. The latter are highly fluorescent (ϕ_F ~ 0.7-0.8) [2] but the long wavelength absorption λ_{max} (428 nm, chloroform) shows a 20 nm bathochromic shift from that of the parent (λ_{max} 406 nm, chloroform) [1,3]. A similar reaction with blue-colored (λ_{max} 639 nm, chloroform) mesobiliverdin-XIIIα dimethyl ester (Scheme 1B) afforded the N_{21},N_{22}-bridged verdin (**1**) in 76% yield. The new "verdin" was neither blue nor green, but exhibited an intense magenta color in chloroform solution (λ_{max} 534 nm) associated with a strong hypsochromic shift relative to the parent. It was also non-fluorescent to the eye. The absence of visible fluorescence at room temperature was confirmed by instrumental measurements in chloroform and trifluoroacetic acid following independent excitation of the three uv-visible absorption bands.

The structure of **1** follows from that of its symmetric verdin precursor [4]. The ^{13}C-nmr (Table 1) of **1** confirmed the expected 35 carbons resonances that correlate with those of the precursor, and a single new carbon signal at 142.9 ppm, characteristic of the carbonyl bridge connecting two nitrogens of a dipyrrinone. If the new carbonyl group had bridged the two lactam nitrogens (N_{21} and N_{24}) or the two pyrrole nitrogens (N_{22} and N_{23}), a symmetrical structure would have resulted, with approximately only one-half the number of ^{13}C signals. (In mesobiliverdin-XIIIα dimethyl ester in chloroform-d, only 18 carbon resonances are seen (Table 1), due to a rapid prototropic shift, N_{22}-H to N_{23}, tautomerism.) The ^{13}C nmr assignments and structure were further confirmed by long range heteronuclear correlation experiment (gHMBC). In particular, the hydrogen at C(5) appeared deshielded to 6.49 ppm as it does in xanthoglow methyl ester (Scheme 1A) and is correlated (^{2}J) to the carbon signals at 132.5 ppm C(4) and 130.2 ppm C(6) and (^{3}J) to C(3) at 146.6 ppm and C(7) at 123.0 ppm. In the opposite half of the molecule, the hydrogen at C(15) is with normal chemical shift at 5.84 ppm and correlated to C(13), C(14), C(16) and C(17). The ^{2}J correlation C(15)-H to C(14) and the unique ^{3}J correlation C(13^1)-CH_3 to C(14) is interesting because it reveals that C(14) is strongly deshielded (to 169.7 ppm) relative to C(6) (130.2 ppm). The carbon and proton nmr spectral data are thus consistent with structure **1** for the new bridged verdin.

Scheme 1 [a]



[a] Reagents and conditions: i, 1,1'-carbonyldiimidazole, 1,8-diazabicyclo-[5.4.0]undec-7-ene, CH_2Cl_2, reflux.

A striking color change, from magenta to bright blue was seen when solutions of **1** were exposed to acid, *e.g.*, chloroform and dimethyl-sulfoxide solutions plus trifluoroacetic acid. The color change is readily measured spectrophotometrically, as seen in the uv-visible spectra of **1** (Figure 1) in a variety of solvents, although solvents such as tetrahydrofuran, dimethylformamide and dimethylsulfoxide require larger excess of trifluoroacetic acid than do benzene, chloroform, *etc*. No similar large wavelength changes are detected for solutions of the parent mesobiliverdin-XIIIα dimethyl ester, but the intensity of its long wavelength band is also enhanced with added trifluoroacetic acid, as is seen for **1**. The spectral shift (summarized for a wide range of organic solvents in Table 2) is completely reversible, and upon addition of triethyl amine to the trifluoroacetic acid solution, the "neutral" spectrum is restored. The acid-base spectral shift cycle has been repeated numerous times with the

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Synthesis, Structure, and Fluorescence of Isomeric Indolizinediones. Carbonyl-Bridged Isodipyrrinones

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Summary. In "one-pot" reactions, pyrrole-α- and β-aldehydes condense readily with 4-ethyl-3-methyl-3-pyrrolin-2-one to give isodipyrrinone analogs, which undergo intramolecular cyclization when the pyrrolealdehyde possesses an α or β-CO_2R group. The resulting regioisomeric pyrroloindolizinediones, with structures confirmed by NMR analysis, exhibit strong fluorescence, with quantum yields (ϕ_F) as high as 0.91 at $\lambda_{em} \sim 450$–550 nm.

Keywords. Pyrrole; Indolizinedione; Fluorescence quantum yield.

Introduction

Dipyrrinones, such as xanthobilirubic acid (*XBR*, Fig. 1A), are yellow pigments with *UV*-visible absorption ($\varepsilon \sim 30000\,dm^3 \cdot mol^{-1}\,cm^{-1}$) near 410 nm and the important chromophore of bilirubin (*BR*), the yellow pigment of jaundice and a bisdipyrrinone [1]. In both *XBR* and *BR*, the dipyrrinone chromophore has the (4*Z*) exocyclic configuration and adopts the *syn* conformation (Fig. 1B). The lowest lying (singlet) excited state of *XBR* and of *BR* relaxes rapidly by $Z \rightarrow E$ diastereomerization, with only extremely weak fluorescence at room temperature [1]. However, when $Z \rightarrow E$ isomerization is inhibited by linking the two nitrogens – by a carbonyl group, as in xanthoglow [2] (Fig. 1B), or by a methylene group – the pigment becomes strongly fluorescent [3–5].

Recently, we explored the possibility of synthesizing xanthoglow [2, 6] analogs with the *anti*- rather than the *syn*-(*Z*) stereochemistry (Fig. 1B) of the dipyrrinone core [7]. From the *anti*-(4*Z*) stereochemistry, the lactam nitrogen and C(7) of the pyrrole are linked to a carbonyl, thereby giving the $\alpha\alpha\beta$-type of skeleton (Fig. 1C), in contrast to the $\alpha\alpha N$ skeleton of xanthoglow (Fig. 1B), where the two nitrogens

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Table 2. Solvent dependence of the fluorescence excitation (λ_{ex}/nm) and emission (λ_{em}/nm) wavelengths and quantum yields (ϕ_F) of **1**–**8**

Compound	Cyclo-C_6H_{12}			C_6H_6			$CHCl_3$		
	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F
1 ($\alpha\beta\beta$)	385	435	0.02	381	449	0.70	388	455	0.86
2 ($\alpha\beta\beta$)	381	441	0.21	408	453	0.75	396	450	0.86
3 ($\alpha\beta\alpha$)	356	474	0.13	355	476	0.22	359	494	0.29
4 ($\alpha\beta\alpha$)	359	466	0.12	361	480	0.27	365	498	0.31
5 ($\alpha\beta\alpha$)	364	407	0.01	396	451	0.09	404	459	0.54
6 ($\alpha\beta\alpha$)	396	449	0.02	408	453	0.10	410	467	0.60
7b ($\alpha\alpha\beta$)	400	453	0.01	400	456	0.06	398	455	0.14
8 ($\alpha\alpha\beta$)	396	465	0.27	400	456	0.82	399	477	0.87

Compound	CH_3OH			$(CH_3)_2SO$		
	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F
1 ($\alpha\beta\beta$)	411	489	0.73	411	479	0.91
2 ($\alpha\beta\beta$)	410	492	0.71	397	479	0.88
3 ($\alpha\beta\alpha$)	363	548	0.02	365	514	0.08
4 ($\alpha\beta\alpha$)	369	542	0.04	368	510	0.15
5 ($\alpha\beta\alpha$)	398	508	0.10	397	475	0.59
6 ($\alpha\beta\alpha$)	396	505	0.13	396	476	0.67
7b ($\alpha\alpha\beta$)	397	502	0.56	398	484	0.46
8 ($\alpha\alpha\beta$)	397	513	0.28	407	499	0.71

example, **1** exhibits large ϕ_F values in all solvents studied, except for cyclohexane, in which it was least soluble. In such instances, diminished fluorescence attended **2** (in cyclohexane) and **3** (insoluble in most solvents), **4**, **5**, **6**, and **7** in all but $CHCl_3$ and $(CH_3)_2SO$ (where they are most soluble). The fluorescence is probably quenched by self-association (aggregation). This possibility is supported by the hypsochromic shifts of both λ_{ex} and λ_{em} from weakly fluorescing solutions of **1**–**8**, *vs*. solutions with strong fluorescence: typically $(CH_3)_2SO$ and $CHCl_3$. Selected fluorescence emission and *UV*-visible absorption curves for **1**–**8** may be seen in Fig. 4, and a comparison of the normalized fluorescence emission spectra of **2**, **4**, **7b**, and xanthoglow (*XG*) may be seen in Fig. 5. From the latter, the xanthoglow emission λ_{max} (Fig. 1) is clearly redshifted from those of **1**–**8**, and the most soluble of **1**–**8** tend to give the larger emission intensities (and ϕ_F, Table 2).

