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Molecular recognition studies with a simple dipyrrinone

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Abstract—We present our investigations of 2-ethyl-3-methyl-(10*H*)-dipyrrin-1-one, its self-association, and anion binding properties. This receptor is easily accessible in a facile single step synthesis with a straightforward workup. An examination of the concentration dependence of the dipyrrinone NH chemical shifts in $CDCl_3$ and $(CDCl_2)_2$ over the temperature range from −20 °C to 100 °C determined the self-association constant to be 3850 M^{-1}. Molecular recognition studies have shown that it has a preference for guests with an OH moiety, such as hydrogen sulfate (HSO_4^-) and carboxylic acids (RCO_2H).

1. Introduction

Anions play an important role in many important chemical and biological processes. More specifically, anions play important roles in medicinal chemistry (misregulation of chloride channels in cystic fibrosis,[1–3] and maintenance of phosphate and sulfate concentrations during dialysis[4]) and catalysis chemistry (such as anion-templated synthesis[5,6]). Some anions have been linked to waterway pollution (from runoff of nitrate- and phosphate-containing fertilizer) and carcinogenesis (metabolites of nitrate[7,8]). In addition, many aspects of anion chemistry are associated with the waste streams from the nuclear fuel processes (e.g., pertechnetate and sulfate) and other toxic or otherwise troubling species (arsenate, chromate, etc.)[9] There has been extensive effort devoted to the development of synthetic anion receptors with a multitude of review articles[10–15] and several monographs[9,16] written on the subject. Their selective recognition is an area of intense interest for a variety of potential applications and is one of the fastest growing areas in supramolecular chemistry.

Pyrromethenones, better known as dipyrrinones, are comprised of lactam and pyrrole rings conjoined by a central methine group to form a conjugated chromophore. Dipyrrinones, typically bright yellow compounds, are well known to be avid participants in hydrogen bonding, and they have been shown to form 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 Figure 1.[17–23] The self-association of dipyrrinones has been extensively studied using vapor pressure osmometry and X-ray crystallography,[24] while the self-association constants have been determined using ^{1}H NMR spectroscopy.[20] For example, the self-association constant of kryptopyrromethenone is rather large ($K_a \approx 23{,}000\ M^{-1}$ at 22 °C in $CDCl_3$).[20] Also, it has been found that the size and nature of the substituent at the 9-position of the dipyrrinone core seem to extensively influence the strength of self-association.[23]

In addition to self-association, dipyrrinones have also been found to form strong hydrogen bonds with carboxylic acid and amide moieties. For example, the ridge-tile, or half-opened book, conformation of bilirubin has been found to be stabilized by six intramolecular hydrogen bonds between each dipyrrinone group and its opposing propionic acid.[25,26]

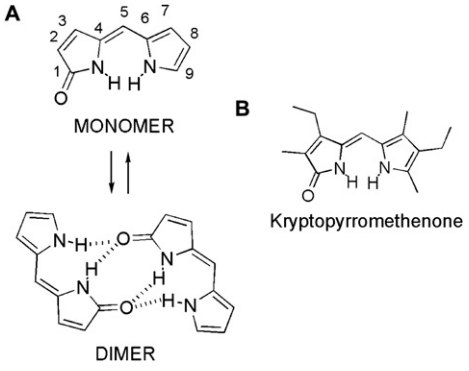

Figure 1. (A) Monomer–dimer equilibrium with generic dipyrrinone showing the four intermolecular hydrogen bonds. (B) Kryptopyrromethenone.

Keywords: Molecular recognition; Dipyrrinones; Hydrogen bonding; Anion binding; Self-association.
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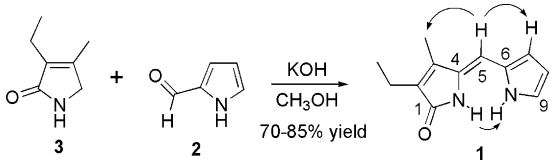
A diverse library of synthetic analogs of bilirubin has been prepared, which demonstrates a strong preference for the carboxylic acid to dipyrrinone hydrogen bonding pattern.[21–23,27–29] Recently, several examples of dipyrrinones, which exhibit strong hydrogen bonds to amide functional groups have also been reported.[30] To date, there have been no published studies using dipyrrinones as molecular receptors for exogenous guests. In the following, we describe our investigations of a simple dipyrrinone analog: its self-association and host–guest properties. Both the self-association and dipyrrinone acid hydrogen bonding motifs take advantage of the lactam C═O to add additional hydrogen bonding interactions. It is anticipated that this additional interaction can be used for the selective recognition of guest species.

