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Synthesis of Sapphyrins, Heterosapphyrins, and Carbasapphyrins by a "4 + 1" Approach†

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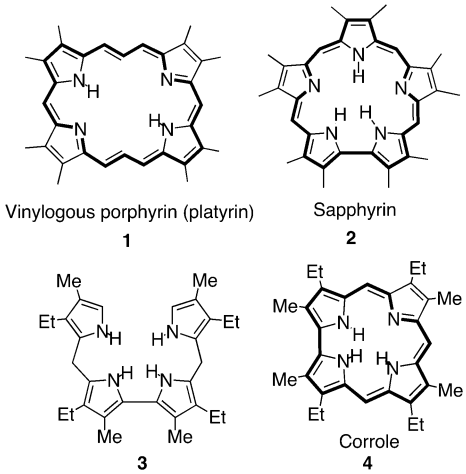
Sapphyrins are an important group of expanded porphyrins that show valuable anion binding characteristics. In this study, a "4 + 1" route to sapphyrin systems has been developed. Reaction of dialdehydes with a known tetrapyrrole intermediate **11b** incorporating a bipyrrolic subunit afforded a wide range of sapphyrin-type products. The best conditions for these reactions involved carrying out the condensation of the dialdehydes with the tetrapyrrole in TFA−dichloromethane, followed by oxidation with dilute aqueous solutions of ferric chloride. A pyrrole dialdehyde reacted under these conditions to give sapphyrin in 50% yield, while furan and thiophene dialdehydes afforded the corresponding oxa- and thiasapphyrins in 66−90% yield. Pyrrole dialdehydes with fused phenanthrene or acenaphthylene rings also reacted with **11b** to give the related phenanthro- and acenaphthosapphyrins in excellent yields. As was the case for acenaphthoporphyrins, the acenaphthosapphyrin gave longer wavelength absorptions than the corresponding phenanthrene fused structure, although the differences were not as marked as those seen in the porphyrin series. Reaction of **11b** with 1,3-diformylindene gave a benzocarbasapphyrin in 38% yield, while a triformyl cyclopentadiene reacted with the tetrapyrrole to give a carbasapphyrin aldehyde in 7−12% yield. The free base carbasapphyrins were unstable but the monoprotonated hydrochloride salts could easily be isolated and characterized. Carbasapphyrins retain a strong diatropic ring current due to the presence of 22π electron delocalization pathways. In the presence of trifluoroacetic acid, C-protonated dications are generated. Condensation of 1,3-azulenedicarbaldehyde with **11b** gave an azulisapphyrin dihydrochloride salt in 35% yield, and this also showed a strong diatropic ring current. Addition of base gave the unstable free base form, while pyrrolidine formed an unstable adduct that showed an intense Soret band at 480 nm. These results demonstrate that many of the themes observed for modified porphyrins and carbaporphyrins also apply to the sapphyrin series, although in some cases reduced stability hampers these investigations.

Introduction

Expanded porphyrins[1−6] fall into two major groups: vinylogous porphyrins or platyrins (e.g. **1**), which have more than four total linking atoms between the four pyrrole units,[7,8] and higher order systems built up from at least five pyrrolic or related subunits (Chart 1).[1] The first example of the latter category, sapphyrin (**2**), was reported by Woodward in 1966 at the Aromaticity Conference in Sheffield in the United Kingdom.[9−11] In relation to the Harvard group's early studies on the total synthesis of Vitamin B_{12},[12] tetrapyrrole **3** was treated with formic acid and HBr in an attempt to produce the

CHART 1



† Part 37 in the series "Conjugated Macrocycles Related to the Porphyrins". For part 36, see: Bergman, K. M.; Ferrence, G. M.; Lash, T. D. *J. Org. Chem.* **2004**, *69*, 8851−8864.