Concluding Comments

New tricyclic skeletal types ($\alpha\beta\beta$ and $\alpha\beta\alpha$, **1**–**6**) based on isodipyrrinones are readily prepared in ''one-pot'' syntheses. The new carbonyl-bridged isodipyrrinones are intensely fluorescent ($\phi_F \sim 0.9$, $\lambda_{em} \sim 450$–515 nm) in organic solvents

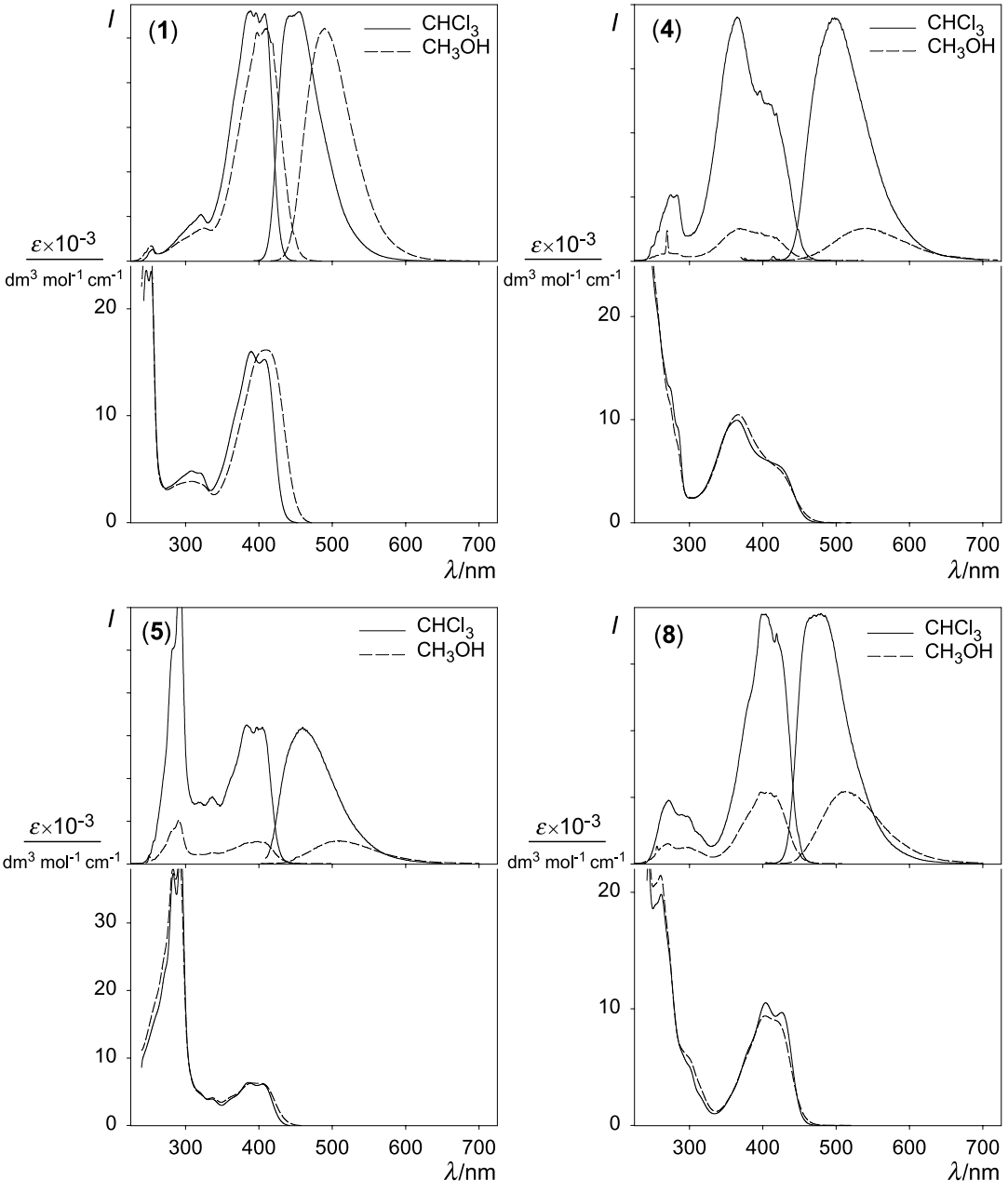

Fig. 4. Comparison of the fluorescence emission and excitation spectra (upper) and *UV*-visible absorption spectra (lower) of dipyrrinones **1**, **4**, **5**, and **8** in $CHCl_3$ and CH_3OH

in which they exhibit good solubility ($CHCl_3$, $(CH_3)_2SO$), but only weak fluorescence ($\phi_F \sim 0.01$–0.1, $\lambda_{em} \sim 450$–550 nm) in solvents such as cyclohexane. Similar results are found with new members (**7** and **8**) of the $\alpha\alpha\beta$ skeletal type based on bridged (4*Z*)-dipyrrinones in the *anti* conformation.

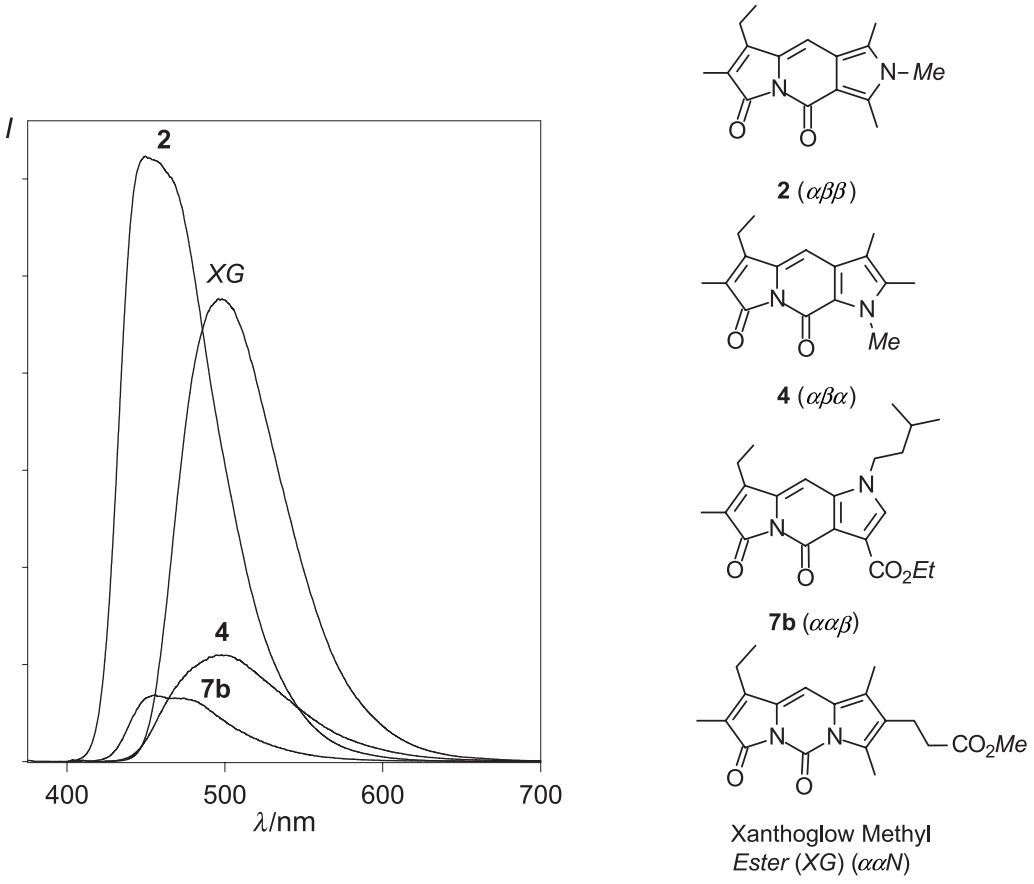

Fig. 5. Normalized relative fluorescence of **2**, **4**, **7b**, and xanthoglow (*XG*) in $CHCl_3$