2. Results and discussion

2.1. Synthesis and molecular structure

For our first foray into this chemistry, we sought a target compound that was easily accessible in large quantities in a relatively short overall synthesis. Fortunately, target dipyrrinone **1** was prepared via a base-catalyzed condensation of commercially available 2-pyrrole carboxaldehyde (**2**) and 3-methyl-4-ethylpyrrolin-2-one (**3**).[31] After recrystallization (methanol–water), the target compound was isolated in 70–85% yield from a single step synthesis, Scheme 1. The structure of **1** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopies. Complete NMR spectroscopic assignments were made by a combination of ^{1}H{^{1}H}-nuclear Overhauser enhancement spectroscopy (NOESY), HSQC, and HMBC techniques. The *Z*-configuration of the C(4)–C(5) exocyclic double bond was confirmed by the observation of a moderate NOE between the C(5)–H and the C(3) methyl in $CDCl_3$.



Scheme 1. Synthetic scheme for preparing dipyrrinone **1**. Arrows shown on **1** indicate selected ^{1}H{^{1}H}-NOEs observed in $CDCl_3$.

2.2. Solid state molecular geometry and hydrogen bonding

Dipyrrinones lacking alkyl substituents at C(7) possess essentially free rotation about the C(5)–C(6) carbon single bond creating the possibility for the pyrrole and lactam NHs to be either *syn* or *anti* to one another. From X-ray crystal structural analysis (single crystals were obtained from slow evaporation of 0.02 M **1** in $CDCl_3$), each dipyrrinone **1** unit was found to exist in the *syn*/*Z*-configuration of the C(4) exocyclic double bond (Fig. 2). The individual dipyrrinone units are nearly planar with a C(4)–C(5)–C(6)–N(2) torsion angle of 8.0°. In addition, the structure clearly shows the existence of the self-associated dimer containing four intermolecular hydrogen bonds between the pyrrole and lactam N–H and the lactam C═O. The two dipyrrinone units are co-planar and the N–H···O═C distances, N(1A)–O(1B)= 2.83 Å; N(2A)–O(1B)=2.80 Å, are all within the expected

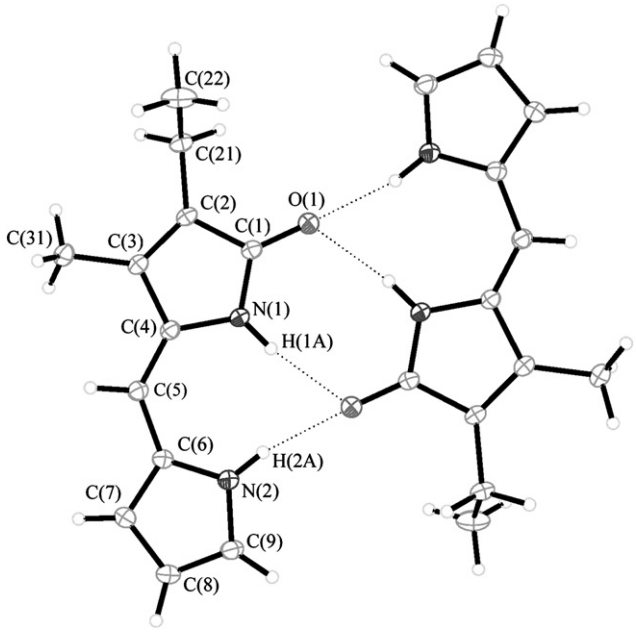


Figure 2. X-ray crystal structure of dipyrrinone **1** showing the dimeric structure with four intermolecular hydrogen bonds. Thermal ellipsoids are drawn at 50% probability.

ranges [less than the sum (2.90 Å) of the van der Waals radii of N (1.50 Å) and O (1.40 Å)].

2.3. Solution state molecular geometry and hydrogen bonding

The geometric structural assignments in $CDCl_3$, particularly the *syn* conformation of the C(5)–C(6) bond of dipyrrinone **1** was confirmed by the observation of strong nuclear Overhauser effects (NOEs) between the lactam and pyrrole NHs, and moderate NOEs between the C(5)–H and the C(7) hydrogen. This is the preferred conformation for **1** acting as a molecular receptor.