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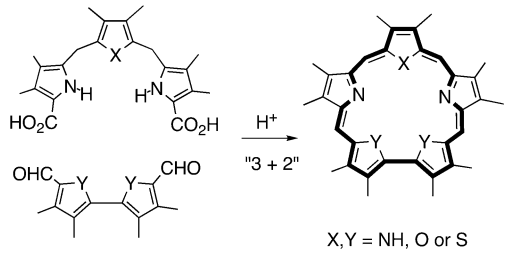
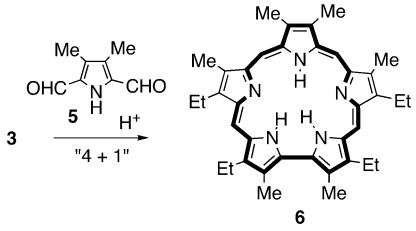
SCHEME 1



SCHEME 2



corresponding corrole **4** (Chart 1).[10] However, the pentapyrrolic sapphyrin system was generated instead, albeit in low yield, as a beautiful blue glass.[10] Due to this intense blue color, Woodward proposed the name sapphyrin for this system.[10,13] The sapphyrins are generally isolated as diprotonated salts and give deep green solutions in dichloromethane with a Soret band at 458 nm.[10] Johnson and co-workers subsequently reported a rational synthesis of sapphyrins and related heteroanalogues using a "3 + 2" version of the MacDonald condensation (Scheme 1) or a related sulfur extrusion strategy.[14,15] Details of the work conducted by Woodward and his collaborators were not published until 1983,[10] but this paper describes independent rational syntheses of sapphyrins with both a "3 + 2" strategy similar to Johnson's work and a "4 + 1" approach.[10] In the latter method (Scheme 2), tetrapyrrole **3** was reacted with 3,4-dimethylpyrrole-2,5-dicarbaldehyde (**5**) in the presence of 88% formic acid to give sapphyrin **6** in modest yield.[10] Interest in the sapphyrin system was later revived by Sessler and co-workers in the early 1990s.[11,16,17] This group also used the "3 + 2" methodology, but explored many features of this pentapyrrolic system that had not previously been recognized.[11] The aromatic character of sapphyrins was the focus of much of the early work,[1] but metalation studies had been largely unsuccessful.[10] Sessler and co-workers demonstrated that sapphyrins were versatile anion binding systems, a feature that had not previously been recognized for expanded porphyrin systems.[18,19] Sapphyrins are also singlet-oxygen-producing photosensitizers[20] and have been explored for potential applications in photodynamic therapy[21] and viral photoeradication.[22] New routes to sapphyrins have been reported where oxidative ring closure takes place to generate the direct pyrrole−pyrrole linkage.[23−25] In addition, *meso*-tetrasubstituted sapphyrins and heterosapphyrins have been produced in moderate yields by using variations on Rothemund-type chemistry.[26]

We have explored alternative ways of modifying the porphyrin system by replacing one or more of the usual pyrrole rings with carbocyclic units.[27,28] Much of this work has made use of the "3 + 1" methodology,[29,30] where a tripyrrane is condensed with carbocyclic dialdehydes to afford carbaporphyrinoids such as **7** or **8** (Chart 2).[31,32] True carbaporphyrins (e.g. **7**) retain strong diatropic ring currents and the proton NMR spectra show the internal CH resonance at −7 ppm.[31,33,34] These porphyrin ana-

(9) Woodward's announcement on the synthesis of the sapphyrin system at the 1966 Aromaticity Conference in Sheffield is consistently acknowledged in the literature[10,11,15] but no mention of this accomplishment is made in the published proceedings for this meeting.

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(30) The "3 + 1" designation refers to the number of pyrrole rings (or surrogates) in each of the components used for these syntheses. In the work discussed here, the "3 + 1", "3 + 2", and "4 + 1" methods are all based upon the MacDonald "2 + 2" condensation where a dipyrrylmethane is condensed with a dipyrrylmethane dialdehyde: Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.