Experimental

All fluorescence spectra were measured on a Jobin Yvon Fluorolog 3 model FL 3-22 instrument by using constant spectral parameters: step resolution (increment) of 1 nm, both excitation and emission slits of 2 nm and integration time of 0.5 sec and were uncorrected. The *UV*-visible spectra were recorded on a Perkin-Elmer Lambda 12 spectrophotometer. NMR spectra were acquired on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating at ^1H frequency of 500 MHz and ^{13}C frequency of 125 MHz in solutions of $CDCl_3$ (referenced at 7.26 ppm for ^1H and 77.00 ppm for ^{13}C) or $(CD_3)_2SO$ (referenced at 2.49 ppm for ^1H and 39.50 ppm for ^{13}C). *J*-Modulated spin-echo (*A*ttached *P*roton *T*est) and gHMBC experiments were used to assign the ^{13}C NMR spectra. Gas chromatography-mass spectrometry analyses were carried out on a Hewlett-Packard 5890A gas chromatograph (30 m DB-1 column) equipped with a Hewlett-Packard 5970 mass selective detector. Radial chromatography was carried out on Merck silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2, or 4 mm thick rotors and analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. The combustion analyses were carried out by Desert Analytics, Tucson, AZ; their results agreed favourably with the calculated values.

JOC Article

Synthesis and Hepatic Transport of Strongly Fluorescent Cholephilic Dipyrrinones

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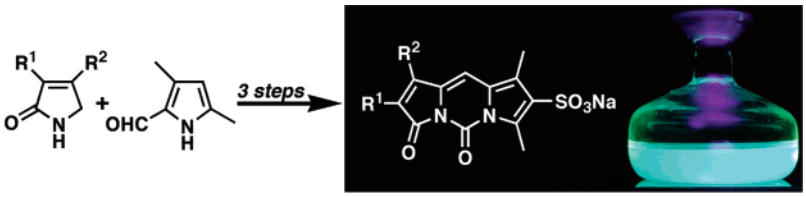

A new class of highly fluorescent (ϕ_F 0.3−0.8) low molecular weight water-soluble cholephilic compounds has been synthesized in two steps from dipyrrinones. The dipyrrinone nitrogens are first bridged by reaction with 1,1′-carbonyldiimidazole to form an *N*,*N*′-carbonyldipyrrinone (3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-dione) nucleus, and a sulfonic acid group is then introduced at C(8) by reaction with concd H_2SO_4. The resulting sulfonated *N*,*N*′-carbonyl-bridged dipyrrinones ("sulfoglows") are isolated as their sodium salts. When the alkyl substituents of the lactam ring are lengthened from ethyl to decyl, sulfoglows become increasingly lipophilic while maintaining water solubility. Low molecular weight sulfoglows were rapidly excreted intact in both bile and urine after intravenous infusion into rats, but higher molecular weight sulfoglows were excreted more selectively in bile. Hepatobiliary excretion of sulfoglows was partially, but not completely, blocked in mutant rats deficient in the multidrug-resistance associated transport protein Mrp2 (ABCC2). These observations point to the feasibility of developing simple sulfoglows with clinical diagnostic potential that are normally excreted in bile but appear in urine when hepatic elimination is impaired by cholestatic liver disease.

Introduction

Bilirubin (Figure 1A), the lipophilic yellow pigment of neonatal jaundice[1] is comprised of two *Z*-dipyrrinone chromophores.[2] In the absence of light-promoted $Z \rightarrow E$ photoisomerization,[3,4] it is unexcretable (across the liver into bile) in normal human metabolism, except following enzymic conjugation with glucuronic acid (Figure 1B).[1,4] Accumulation of bilirubin and its glucuronides leading to jaundice is a well-known sign of liver disease.[1] In contrast to bilirubin, xanthobilirubic acid[5] (Figure 1C), a polar, but water-insoluble synthetic analogue for one-half of bilirubin, is readily excreted intact in bile without the need for glucuronidation.[6] Both xanthobilirubic acid and bilirubin are essentially nonfluorescent at room temperature, e.g., with fluorescence quantum yields ϕ_F $<10^{-3}$ because of rapid $Z \rightarrow E$ isomerization in the excited states.[2,7] In earlier work, we demonstrated a dramatic

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Synthesis, properties, and hepatic metabolism of strongly fluorescent fluorodipyrrinones

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Abstract—From non-fluorescent 8-*H* fluorophenyldipyrrinones, highly fluorescent (ϕ_F 0.4–0.6) analogs have been synthesized by reaction with 1,1′-carbonyldiimidazole to bridge the dipyrrinone nitrogens and form an *N*,*N*′-carbonyldipyrrinone (3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]-pyrimidine-3,5-dione). Amphiphilic, water-soluble 8-sulfonic acid derivatives are then obtained by reaction with concd H_2SO_4. The resulting fluorinated and sulfonated *N*,*N*′-carbonyl-bridged dipyrrinones, isolated as their sodium salts, are potential cholephilic fluorescence and ^{19}F MRI imaging agents for use in probing liver and biliary metabolism. After intravenous injection in the rat they were excreted rapidly and largely unchanged in bile. ^{19}F NMR spectroscopy of a pentafluorophenyl-tosylpyrrolinone synthetic precursor exhibited rarely seen diastereotopicity.

1. Introduction

The natural pigment bilirubin (Fig. 1A) is produced continuously in animals during normal catabolism of heme.[1] It is a bichromophoric structure comprised of two *Z*-dipyrrinones bearing intramolecularly hydrogen-bonded propionic acid side-chains.[2,3] It is lipophilic and has low solubility in water at physiologic pH. In humans accumulation of bilirubin is thwarted by its efficient clearance from the blood by the liver and elimination in bile as ester glucuronide conjugates of the propionic acid side-chains.[1,4] Formation of the glucuronides is catalyzed by a specific glucuronosyl transferase enzyme (UGT1A1)[5] and their excretion from the liver is mediated by a membrane transporter known as MRP2 (multidrug resistance associated protein 2).[6] These two proteins are important in the metabolism and hepatic elimination of a large number of xenobiotics in addition to bilirubin. Genetic deficiencies of either UGT1A1 or MRP2 and a variety of liver disorders can cause accumulation of bilirubin or its glucuronides and clinical jaundice.[5,6] In the absence of UGT1A1, elimination of bilirubin is almost totally impaired. If the concentration of unconjugated bilirubin in the circulation exceeds the binding capacity of serum albumin, movement of the pigment across the blood–brain barrier and deposition within the brain can cause toxicity.[1] In contrast to bilirubin, xanthobilirubic acid (Fig. 1B),[7] a polar but water-insoluble synthetic dipyrrinone analog for one-half of bilirubin, is readily excreted intact in bile without the need for glucuronidation.[8] Thus, bilirubin and its analogs are useful probes for hepatobiliary disfunction and mechanisms of glucuronidation and biliary excretion.

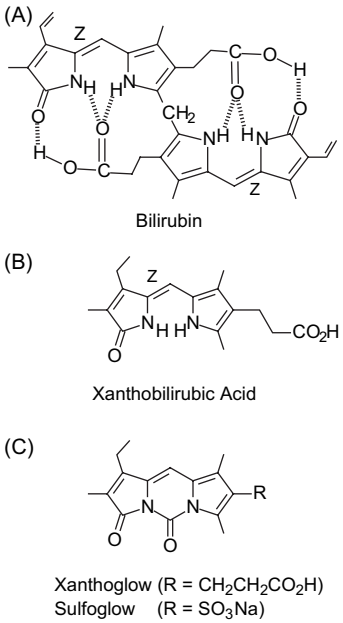

Figure 1. (A) Bilirubin. (B) Xanthobilirubic acid, a dipyrrinone model for bilirubin. (C) Xanthoglow, a highly fluorescent (ϕ_F 0.80, cyclohexane) *N*,*N*′-carbonyl-bridged analog of xanthobilirubic acid and sulfoglow, a water-soluble analog.