In order to assess the self-association properties, we investigated possible dimer formation in chloroform solutions by vapor pressure osmometry (VPO). Previously it had been shown by VPO that dipyrrinones with relatively large self-association constants (~23,000 M^{-1}) give molecular weights consistent with their dimeric structures while dipyrrinones that do not self-associate (or have substantially smaller self-association constants) give their monomeric molecular weights.[22,23,32] In chloroform at 45 °C, dipyrrinone **1** (monomer MW=202 g/mol; dimer MW=404 g/mol) gave a molecular weight of 303±20 g/mol indicating that the self-association constant for this compound was weaker than normal for dipyrrinones of this type.[23]

An examination of concentration dependence of the dipyrrinone NH chemical shifts in $CDCl_3$ (−20 °C to +40 °C) and $(CDCl_2)_2$ (+60 °C to +100 °C) over the temperature range from −20 °C to +100 °C shows considerable variation. (Lightner et al. have previously shown that $CDCl_3$ and $(CDCl_2)_2$ can be used interchangeably for such studies with dipyrrinones.[20]) The sets of curves for the pyrrole NH show a clear plateau at 10.91 ppm in the high concentration region at −20 °C and a second plateau at 8.31 ppm in the

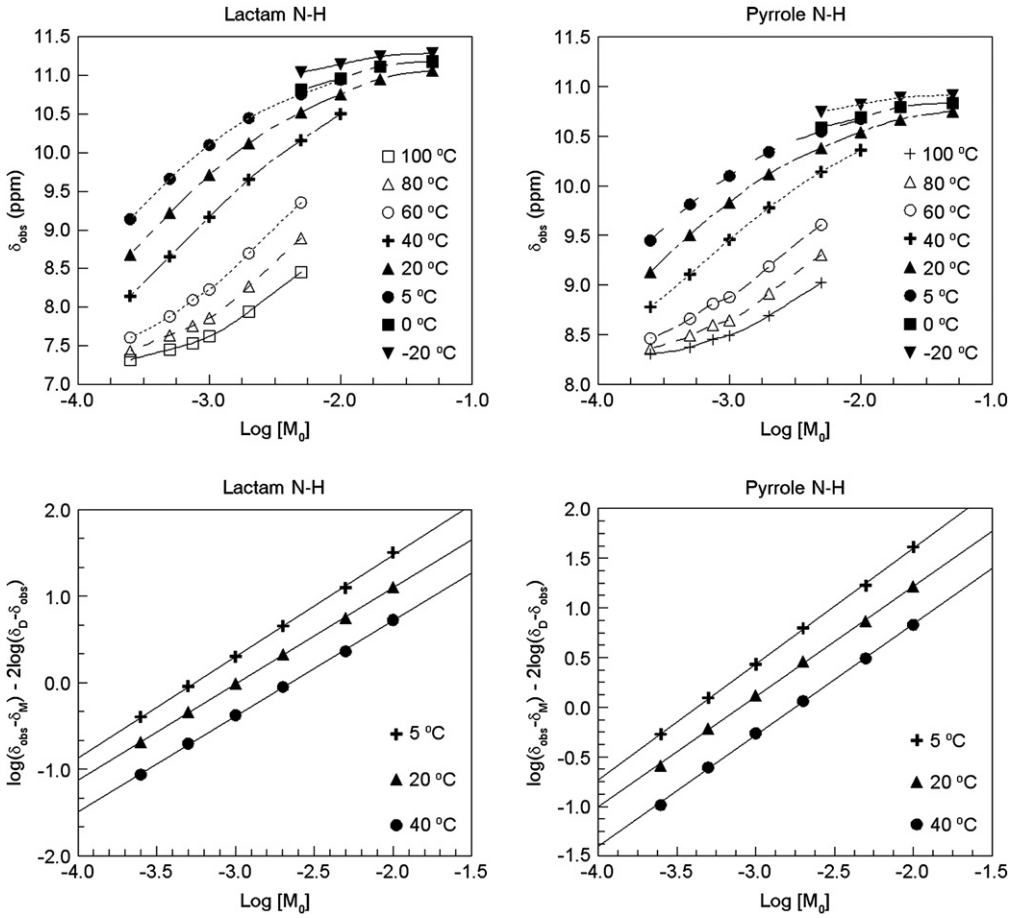


Figure 3. Behavior of the lactam (left) and pyrrole (right) NH ^{1}H NMR chemical shifts between −20 °C and +100 °C over a concentration range of 5.0×10^{-2}–2.5×10^{-4} M. Upper: δ_{NH} vs log of initial concentration of monomeric dipyrrinone; lower: $[\log(\delta_{obs}-\delta_{monomer})-2\log(\delta_{dimer}-\delta_{obs})]$ vs logarithm of initial concentration of monomeric dipyrrinone from +5 °C to +40 °C.