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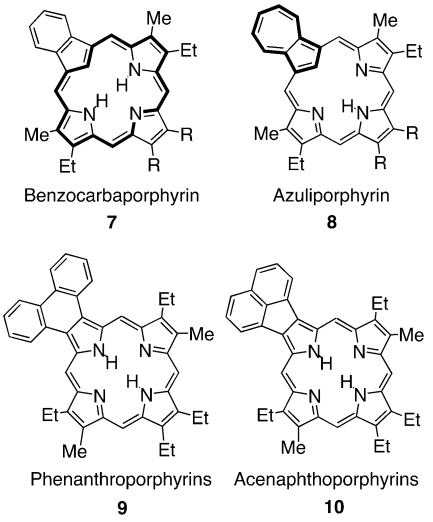
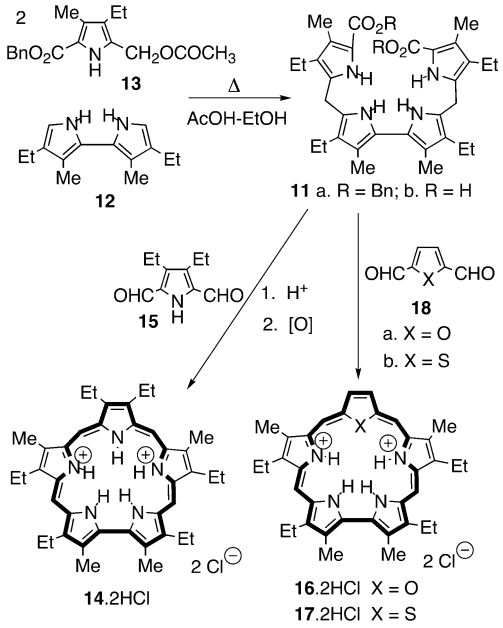
CHART 2



logues also exhibit unique chemical properties undergoing unusual oxidation reactions[35] and acting as superior organometallic ligands for silver(III) and gold(III).[36] In contrast, azuliporphyrins **8** show reduced aromatic character due to the presence of a cross-conjugated azulene subunit.[32,37] However, this system also has interesting chemistry[38,39] and acts as an effective ligand for nickel(II), palladium(II), and platinum(II).[40] In other work, we have prepared modified systems by fusing aromatic rings to the porphyrin nucleus.[41−46] Although some of these systems (e.g. phenanthroporphyrins **9**[42,43]) show only small changes in their spectroscopic properties, acenaphthoporphyrins (e.g. **10**) have highly red-shifted UV−vis spectra and give strong absorptions in the far-red region.[44,45] These compounds are also readily synthesized by application of the "3 + 1" methodology.[29] As this approach had been so successful, we were interested in synthesizing sapphyrin analogues using the same general principles. Apart from the early study by Woodward's group on the synthesis of decaalkylsapphyrin **6**,[10] the "4 + 1" route to sapphyrins had not seen any significant applications. An improved route to the required tetrapyrrole intermediate **11** (Scheme 3) had been developed by Sessler and co-workers in relation to their synthesis of rubyrins,[47] and the availability of this compound together with our extensive experience with the "3 + 1" methodology has allowed the synthesis of novel sapphyrin-type structures. These include new macrocyclic systems with fused phenanthrene and acenaphthylene units, as well as carbasapphyrins and an azulisapphyrin.[48,49]

SCHEME 3



Results and Discussion

Bipyrrole **12**[50] was reacted with 2 equiv of acetoxymethylpyrrole **13** in refluxing acetic acid−ethanol to give the corresponding tetrapyrrolic dibenzyl ester **11a** in 74% yield (Scheme 3). The proton NMR spectrum for **11a** was essentially identical with the data reported previously by Sessler et al.[47] It is noteworthy, however, that the bridging methylenes in **11a** produce a broad 4H singlet at 3.7 ppm, while the benzyl ester OCH_2 groups are shifted upfield from a typical value of 5.3 ppm to give a broad 4H resonance at 4.6 ppm. Similar effects are

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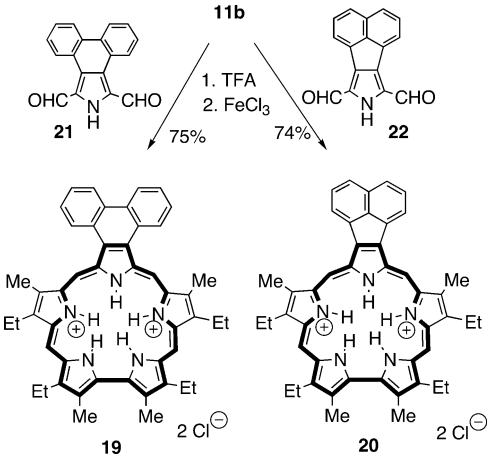
(50) Sessler, J. L.; Hoehner, M. C. *Synlett* **1994**, 211.

commonly noted for tripyrranes and have been attributed to these oligopyrroles taking on a helical conformation in solution.[29,51] This conformational preference is believed to be beneficial to macrocycle formation and allows excellent yields to be obtained without the necessity of using high-dilution techniques.[29] Cleavage of the benzyl ester protective groups with hydrogen over 10% palladium−charcoal gave the corresponding dicarboxylic acid **11b** and this was used in crude form for sapphyrin synthesis.