Keywords: Dipyrroles; Perfluorophenyl; ^{19}F NMR; Fluorescence.
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3. Concluding comments

Two new, highly fluorinated (perfluorophenyl and *p*-ethoxytetrafluorophenyl substituents) *N*,*N*′-carbonyl-bridged dipyrrinones were converted to amphiphilic derivatives by sulfonation. The highly fluorescent sulfoglows (**1** and **2**) so obtained are excreted rapidly and principally in unchanged form in bile in the rat after intravenous infusion. Some excretion in urine also was observed. These compounds may form the basis for development of ^{19}F MRI and fluorescence agents for probing liver metabolism and disease.

4. Experimental

4.1. General procedures

Nuclear magnetic resonance spectra were acquired on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating at an ^{1}H frequency of 500 MHz, ^{13}C frequency of 125 MHz, and ^{19}F frequency of 470 MHz in solutions of $CDCl_3$ (referenced at 7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C) or $(CD_3)_2SO$ (referenced at 2.49 ppm for ^{1}H and 39.50 ppm for ^{13}C). All ^{13}C NMR spectra were broadband ^{1}H decoupled, and *J* constants indicated for some signals are from ^{13}C–^{19}F coupling. The ^{19}F NMR spectra were referenced to external C_6F_6 in $CDCl_3$ at −162.90 ppm. UV–vis spectra were recorded on a Perkin Elmer Lambda 12 spectrophotometer. All fluorescence spectra were measured on a Jobin Yvon FluoroMax 3 by using constant spectral parameters: step resolution (increment) of 1 nm, both excitation and emission slits of 2 nm, and integration time of 0.5 s. Radial chromatography was carried out on Merck preparative layer grade silica gel PF_{254} with $CaSO_4$ binder, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2 or 4 mm thick rotors. Analytical thin-layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μm layer). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. High resolution mass-spectra were obtained from Nebraska Center for Mass Spectrometry, Lincoln, NE.

Spectral data were obtained in spectral grade solvents (Aldrich or Fischer), which were distilled under Ar just prior to use. Before distillation, $CHCl_3$ was passed through a basic alumina column (Woelm, Eschwege, Act. 0). Distillation of $(CH_3)_2SO$ solvent was carried out under vacuum (0.5 mmHg) collecting the solvent at 0 °C and thawing it under Ar. Pyrrole **16**,[12] tosylpyrrolinone **14** (derived from **16**),[12] and pyrrolinone **12**,[12] as well as 3,5-dimethyl-2-formyl-1*H*-pyrrole,[15] were synthesized according to previously published methods.

The concentration study (Table 1) of dipyrrinones **7**–**9** NH ^{1}H NMR chemical shifts was conducted as follows. All solutions were prepared in $CDCl_3$ that had been freshly treated (freshly distilled in two cases) by passing through Woelm Activity 0 basic alumina. Stock solutions concentrated to approximately the upper limit of solubility at 25 °C were prepared (in the case of **9** this limit was 20 mM and for pentafluorophenyl **7** it was only 10 mM) then consecutively diluted in 10-fold increments to 10 μM. The ^{1}H NMR spectra were acquired using a high sensitivity probe for indirect detection. The pulse width was set at about the optimum 65° flip angle and the total repetition time was kept at 8–10 times the *T*1 values of NH signals to allow for complete relaxation. Artificial high line broadening was used in the processing to smoothen the low intensity signals, in particular at low concentrations. Overall, meticulously identical experimental conditions with samples at the same concentrations were used and all spectra were referenced to the residual $CHCl_3$ signal at 7.260 ppm. This precision was necessary to measure the chemical shifts with 10^{-3} ppm confidence.

4.1.1. 4-Methyl-3-pentafluorophenyl-2-(4-toluenesulfonyl)-1*H*-pyrrole (15).

4.1.1.1. 2-Nitro-1-pentafluorophenylpropanol. To a solution of 23.53 g (120 mmol) of perfluorobenzaldehyde and 11.26 g (150 mmol) of nitroethane in 12 mL of anhyd CH_3CN was slowly added 1.8 mL (12 mmol) of DBU, and the mixture was stirred for 30 h at room temperature. The mixture was diluted with 200 mL of CH_2Cl_2, washed with 3% aq HCl (100 mL), H_2O (3×100 mL), dried over anhyd $MgSO_4$, filtered, and the solvent was evaporated under vacuum (1 h at 40 °C). The crude nitropropanol is a 1:1 mixture of diastereomers: ^{1}H NMR *δ*: 1.40, 1.76 (2×1.5H, 2×d, *J*=6.9 Hz), 5.03–5.08 (1H, m), 5.43–5.52 (1H, m) ppm; ^{13}C NMR *δ*: 16.1, 19.5, 61.2, 67.3, 85.0, 86.0, 112.4 (m), 136.1 (dm, ^{1}J=250.7 Hz), 143.4 (dm, ^{1}J=249.8 Hz), 146.7 (dm, ^{1}J=250.2 Hz) ppm and was used directly in the next step.

4.1.1.2. 1-Acetoxy-2-nitro-1-pentafluorophenylpropane. To a solution of the alcohol (26.1 g) from above in 70 mL of anhyd CH_2Cl_2 and 50 mg of DMAP was added acetic anhydride (18.1 mL, 193 mmol) during 10 min, and the mixture was stirred for 16 h. Methanol (25 mL) was added during 15 min, and after 1 h stirring the mixture was diluted with 200 mL of CH_2Cl_2 and then carefully poured into 150 mL of satd aq $NaHCO_3$. The organic layer was washed with H_2O (3×100 mL), dried over anhyd $MgSO_4$, filtered, and the solvent was evaporated under vacuum to give 29.3 g (~78%) of a 1:1 diastereomeric mixture of nitroacetates. ^{1}H NMR *δ*: 1.46, 1.48 (2×1.5H, 2×d, *J*=6.8 Hz), 2.04, 2.21 (2×1.5H, 2×s), 4.91–4.99 (1H, m), 5.19–5.29 (1H, m) ppm; ^{13}C NMR *δ*: 14.6, 14.7, 20.0, 21.8, 67.4, 67.7, 83.8, 84.0, 108.5 (m), 136.0 (dm, ^{1}J=250.9 Hz), 143.6 (dm, ^{1}J=248.7 Hz), 145.9 (dm, ^{1}J=251.1 Hz), 167.0, 168.1 ppm. This mixture was used directly in the next step without further purification.

4.1.1.3. Pyrrole ring formation. To a solution of 24.40 g (125 mmol) of 4-toluenesulfonylmethyl isocyanide (TosMIC)[29] and 25 mL (200 mmol) of tetramethylguanidine in 100 mL of a mixture anhyd THF/isopropyl alcohol=1:1 (v/v) kept at 0 °C was added over 1 h a solution of the nitroacetate from above dissolved in 25 mL of the same solvents. The mixture was warmed slowly to room temperature and stirred for 28 h. Then it was diluted with 400 mL of CH_2Cl_2, poured into 300 mL of ice-5% aq HCl, and the organic layer was washed with 5% aq $NaHCO_3$ (100 mL) and H_2O (3×100 mL). The extract was dried (anhyd $MgSO_4$), filtered through a silica pad, evaporated, and the residue was recrystallized from ethyl acetate/hexane to afford

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DIPYRRINONES - CONSTITUENTS OF THE PIGMENTS OF LIFE. A REVIEW

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DIPYRRINONES - CONSTITUENTS OF THE PIGMENTS OF LIFE. A REVIEW

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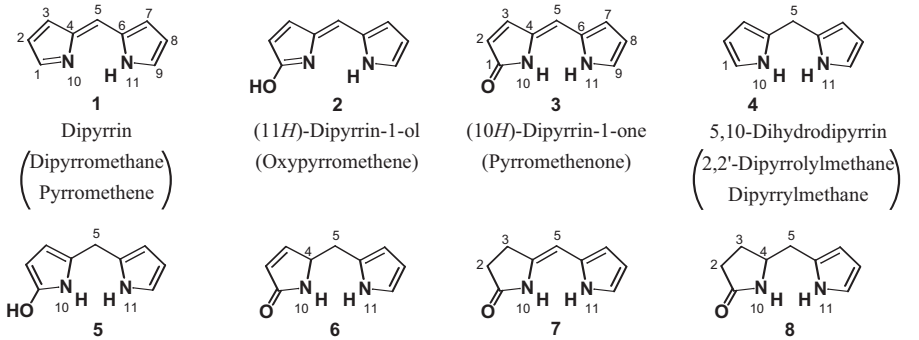
INTRODUCTION