dilute concentration at +100 °C. These data are consistent with $\delta_{monomer}$=8.31 and δ_{dimer}=10.87 ppm. Observing the curves for the lactam NHs gives a plateau at 7.30 ppm for the monomer at +100 °C, and we observe a second one at 11.28 ppm at −20 °C for the dimer. From these data, and assuming a simple monomer–dimer equilibrium (K_a=[dimer]/[monomer]^2), by plotting $\log(\delta_{obs}-\delta_{monomer})-2\log\delta_{dimer}$ vs log[sample] we obtain straight-line plots for three temperatures (Fig. 3). From such plots, one obtains self-association constants, K_a, at each temperature, see Table 1. Plots of ln K_a vs $1/T$ for the pyrrole and the lactam NH data give straight-line plots from which various thermodynamic parameters may be obtained. As expected, the self-association constant is small (K_a=3850 M^{-1}) when compared to kryptopyrromethenone at room temperature, and ΔS^0 is negative. The discrepancy in K_a values derived from the pyrrole NH and lactam NH is probably related to a greater inaccuracy in determining the δ_{obs} for the broader lactam NH resonance. Strong dimerization may be hindered by the deficiency in preorganization of the dipyrrinone core due to the lack of a C(7) alkyl substituent. Dipyrrinones possessing an alkyl substituent at this position typically have substantially larger self-association constants.[20]

Table 1. Dipyrrinone NH chemical shifts and thermodynamic parameters[a] for the self-association of **1**

Parameter	Lactam-NH	Pyrrole-NH
δ_M (ppm)	7.30	8.31
δ_D (ppm)	11.28	10.91
K_a (5 °C, M^{-1})	13,200	11,000
K_a (20 °C, M^{-1})	4080	3610
K_a (40 °C, M^{-1})	1640	1560
ΔH^0 (kcal/mol)	−42.8	−40.1
ΔS^0 (e.u.)	−75.8	−67.5
ΔG^0 (kcal/mol)	−20.6	−20.3

[a] K_a: ±10%, ΔH^0 and ΔG^0: ±2.0 kcal/mol, ΔS^0: ±1.0 e.u.; all plots (Fig. 3) have R-values above 0.99.

2.4. Molecular recognition studies

Due to the monomer–dimer equilibrium present for dipyrrinone **1**, attempts to use **1** as a molecular receptor create a competitive binding environment where the exogenous guest must compete with the self-association process. Unfortunately, attempts at using UV–vis spectroscopy to study the host–guest interactions failed to induce a significant change in the UV–vis spectrum for the dipyrrinone chromophore. Studies to determine if the presence of a guest species disrupts the monomer–dimer equilibrium were conducted by titration of **1** in $CDCl_3$ with tetra-*n*-butylammonium hydrogen sulfate in $CDCl_3$ (Fig. 4). The results show that lactam N–*H* resonance shifts from 10.92 ppm to 10.47 ppm upon addition of 2.6 molar equiv of the hydrogen sulfate anion. The resonance for the pyrrole N–*H* experiences only a slight