Initial studies were carried out on the synthesis of the known sapphyrin **14**[17a] from **11b** and pyrrole dialdehyde **15** (Scheme 3). In all of these condensations, including the "3 + 1", "3 + 2", and "4 + 1" methodologies, an oxidation step is necessary. Tetrapyrrole **11b** was treated with TFA, diluted with dichloromethane and condensed with dialdehyde **15**. The solution was then neutralized with triethylamine and the reaction mixture oxidized with 1 equiv of DDQ. Following extraction, the solutions were washed with hydrochloric acid to generate the dihydrochloride salt. After chromatography, the sapphyrin was obtained as a blue glass and recrystallization from chloroform−hexanes gave **14** in 36% yield.[48a] In a typical "3 + 2" synthesis, tripyrrane is condensed with bipyrroledialdehyde in the presence of *p*-toluenesulfonic acid, and following O_2 oxidation over a period of 18 h, sapphyrin **14** can be isolated in 44% yield.[17a] Hence, our method compares favorably with alternative routes to this system. Unfortunately, our studies gave the related sapphyrin systems discussed below in inferior yields and we speculated that the use of DDQ as an oxidant gave rise to significant degradation. In other studies, we had used dilute solutions of aqueous ferric chloride as an oxidant.[52] This proved to be an excellent reagent for these "4 + 1" syntheses and gave much improved yields of sapphyrin products.[48b] The reaction solution is placed in a separatory funnel and shaken vigorously for 5−10 min with a 0.1% w/v solution of ferric chloride in water. With use of this simple method, sapphyrin **14** was obtained in 50% yield. For all of the systems described below, even larger improvements in the yields were noted.

Oxasapphyrin **16** and thiasapphyrin **17** were previously prepared in 26% and 36% yields, respectively, using the "3 + 2" methodology.[17a] By using our conditions with ferric chloride as the oxidant, reaction of **11b** with 2,5-furandialdehyde **18a** gave **16** as the dihydrochloride salt in 68% yield. Similarly, condensation of **11b** with thiophene dialdehyde **18b** afforded thiasapphyrin **17** in a remarkable 90% yield. Hence, the ferric chloride conditions represent an important innovation for the synthesis of sapphyrin-type systems. Sapphyrin **14** and heterosapphyrins **16** and **17** all show strong Soret bands near 460 nm in their UV−vis spectra, and are highly diatropic reflecting the presence of 22π electron delocalization pathways within these structures. The proton NMR spectrum of **12**·2HCl shows three resonances for the five NH protons between −4 and −5 ppm, while the external *meso*-protons are deshielded giving rise to two singlets near 11.7 ppm. As the properties of these systems have been examined in detail by others,[10,15,17] further details will not be repeated in this paper.

SCHEME 4



The success of the "4 + 1" method enabled us to consider the synthesis of new types of sapphyrin structures. Fusion of a phenanthrene unit to the porphyrin chromophore leads to very small changes in the UV−vis spectra,[42,43] but acenaphthylene gives much larger bathochromic shifts.[44,45] In addition, free base monoacenaphthoporphyrins **10** (Chart 2) give three Soret bands[44] while phenanthroporphyrins **9** afford a single strong absorption in this region.[43] To see whether these structural units have the same effects in the sapphyrin series, the ring-fused sapphyrins **19** and **20** were targeted for synthesis (Scheme 4).[53] Reaction of **11b** with phenanthropyrrole dialdehyde **21**,[44b] followed by oxidation with DDQ, gave phenanthrosapphyrin **19** in a respectable 33% yield, although acenaphthopyrrole dialdehyde **22**[44b] reacted with **11b** to give acenaphthosapphyrin **20** in only 16% yield. However, when aqueous ferric chloride was used as the oxidant, the yields increased to 75% and 74%, respectively. The free base spectrum of phenanthrosapphyrin **19** in 1% $Et_3N-CHCl_3$ gave a Soret band at 473 nm (Figure 1), significantly shifted compared to the spectrum for **14**, which gave the corresponding band at 457 nm under these conditions. Acenaphthosapphyrin **20** gave a more complex Soret band region with the strongest band at 500 nm (Figure 1). The Q-bands for **20** were also slightly red shifted compared to those for **19**. The protonated forms in chloroform gave Soret bands at 474 and 486 nm for **19** and **20**, respectively, and the longest wavelength Q-band for **20** appeared at 710 nm compared to a value of 697 nm for **19**. The data demonstrate that the acenaphthylene unit has a stronger effect on the sapphyrin chromophore than phenanthrene, and like acenaphthoporphyrins **10**,[44] **20** shows a split Soret band region for the free base structure. However, phenanthrene has a much larger effect on the sapphyrin chromophore than it does for regular porphyrins,[43] and the difference between the two sapphyrin systems is much reduced. The diatropic ring current for **19** and **20** is undiminished, and the *meso*-protons showed up as two 2H singlets for both systems at >11.6 ppm for the proton NMR spectra in TFA−$CDCl_3$, while the NHs resonated between −5 and −6.2 ppm. The proton and carbon-13