The systematic name of the most unsaturated system (*Fig. 1*) arising from two pyrrole rings conjoined by one carbon atom is 2-[(2*H*)-pyrrol-2-ylidenemethyl]pyrrole; however, the trivial name dipyrrin (**1**) implies that N(11) is saturated and is recommended by IUPAC.[1] With a hydroxyl substituent at C(1), the dipyrrin becomes a dipyrrin-1-ol (**2**), the lactim tautomer favored by Hans Fischer (the "father" of pyrrole chemistry and 1930 Nobel Prize in chemistry awardee) that is now known to be less stable than the lactam form (**3**), a dipyrrinone (formerly pyrromethenone, or as Fischer preferred: oxypyrromethene). The designation (10*H*) specifies the lactam form. Further saturation of dipyrrin **1** at C(4)-C(5) leads to the well known dipyrrylmethane skeleton **4**, whose C(1) hydroxylated derivative, now known to be the more stable 4,5-dihydrodipyrrinone tautomer **6**, was important historically as the first dipyrrinone. Its isomer **7** and tetrahydrodipyrrinone **8** are found in the literature, and as core components of natural products.



Dipyrroles Relevant to this Review and their Nomenclature

Fig. 1

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Strongly fluorescent dipyrrinones. Internal quenching

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Abstract Yellow *N*,*N*′-carbonyl-bridged dipyrrinones can generally be prepared from dipyrrinones simply by reaction with *N*,*N*′-carbonyldiimidazole in the presence of a strong, non-nucleophilic base. They are typically intensely fluorescent, with fluorescent quantum yields approaching 1.0. In an effort to shift the excitation wavelength, and thus the fluorescence emissions, strongly to the red, we prepared bridged dipyrrinones conjugated with thiobarbituric acid and *Meldrum*'s acid substituents at C-9. Such conjugation causes the dipyrrinones to have a magenta color (absorption wavelength shifted from $\sim$400 nm of a typical dipyrrinone to $\sim$550 nm of the dipyrrinone conjugate). For comparison, we also prepared analogs with formyl, carboxyl, acrylate, and acetyl substituents at C-9. Unexpectedly and uniquely, the 9-CHO substituent caused the fluorescence quantum yield to drop to $\sim 10^{-3}$ while carboethoxy substituent exerted only a minor influence.

Keywords Pyrrole; Synthesis; Fluorescence.

Introduction

N,*N*′-Carbonyl-bridged dipyrrinones were first prepared only a few years ago [1] and were discovered to be intensely fluorescent [1, 2]. Shortly thereafter, it was shown that other carbonyl-bridged dipyrrinones [3] and verdins were intensely fluorescent [4], with fluorescence quantum yields (ϕ_F) approaching unity in organic solvents. The chromophore has been used to probe chirality in circular dichroism (*CD*) spectroscopy [5] and studies are currently in progress on their use in fluorescence-detected *CD*. Most recently, analogs with potential medical applications, to detect cholestasis, and in fluorescence imaging were prepared [6]. The majority of the bridged dipyrrinones exhibited intense fluorescence, in only a few instances did we find markedly reduced fluorescence – and then only with two substituents at a pyrrole β-position: $-CH{=}C(CN)CO_2CH_2CH_3$ and $-CH{=}C(CO_2CH_2CH_3)_2$ where ϕ_F dropped to $\sim$0.1 in cyclohexane and $\sim 10^{-3}$ in *DMSO*.

Seeking strongly red-shifted fluorescence emitters, we turned our attention toward *N*,*N*′-carbonyl-bridging of the magenta-colored dipyrrinone derivatives obtained *via* a *Mannito–Monti* cleavage of biliverdinoids with thiobarbituric acid [7] (Fig. 1). Finding that we could not insert the bridge directly into an adduct like **A** of Fig. 1, we prepared a bridged 9-CHO dipyrrinone as a potential precursor to adducts like **C** of Fig. 1 to be obtained by a *Knövenagel* reaction at the final step. In the following, we describe the synthesis and characterization of wavelength shifted adducts **1** and **2**, obtained from **3**, and a collection of other 9-substituted bridged dipyrrinones (**4**–**9**) (Fig. 2), and we report on the surprising influence of the 9-substituents on the fluorescence properties of *N*,*N*′-carbonyl-bridged dipyrrinones.

Results and discussion

Manitto and *Monti* [7] showed nearly 3 decades ago that biliverdinoids can be cleaved with thiobarbituric acid (*TBA*) at C(10) to afford *TBA* adducts (*e.g.*, **A**,

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Table 2 Solvent dependence of the UV-Vis spectra of **1**–**9**

Compound	λ_{max}/nm (ε/dm^{3}mol^{-1}cm^{-1})				
	Cyclohexane	C_6H_6	$CHCl_3$	CH_3OH	$(CH_3)_2SO$
1	–	532 (34100) 499 (27700)^{sh} 343 (19300)	539 (32800) 507 (24500)^{sh} 342 (25100)	532 (30200) 341 (24300)	537 (31300) 345 (22300)
2	483 (19700) 318 (22100) 266 (9700)	497 (21300) 324 (22600)	502 (22200) 325 (23800) 270 (9700)	501 (23800) 324 (23200) 269 (9200)	508 (24400) 327 (21000) 270 (9400)^{sh}
3	420 (19200) 398 (19400) 268 (8900)	419 (18000) 404 (18000)	413 (17900) 319 (3200)^{sh} 272 (10100)	412 (17800) 317 (3400)^{sh} 271 (10800)	413 (17900) 317 (3200)^{sh} 269 (11400)
4	432 (24400) 406 (23900) 387 (14600)^{sh} 268 (24300)	437 (21500) 412 (21700) 392 (13400)^{sh}	439 (23200) 413 (23200) 392 (14100)^{sh} 273 (25300)	435 (22400) 411 (23300) 392 (14800)^{sh} 272 (26000)	439 (22800) 414 (23100) 394 (14100)^{sh} 273 (25100)
5	425 (19000) 399 (19500) 253 (18700)	429 (17800) 404 (18200)	428 (18700) 404 (19200) 258 (21300)	419 (17300) 402 (17100) 257 (15500)	421 (17200) 403 (17400)
6	421 (20000) 397 (20500) 252 (15100)	422 (18100) 399 (18900)	423 (18000) 401 (18800) 258 (15900)	416 (17600) 398 (18300) 257 (17000)	419 (17900) 400 (18800)
7	428 (20100) 403 (20400) 320 (2800) 263 (16800)	429 (18200) 407 (18700) 315 (2600)^{sh}	431 (18600) 408 (19300) 316 (3000)^{sh} 271 (17300)	425 (18200) 406 (18900) 316 (3200)^{sh} 270 (17800)	428 (18300) 408 (19000) 317 (3100)^{sh} 270 (18100)
8	452 (21500)^{sh} 435 (24000) 292 (23000)^{sh} 285 (23400)	466 (19500)^{sh} 443 (23700) 298 (22000) 290 (21300)^{sh}	465 (20600)^{sh} 445 (23900) 298 (24800) 253 (9900)	463 (21000)^{sh} 443 (24700) 293 (25700) 252 (9500)	467 (21100)^{sh} 445 (24600) 301 (23700) 293 (23100)^{sh}
9	421 (19600) 397 (20100) 252 (15400)	422 (17900) 400 (18700)	423 (17800) 401 (18700) 259 (16100)	417 (17800) 399 (18500) 258 (17700)	420 (17600) 400 (18500)

respectively, in **7** relative to **1**. And, one finds that the UV-Vis spectral data of **7** are closer to those of **5** (or **6** and **9**) than to **4**.