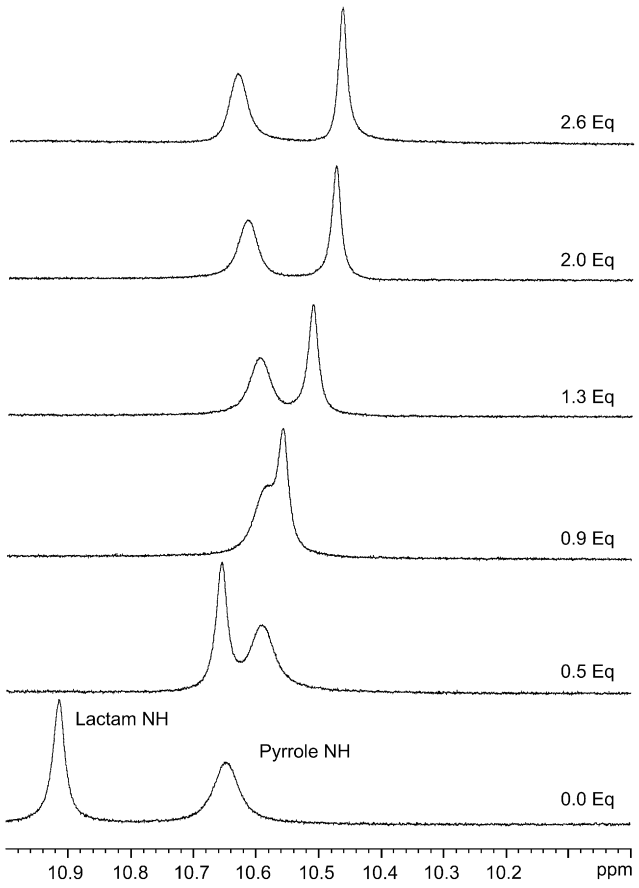


Figure 4. ^{1}H NMR spectra for the titration of tetra-*n*-butylammonium hydrogen sulfate into a 0.02 M solution of dipyrrinone **1** in $CDCl_3$. Equivalents of $TBA\cdot HSO_4$ indicated on the left side of the plot.

change in chemical shift over the course of the addition. Presumably, the anion forms hydrogen bonds with the lactam and pyrrole NHs, which is disrupting the self-association of **1**.

Additional ^{1}H NMR titration studies were conducted with **1** and various guests (chloride, bromide, and nitrate as their respective tetra-*n*-butylammonium salts and benzoic acid). Analysis of the titration data using a 1:1 host–guest binding mode which allowed for the incorporation of the host self-association (K_a=3850 M^{-1}), also in a 1:1 binding mode, in a linear regression model[33] revealed the stability constants given in Table 2. With the anionic guests, data analysis was performed on the lactam NH signal, which in all cases experienced a 0.4–2.0 ppm upfield shift upon addition of the guest. In the case of benzoic acid, addition of the guest resulted in a minimal change in the lactam NH chemical shift. Fortunately, the pyrrole NH resonance experienced a reasonable change in chemical shift, ~0.5 ppm. In the case of the benzoic acid and hydrogen sulfate, the changes in chemical shifts for the lactam and pyrrole NHs were substantially smaller than those for the nitrate, chloride, and bromide. This can be explained by examining the hydrogen bonding motifs in comparison to the self-associated dimers. When associated with benzoic acid or hydrogen sulfate, dipyrrinone **1** is participating in three intermolecular hydrogen bonds, similar to the self-associated dimer. As such, the NH signals should not experience substantial changes in the chemical shifts. However, when dipyrrinone **1** has formed a host–guest complex with nitrate, chloride or bromide, there

Table 2. Association constants (K_a) of **1** with various guest species[a]

Guests		K_a (M^{-1})
Chloride	Cl^-	122
Bromide	Br^-	<10
Nitrate	NO_3^-	94
Hydrogen sulfate	HSO_4^-	1680
Benzoic acid	$C_6H_6CO_2H$	1280

[a] Anions were used as their respective tetra-*n*-butylammonium salts. Association constant uncertainty estimated at ±15%. All measurements made in $CDCl_3$ at 22 °C.

are only two intermolecular hydrogen bonds. In addition, an electrostatic repulsion between the anion and the lactam carbonyl should lead to a weaker hydrogen bond between the lactam NH and the guest species. This explains the larger change in lactam NH chemical shifts observed upon addition of the nitrate, chloride, and bromide.

The results show relatively weak stability constants to all guest species. However, a strong selectivity was observed for the species possessing the OH moiety, i.e., benzoic acid (1280 M^{-1}) and hydrogen sulfate (1680 M^{-1}). The selectivity is based on species of this nature taking advantage of the lactam C=O to form an additional hydrogen bond. Anions lacking a hydrogen bond donor group (i.e., lacking OH) have significantly lower association constants, <100 M^{-1}. Unfortunately, Job plot analyses could not be performed to study the binding stoichiometry due to the competitive self-association. The solution state conformation of dipyrrinone **1** in the presence of 2 equiv of hydrogen sulfate was confirmed by NOESY in $CDCl_3$, Figure 5. The *Z*-configuration of the C(4)–C(5) exocyclic double bond was confirmed by the observation of a moderate NOE between the C(5)–H and the C(3) methyl in $CDCl_3$, and the *syn* conformation of the C(5)–C(6) bond **1** was confirmed by the observation of strong nuclear Overhauser effects (NOEs) between the lactam and pyrrole NHs, and moderate NOEs between the C(5)–H and the C(7) hydrogen. In addition, an NOE was observed between the lactam NH and hydrogen sulfate OH moiety. NOE studies on the dipyrrinone **1** complexes with the other guest species gave the same results. While not proving binding stoichiometry, this does indicate that no significant changes in conformation were induced by the complexation of the guest species.