(51) Jiao, W.; Lash, T. D. *J. Org. Chem.* **2003**, *68*, 3896.
(52) Lash, T. D.; Richter, D. T.; Shiner, C. M. *J. Org. Chem.* **1999**, *64*, 7973.
(53) The first syntheses of benzosapphyrins using the "3 + 2" MacDonald route has recently been reported: Ono, N.; Kuroki, K.; Watanabe, E.; Ochi, N.; Uno, H. *Heterocycles* **2004**, *62*, 365.

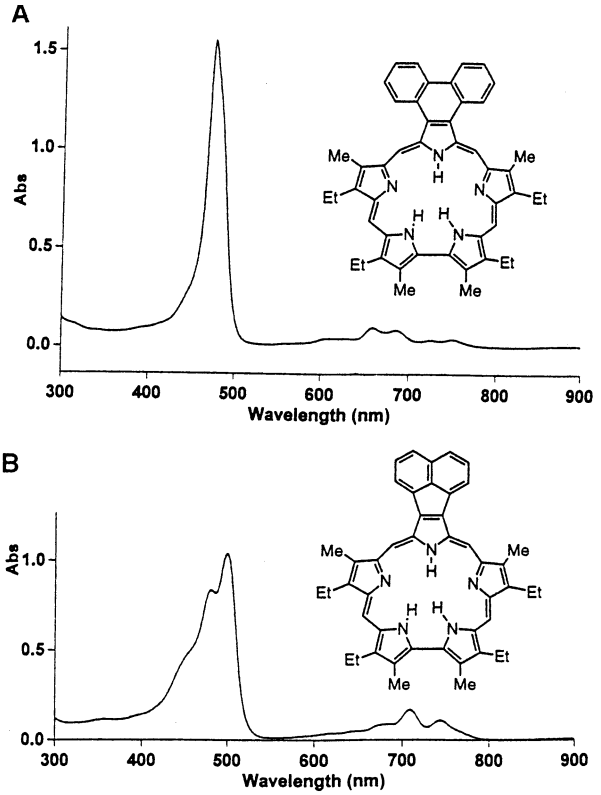
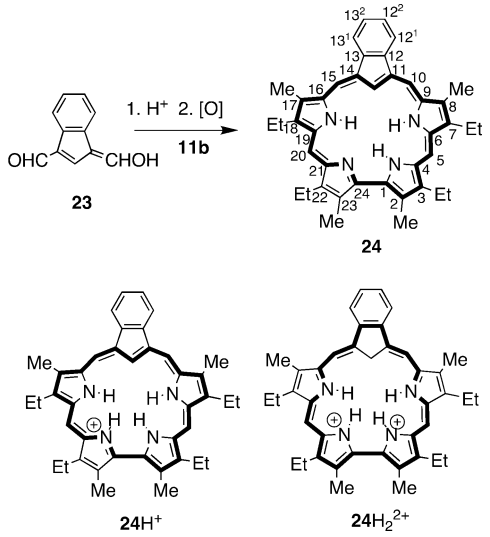


FIGURE 1. UV−vis spectra of ring-fused sapphyrins in 1% triethylamine−chloroform: (A) free base phenanthrosapphyrin **19** and (B) free base acenaphthosapphyrin **20**.