Concluding comments

In our attempts to prepare *N*,*N*′-carbonyl-bridged dipyrrinones with strong fluorescence at $\lambda_{em} > 550$ nm, we prepared such analogs from magenta-colored thiobarbituric acid and orange-colored *Meldrum*'s acid adducts **1** and **2**. Unexpectedly, they were nonfluorescent at room temperature. Their precursor, dipyrrinone 9-aldehyde **4** similarly was nonfluorescent. Yet the parent bridged dipyrrinone **3** and derivatives with carbonyl groups at C-9, such as CO_2H, CO_2CH_3, $COCH_3$, and $CO_2CH_2CH{=}CH_2$, and even the conjugate $CH{=}CHCO_2CH_3$ were all strongly fluorescent. It is unclear why **1** and **2** are nonfluorescent, and it is surprising that **4** was also. Orientation of the group attached to C(9) may play a role: the *syn* appears to be preferred in **1**, **2**, and **4**, but deexcitation of the long wavelength excited state of **4** may occur from facile motion about the C(9)–C(10) bond.

Experimental

All fluorescence spectra were measured on a Jobin Yvon Fluorolog 3 model FL 3-22 instrument by using constant spectral parameters: step resolution (increment) of 1 nm, both excitation and emission slits of 2 nm and integration time of 0.5 sec and were uncorrected. The UV-Vis spectra were recorded on a Perkin-Elmer Lambda 12 spectrophotometer. NMR spectra were acquired on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating

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Fluorescence detected circular dichroism of a red-shifted exciton-coupling chromophore *N*,*N*′-carbonyl-bridged dipyrrinone derivative using an ellipsoidal device

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Abstract A fluorescent red-shifted exciton-coupling chromophore, *N*,*N*′-carbonyl-bridged dipyrrinone, was subjected to fluorescence-detected CD (FDCD) measurements as a primitive structure-elucidating probe with *trans*-1,2-cyclohexanediol template in several solvents under various instrumental conditions. With the help of a JASCO ellipsoidal mirror device FDCD465, a chloroform solution achieved the sensitivity enhancement by 50 times of the transmission CD and 5 times of the conventional FDCD. All FDCD spectra were completely free from the polarization artifacts.

Keywords Circular dichroism; Chromophore; Chirality; Configuration.

Introduction

The CD exciton chirality method [1–3] is a powerful option when elucidation of the absolute configuration is required, especially if the X-ray crystallographic analysis is not executable for the molecule of interest. The exciton-coupled CD (ECCD) becomes observable when two or more chromophores with distinct transition moments interact one another through space. The coupling gives rise to a pair of intense *Cotton* effects with opposite signs reflecting the spatial relation of those transition moments. When the preferred conformation of the chromophores is clearly grasped, the sign of *Cotton* effects is unambiguously correlated to the absolute configuration for the molecule of interest. Chromophores can be intrinsic or synthetically introduced as long as the principle of exciton is fulfilled, and the method has been applied to a variety of compounds [2]. Developments for ECCD applications, that have been devoted to the course of enriching the list of options, include exploration for a new way to introduce chromophores [4], searches for new useful chromophores [5, 6], and survey for an alternative CD detection [7].

It was reported that certain dipyrrinone derivatives can be good exciton-coupling chromophores [8] of the following features: (1) They possess absorption in a red-shifted region (∼410 nm), (2) The internal carbonyl bridge makes the chromophore fluorescent, (3) The shorter belt results in the more intense ECCD, and (4) The derivatives possess potential for complementary CD studies. Particularly the benzoyl analogue of xanthoglow shown in Fig. 1 was considered as an attractive exciton-coupling chromophore since it possesses the absorption at a long wavelength and the emission in high efficiency ($\phi_F =$ 0.65 in chloroform).

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Slipping Past UGT1A1 and Multidrug Resistance-Associated Protein 2 in the Liver: Effects of Steric Compression and Hydrogen Bonding on the Hepatobiliary Elimination of Synthetic Bilirubins

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ABSTRACT:

The hepatobiliary metabolism and excretion of three isomeric bilirubin analogs with propanoic replaced by benzoic acid side-chains were studied in the rat. Despite their isomeric relationship and similar constitutions, the three analogs were metabolized quite differently from each other and from bilirubin. In the di-*o*-benzoic compound, steric hindrance involving the phenyl groups reinforces intramolecular hydrogen bonding of the two carboxyl groups. This compound is considerably less polar than bilirubin on reverse-phase high-performance liquid chromatography and, like bilirubin, was not excreted in bile in UGT1-deficient (Gunn) rats. But, quite unlike bilirubin, it was not glucuronidated or excreted in bile in normal rats. In contrast to both bilirubin and the di-*o*-benzoic isomer, the more polar *m*- and *p*-isomers, in which intramolecular hydrogen bonding of carboxyl groups is sterically difficult, were excreted rapidly in bile in unchanged form in both normal and Gunn rats. However, only one of them, the di-*m*-isomer, was excreted rapidly and unchanged in bile in rats (TR$^-$ rats) congenitally deficient in the canalicular ATP-binding cassette transporter Mrp2. The marked differences in hepatobiliary metabolism of the three isomers studied can be rationalized on the basis of their computed three-dimensional structures and minimum-energy conformations and the remote effects of steric compression on intramolecular hydrogen bonding.

Bilirubin (**1**) (Fig. 1) is formed in mammals by reduction of biliverdin (**2**), end product of most heme catabolism. It is insoluble in water, lipophilic, extensively protein-bound in plasma, and, unlike biliverdin, requires phase-2 metabolism, mainly to mono- and diglucuronides, for elimination. Once used as a liver function test (Harrop and Barron, 1931; Kornberg, 1942), bilirubin is a constituent of several Asian traditional medicines (McDonagh, 1990), and its antioxidant/anti-inflammatory properties are currently attracting attention (Stocker et al., 1987; Stocker, 2004; Ollinger et al., 2007a,b). Historically, bilirubins have been useful for investigating mechanisms of acyl glucuronidation, membrane transport, and hepatobiliary excretion. Bilirubin and its two monoglucuronides are isozyme-specific substrates for the glucuronosyl transferase UGT1A1 (Owens et al., 2005), and its three acyl glucuronides are classic examples of compounds that depend wholly on the ATP-binding cassette transporter MRP2 (ABCC2) for elimination in bile (Nies and Keppler, 2007). Deficiencies of UGT1A1 cause neonatal jaundice, Gilbert's and Crigler-Najjar syndromes (Kaplan and Hammerman, 2005), and congenital deficiency of MRP2 underlies the rare Dubin-Johnson syndrome (Nies and Keppler, 2007). Studies on bilirubin glucuronides led to the discovery that acyl glucuronides of many drugs are reactive, potentially toxic, metabolites (Smith et al., 1986), and studies on bilirubin analogs have revealed how subtle changes in molecular conformation can profoundly influence hepatic metabolism (McDonagh and Lightner, 1991; McDonagh et al., 2001; McDonagh and Lightner, 2007). Thus, although not generally considered drugs, bilirubins offer insight for the study of many aspects of drug metabolism.

Although often depicted as in **1**, bilirubin is not linear (Person et al., 1994). It is conformationally mobile and tends to adopt chiral conformations that are stabilized by intramolecular hydrogen bonding between the carboxyl (or carboxylate) groups and juxtaposed NH and NHCO functions (Fig. 2). Such "ridge-tile" conformers occur in crystalline bilirubin and its salts, in solution, and probably in bilirubin serum-albumin complexes. Their predominance seems to dictate bilirubin's metabolism. Minor modifications of the alkyl side-chains have little effect on metabolism, but structural modifications that prevent or stress the intramolecular hydrogen bonding have a marked effect.

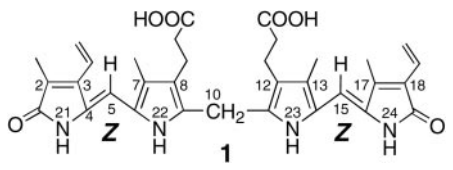

FIG. 1. Constitutional structure and numbering system of bilirubin IXα. The 4,5 and 15,16 carbon-carbon double bonds have the *Z* configuration, as opposed to the *E*.

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This work is dedicated to Professor Leslie Z. Benet on the occasion of his 70th birthday and to the memory of Professor Emeritus Rudi Schmid, who died on October 20, 2007, at the age of 85.

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ABBREVIATIONS: MRP2/Mrp2, multidrug resistance-associated protein 2; MeDocta, 0.1 M di-*n*-octylamine acetate in MeOH; TR$^-$, Mrp2-deficient; HPLC, high-performance liquid chromatography.