Single crystals of dipyrrinone **1** bound with tetra-*n*-butylammonium hydrogen sulfate were obtained by slow diffusion of diethyl ether into a 0.02 M solution of **1** and 0.2 M tetra-*n*-butylammonium hydrogen sulfate in methylene chloride, Figure 6. The hydrogen bonded complex shows a 1:1 stoichiometry with three hydrogen bonds between the hydrogen sulfate and dipyrrinone moieties. In addition to two hydrogen bonds involving the pyrrole and lactam NHs, there is

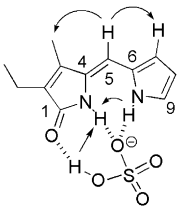


Figure 5. NOE data for **1**–$HSO_4\cdot$TBA complex in $CDCl_3$. Arrows indicate important observed NOEs.

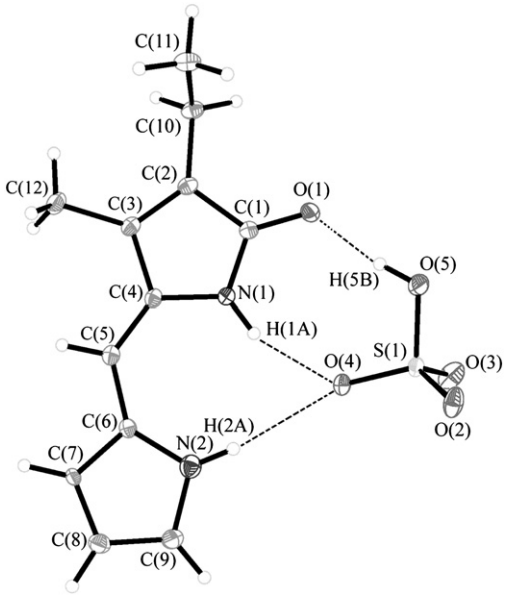


Figure 6. X-ray crystal structure of the dipyrrinone **1**–tetra-*n*-butylammonium hydrogen sulfate complex showing the three intermolecular hydrogen bonds. The tetra-*n*-butylammonium cation has been omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

a single hydrogen bond between the OH of the hydrogen sulfate and the lactam C═O. The OH···O═C and S–O···HN (lactam) distances are within the expected ranges (2.60 and 2.79 Å, respectively); however, the S–O···HN (pyrrole) distance is a little long, 3.30 Å. The dipyrrinone backbone is planar (N(1)–C(4)–C(5)–C(6) torsion angle=0°), similar to what was found for the previously discussed self-associated dipyrrinone dimer, Figure 2.

3. Conclusion

In conclusion, we have shown that dipyrrinones have the potential to be used as an effective receptor in non-polar organic solvents for guests that contain an OH moiety. The additional hydrogen bonding opportunities provided by this group allow for discrimination between guests containing this group and those that do not. This new dipyrrinone analog also had an unusually small self-association constant as compared with previously studied dipyrrinone analogs. Additional studies are underway to design dipyrrinone-based systems where self-association is less likely to occur in order to further investigate the potential of these molecules as anion and neutral molecule receptor systems.

4. Experimental section

4.1. Synthetic procedures: 2-ethyl-3-methyl-(10*H*)-dipyrrin-1-one (1)

3-Ethyl-4-methyl-3-pyrrolin-2-one (0.6 g, 4.79 mmol) and 2-pyrrole carboxaldehyde (0.46 g, 4.79 mmol) were dissolved in methanol (30 mL). To the mixture was added 4 M potassium hydroxide (20 mL), and the reaction mixture was stirred at room temperature for 24 h. The yellow precipitate obtained was collected by vacuum filtration and washed with cold methanol (5 mL). The crude product was re-crystallized from methanol and water and dried in vacuo to give 0.81 g (77%) of pure product. It had mp 208–210 °C (lit. mp[31] 213–215 °C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.65, 13.45, 16.98, 109.9, 116.0, 123.4, 127.4, 130.5 130.6, 142.1, 174.1, 103.4 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, 7.6 Hz), 2.11 (s, 3H), 2.43 (q, 2H, 7.6 Hz), 6.16 (s, 1H), 6.27 (m, 1H), 6.44 (m, 1H), 7.04 (m, 1H), 10.79 (br s, 1H), 11.12 (br s, 1H) ppm.

Acknowledgements

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Supplementary data

General experimental information, methods for molecular recognition studies, and the **1**–HSO_4^-·TBA complex, and representative molecular recognition data are available as supplementary data. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 655346 and 655347. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.033.

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