SCHEME 5



NMR spectra also demonstrate that these molecules retain a plane of symmetry.

Reaction of **11b** with diformylindene **23**, followed by oxidation with DDQ, gave benzocarbasapphyrin **24** as the monohydrochloride salt in 18% yield (Scheme 5). Again, using ferric chloride as the oxidant gave much improved yields and carbasapphyrin **24**·HCl was isolated under these conditions in 38% yield. Unlike most sapphyrins and heterosapphyrins, carbasapphyrin **24** only has one imine-type nitrogen that can be protonated. Prior to purification, the reaction solution was washed with 10% hydrochloric acid to give the stable protonated form **24**H^+

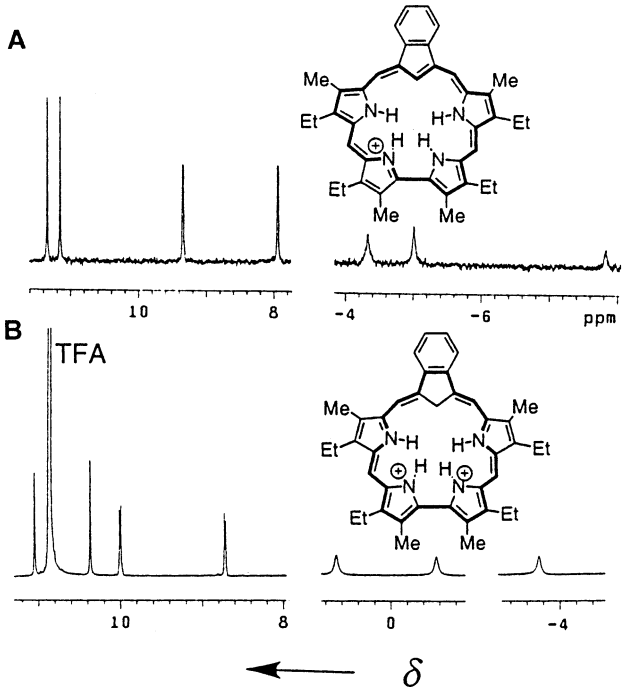
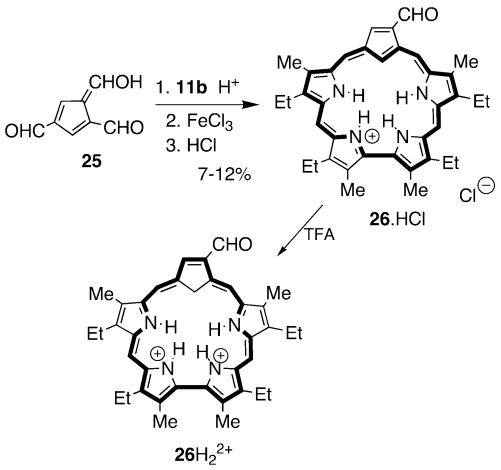


FIGURE 2. Upfield and downfield regions for the 400-MHz proton NMR spectra of benzocarbasapphyrin **24**: (A) monocation in $CDCl_3$ and (B) C-protonated dication on TFA−$CDCl_3$.

and this was isolated as blue crystals after recrystallization from chloroform−hexanes. The UV−vis spectrum of **24**·HCl in chloroform gave a Soret band at 476 nm, with a secondary band at 496 nm and a series of Q-bands at 613, 669, 708, and 788 nm. In 1% pyridine−chloroform, the spectrum was essentially unaltered, while solutions in 1% triethylamine−chloroform appeared to correspond to a mixture of the free base and protonated forms. By using 1% DBU−chlorofrom, the free base spectrum could be obtained and this showed a Soret band at 470 nm and Q-bands at 596, 645, 710, and 793 nm. The free base form was unstable and gradually degraded in solution. Addition of 1% TFA to chloroform solutions of **24**·HCl gave rise to a new species assigned as the dication **24**H_2^{2+}. This gave a very strong Soret band at 482 nm and several minor bands at longer wavelengths. The 400 MHz proton NMR spectrum of **24**·HCl in $CDCl_3$ demonstrated that the macrocycle has overall aromatic character and the internal CH gave a broadened 1H singlet at −7.9 ppm while the NHs afforded two broad 2H singlets at −5.1 and −4.4 ppm (Figure 2). The exterior *meso*-protons are also strongly deshielded giving two 2H singlets at 11.1 and 11.3 ppm. The methyl groups are indirectly affected by the aromatic ring current, and can provide a useful measure of the aromatic character. Porphyrin methyl groups generally resonate at 3.6 ppm,[54] while sapphyrin **14**·2HCl gave singlets at 4.1 and 4.2 ppm. It is significant, therefore, that **24**·HCl gave two 6H resonances near 4.1 ppm. Addition of one drop of TFA to the NMR tube gave the C-protonated dication **24**H_2^{2+}. Carbaporphyrins **7** also give rise to C-protonated dications,[31,33] but these are only favored in 50% TFA−chloroform. The heightened