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ORIGINAL PAPER

^{13}C-labeled bilirubin: synthesis of 3^1(3^2),17^1(17^2)-di-[^{13}C]-mesobilirubin-XIIIα

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Abstract The title compound, labeled with ^{13}C in the ethyl groups was synthesized from K^{13}CN and low-molecular-weight components. The synthetic relay compound was 3^1(3^2)[^{13}C]-xanthobilirubinic acid methyl ester in a synthetic route that leads to a label in the ethyl β-substituent of a dipyrrinone model for bilirubin. This labeled dipyrrinone was oxidatively coupled to the dimethyl ester of mesobiliverdin-XIIIα, thereby providing a route to a ^{13}C-labeled mesobiliverdin and mesobilirubin, with one carbon of each ethyl being 98% ^{13}C-enriched.

Keywords Pyrrole · Synthesis · ^{13}C-isotope

Introduction

Bilirubin (Fig. 1a), the yellow-orange, neurotoxic pigment of jaundice [1–4] and the end product of heme metabolism in mammals is a lipophilic linear tetrapyrrole [2–5]. It circulates through the body as a tightly-bound complex with serum albumin and is disposed of by hepatic uptake, conjugation to glucuronic acid and excretion into bile [1, 6, 7]. Although much is becoming known of its structure, e.g., bilirubin has been shown to adopt a folded ridge-tile-like conformation in the crystal [8–13] and in solution [14–16], the details of its metabolism remain sketchy. And although it is thought that bilirubin binds to albumin enantio-specificially in a ridge-tile conformation (Fig. 1b) [17–20], its binding site is open to conjecture. To address the question of bilirubin's binding site on serum albumin, especially human serum albumin (HSA), some years ago we synthesized the first ^{13}C-labeled bilirubin, di-[^{13}CO$_2$H]-mesobilirubin-XIIIα [21–23]. It proved to be most useful in assessing the conformation of bilirubin in solution and its pK_a, but it has proven to be not quite adequate for determining the pigment's binding site on HSA. In order to continue our quest to learn more of the binding of bilirubins to HSA, it was becoming clear that the ^{13}C label should be located in an alkyl group. Thus, in the following we report the synthesis of a new ^{13}C-labeled analog, labeled in the ethyl groups, which is only the second example of a highly-enriched bilirubinoid (**1**, Fig. 1c) with 98% ^{13}C-enrichment on carbons of each of the two ethyl groups of mesobilirubin-XIIIα (**1**).

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Results and discussion

Synthesis aspects

The synthesis of ^{13}C-labeled mesobilirubin-XIIIα is outlined in Scheme 1. The later steps (**8** → **1**) in the synthesis are known from earlier work [24–26] but were not usually carried out on a small scale or with the care necessary for such. The early stages of the synthesis were designed to incorporate the ^{13}C label using either ^{13}CH$_3$I or K^{13}CN (98% ^{13}C) as the source of the label. Our thoughts were of using the former, as its *Grignard* reagent to react with the aldehyde group of ethyl 3,5-dimethyl-4-formyl-1*H*-pyrrole-2-carboxylate, a reaction reported by Fischer and Zeile [27] to afford an 80% yield of the 1-hydroxyethyl addition product, a solid and presumable stable secondary alcohol. Despite its attraction, we found that by following the literature procedure—pouring a slurry of the pyrrole aldehyde in ether into one equiv. of an ethereal solution of

VIBRATIONAL CIRCULAR DICHROISM AND CONFORMATIONAL ANALYSIS OF DIMETHYL MESOBILIRUBINS-XIIIα

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ABSTRACT

The Vibrational Circular Dichroism (VCD) spectra of (α*R*,α′*R*), (α*S*,α′*S*) and of (β*R*,β′*R*), (β*S*,β′*S*)-dimethylmesobilirubin-XIIIα have been recorded in the region 1800-900cm^{-1} in $CDCl_3$ solution and in mixed DMSO-d_6-$CDCl_3$ solutions. Ab-initio DFT calculations have allowed to predict IR Vibrational Absorption (VA) and VCD spectra in excellent to good correspondence with observed data; the same calculations have confirmed the expected ridge-tile conformation that has been known for a long time. Assignment of Vibrational Normal Modes allows to shed light onto the relative importance of local moieties and groups in understanding fine details related to conformational properties of the molecules, as well as their interaction with solvent molecules.

KEY WORDS: Bilirubin, Vibrational Circular Dichroism (VCD), Density Functional Theory (DFT), Hydrogen Bond

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CHAPTER **5**

Chiroptical properties of compounds containing C=O groups

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I. INTRODUCTION

Chiroptical properties of compounds containing a carbonyl group are among the most studied in organic chemistry. Among the many different carbonyl-containing functional

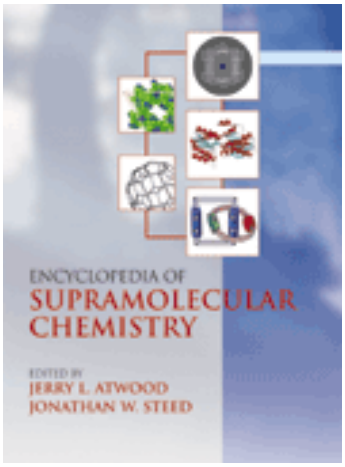
groups, in this series chiroptical properties of carboxylic acids and their simple derivatives (esters, lactones, amides, lactams) and thio analogues have been reviewed most recently in 1992[1]. This review also included a section on exciton chirality. Chiroptical properties of ketones and aldehydes, on the other hand, have not been reviewed in this series, except for α,β-unsaturated ketones[2]. Since Djerassi's book on optical rotatory dispersion (ORD) appeared in 1960[3], many monographs have appeared covering chiroptical properties of organic chromophores[4–15]. Most of these appeared in the 1960s and 1970s, whereas from 1982[13] until 1994[14,15] none appeared. Since the mid-1960s the most studied chiroptical property of ketones and aldehydes has been circular dichroism (CD), and while books on CD have appeared periodically, they have covered many different aspects of CD spectroscopy.

Since the chiroptical properties of most compounds containing C=O groups have been reviewed recently in this series, in the following we focus on CD of ketones and the relatively few aldehydes that have been studied by CD spectroscopy. Because most studies of saturated ketones have focussed on their octant rule behavior, a description of the octant rule and how to apply it appears early in this chapter. This is followed by an easy-to-read graphic compilation of the published work on saturated aldehydes and ketones since 1977, the date of the most recent comprehensive review[10] with many literature references. Conjugated ketones implicitly do not obey the octant rule. We discuss rules for interpreting the CD spectra of α,β-and β,γ- unsaturated ketones. This discussion is also followed by a graphical updating of their CD spectra. Finally, we attempt to update the reader on applications of the exciton chirality rule to ketones.

II. THE OCTANT RULE

The octant rule remains the most successful and longest serving chirality rule for interpreting ORD and CD spectra. It was formulated by Djerassi and colleagues[3,16,17] more than 35 years ago and provided a way to determine (i) the absolute configuration of a saturated alkyl ketone or aldehyde when its conformation is known, or (ii) the conformation when the absolute configuration is known. It is doubtless the most important of the many chirality sector rules proposed for various chromophores[10,18]. Sector rules focus on the chromophore in a molecule and relate the CD spectrum to the chirality of the extra chromophoric environment, to the chirality of the chromophore, or to both[19]. The octant rule relates the $n \rightarrow \pi^*$ CD spectrum of a saturated ketone or aldehyde to the extra chromophoric environment, to the molecule's structure surrounding the C=O group. In chirality rules for unsaturated ketones, considerations of the chirality of the extended chromophore become important.

The octant rule is probably best summarized by the graphics of Figure 1. The ketone or aldehyde carbonyl chromophore is oriented along the Z axis while its oxygen and carbon and atoms conjoined lie in the *YZ* plane. The two local symmetry planes, *XZ* and *YZ* of the C=O, divide all surrounding space into quadrants, and a nonsymmetry-derived third nodal surface (A or B) divides quadrant space into octants. In the classical octant rule[16], the third nodal surface was approximated as a plane (A). Subsequent theoretical and experimental studies defined it as a concave surface (B) in the revised octant rule[20,21]. To apply the octant rule, the observer looks down the C=O axis, from O to C. Front octants are nearer the observer; back octants are farther away, behind A or B. Groups or atoms lying on or near the octant surfaces make essentially no contribution to the octant rule and the CD of ketone or aldehyde. Groups or atoms lying off the octant surfaces make signed contributions according to the sign ascribed to each octant (Figure 1). These contributions are summed and weighted to predict the CD of the saturated ketone or aldehyde.



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Molecular Recognition with Dipyrrinones and Pyrrole-Based Derivatives

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Abstract
One of the most characteristic features of dipyrrinones is their preorganized arrangement of hydrogen bonding sites capable of self-recognition. Dipyrrinones' intra- or intermolecular recognition of carboxylic acid/carboxylate anion, carboxamide, or various inorganic anions is due to the complementarity of their hydrogen bonding patterns, best illustrated by the 3-D structure of bilirubin. Anion recognition using pyrrole-based receptors will also be briefly discussed as an extension of the dipyrrinone receptor.

INTRODUCTION

Pyrromethenones, better known as dipyrrinones, have been well-studied because of their connection to the bile pigments (linear tetrapyrroles) including the most studied of them—bilirubin (see section on dipyrrinone–carboxylic acid hydrogen bonding). Among the earliest dipyrrinones were the xanthobilirubic acids, prepared long ago by Fischer following treatment of bilirubin dimethyl ester with molten resorcinol,[1] and have subsequently been prepared by Fischer and others via rational synthesis.[2–6] Structurally, dipyrrinones are composed of lactam and pyrrole rings conjoined via a central methine group to form a bright yellow conjugated chromophore that is typically planar or nearly planar in shape. In addition, the C-4–C-5 double bond is generally in the Z configuration and the conformation around C-5–C-6 single bond is *syn*, which leads to the creation of a hydrogen bonding pocket containing the lactam and pyrrole NHs and the lactam C=O, as shown in Fig. 1.[7] The conformational and stereochemical aspects of dipyrrinone chemistry have been exhaustively studied to identify methods for controlling these two sites for isomerization—configuration of C-4–C-5 double bond and conformation about C-5–C-6 single bond.[7–9] The substituents along the dipyrrinone backbone (dipyrrinone carbons 2, 3, 7, and 8; see Fig. 1 for numbering scheme) are located opposite to the binding pocket and are not involved in the hydrogen bonding interactions. However, these substituents do impose a significant impact on the solubility of the compounds.

As they are essential building blocks in linear oligopyrrole chemistry, dipyrrinones have an extensive array of synthetic techniques available for their preparation. A recent review exhaustively documented the synthetic methodologies available, and the wide array of dipyrrinone analogs that have been prepared for various purposes,[10] therefore, the synthetic aspects of dipyrrinone chemistry will not be addressed here. The most common synthetic routes to variously substituted dipyrrinones include base-catalyzed condensation between a pyrrolinone and pyrrole-2-carbaldehyde, Wittig-type reaction between a 5-tosylpyrrolinone and pyrrole-2-carbaldehyde, and specifically for xanthobilirubic acids–acid catalyzed condensation between a bromomethylene pyrrolinone and different pyrrole-2-carboxylic acids. In rare cases, the lactam ring is constructed via cyclization of suitable open chain precursor (Scheme 1). In this entry, the hydrogen bonding properties of dipyrrinone analogs will be presented to show their versatility and potential as building blocks in larger supramolecular systems.

SELF-ASSOCIATION: DIPYRRINONE–DIPYRRINONE DIMERS

Dipyrrinones have been shown to form dipyrrinone–dipyrrinone dimers via a network of four intermolecular hydrogen bonds incorporating amide–amide hydrogen bonds between the lactam moieties as well as H bonds between the pyrrole N–H and lactam carbonyl, see Fig. 2a.

Dipyrrinone dimerization, arising from hydrogen bonding, is thus apparently strongly preferred in nonpolar solvents. Self-recognition of dipyrrinones is best observed by the large ^{1}H NMR downfield shift of lactam and pyrrole NH signals.[11] Their relative shielding is considerably concentration dependent. The self-association of dipyrrinones has been extensively studied using vapor pressure osmometry,[12,13] ^{1}H NMR spectroscopy[11,14,15] and x-ray crystallography.[16–18] In the crystal structures, the nonbonded donor–acceptor distances fall into the accepted

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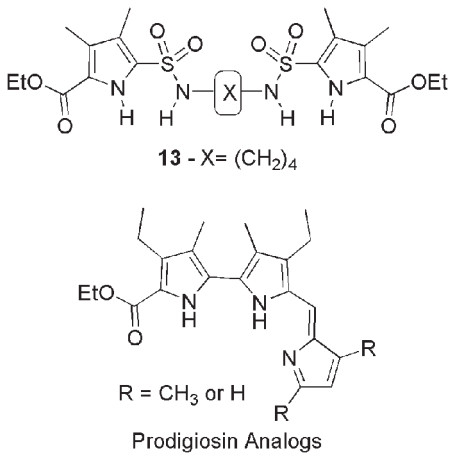

Fig. 8 Bis-sulfonamide **13** and prodigiosin analogs that are used as anion receptors.

carbonate anion in DMSO-d_6/0.5% water (see Fig. 9).[69] These fluorescent dicarbazolylurea analogs were found to have bindings affinities of $>10^4$ M^{-1} for acetate and bicarbonate and ~100 M^{-1} for chloride. 1,3-Diindolylureas and thioureas were synthesized and studied for their anion binding ability. The thiourea analogs showed only moderate binding affinities in DMSO/0.5% water, while the urea compounds displayed strong affinity for carboxylates (acetate and benzoate) as well as dihydrogen phosphate in the same solvent mixture.[70] Beer et al. have used an indolocarbazole–sulfate system to develop a pseudorotaxane that used the sulfate recognition to template formation of the pseudorotaxane.[71] Formation of the pseudorotaxane system was described both in solution as well as in surfaced assembled monolayers. Propargyl alcohol modified indolocarbazole has been shown to bind well to chloride, phosphate, and acetate anions.[72] The simpler 1,8-diamido-modified carbazole scaffold has been used for recognition of chloride, hydrophosphate, and benzoate anions.[73]

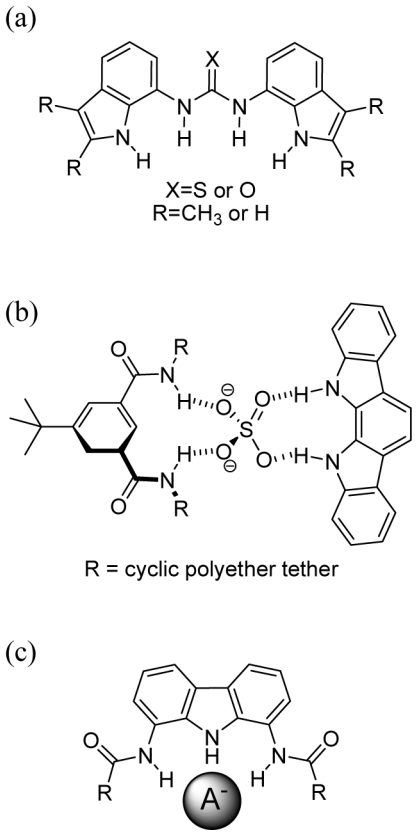

Fig. 9 (a) Biindolylurea anion receptors. (b) Sulfate template pseudorotaxane. (c) 1,8-Diaminocarbazole anion receptor.

CONCLUSIONS AND FUTURE DIRECTIONS

As a mature class of molecules, the synthetic routes to preparing and the basic molecular recognition properties of dipyrrinones have been well studied. As discussed, dipyrrinones have been shown to have a strong binding affinity for carboxylic acids, amides, and various anions, as well as for itself via self-association. Dipyrrinones binding ability is due to specific arrangement of hydrogen bond donor and acceptor sites capable of simultaneous formation of multiple intra- or intermolecular H-bonds. However, there has been very little effort devoted to using these molecules as a supramolecular building block. With well established methods for studying the hydrogen bonding patterns and aggregation states, the dipyrrinone makes an attractive candidate for use as the molecular recognition unit for sensor development, supramolecular polymers, anions transport systems, and much more.

Pyrrole and polypyrrole-based molecular receptors have been an area of intense research, especially in the anion binding arena. This area is expected to experience continued exploration and should begin seeing specialized applications nearing the market.

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