(54) Medforth, C. J. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 5, pp 1−80.

SCHEME 6



ability of the larger sapphyrin system to delocalize the positive charges is no doubt responsible for the increased ease of C-protonation in this case.[55] This species is also aromatic, although the diatropicity is somewhat reduced. The interior CH_2 gives a resonance at −3.75 ppm, while the NH protons produce two broad 2H singlets at −0.56 and +0.67 ppm (Figure 2). More telling is the upfield shift of the *meso*-protons to 10.37 (2H, s) and 11.05 (2H, s) ppm, while the methyl groups now produce two 6H singlets at 3.43 and 3.66 ppm. We believe that the macrocyclic ring current must be relocated through the benzene unit (shown in bold), and this idea is supported by the downfield shifts for the benzo-protons. In the monocation, the benzo-protons gave two 2H multiplets at 7.96 and 9.35 ppm, but these resonances appear at 8.72 and 10.00 for **24**H_2^{2+} in TFA−$CDCl_3$. As expected, addition of three drops of *d*-TFA to a solution of **24**·HCl in $CDCl_3$ led to the immediate exchange of the internal CH and NH protons. This is observed for carbaporphyrins **7** as well, but these also show slow exchange at the *meso*-positions. However, even after several days at room temperature, no exchange could be observed at the *meso*-positions for **24**. This result demonstrates that C-protonation does not occur at the *meso*-carbons for the carbasapphyrin system. Attempts to obtain a proton NMR spectrum for the free base form of **24** were largely unsuccessful, apparently due to the low stability of this species. However, a poor quality proton NMR spectrum of **24** was obtained in d_5-pyridine and this showed the internal CH at −5 ppm.

Cyclopentadiene trialdehyde **25** has been used to prepare carbaporphyrins with use of the "3 + 1" approach, although the yields were typically in the range of 5−7%.[31,33,56] Reaction with **25** with **11b** in TFA−CH_2Cl_2, followed by ferric chloride oxidation, gave the carbasapphyrin aldehyde **26** in 7−12% yield (Scheme 6). The low yields are most likely due to the presence of an extra aldehyde unit that can lead to unwanted side reactions. However, this chemistry gave sufficient material to characterize the formylcarbasapphyrin **26**. The UV−vis spectrum for **26**·HCl in chloroform gave a broad Soret band at 480 nm, and Q-bands at 612, 671, 755, and 844 nm (Figure 3). In 2% TFA−chloroform, the Soret band for **26**H_2^{2+} is split into two absorptions at 469 and 490 nm, while a series of weaker Q-bands are present at 632, 685, and 745 nm (Figure 3). The proton NMR spectrum of **26**·HCl in $CDCl_3$ shows that the ring current is undiminished, giving a resonance for the internal CH at −8.5 ppm, while the NHs appear between −4.7 and −5.6 ppm. Addition of TFA afforded dication **26**H_2^{2+}, and this showed a similarly strong ring current with the internal CH_2 producing a 2H singlet at −7.1 ppm. The monocation gave four 3H singlets for the methyl groups between 4.0 and 4.1 ppm, while **26**H_2^{2+} gave these between 3.8 and 4.1 ppm. The *meso*-protons for the dication were shifted downfield beyond 11 ppm for **26**H_2^{2+}, while the monocation gave these in the range of 10.7 to 11.3 ppm. The increased aromatic character for diprotonated **26** compared to the dication for benzocarbasapphyrin **24** is probably due to two factors. First, the benzene ring in **24** loses some of its aromatic character by using two of its carbons in the 22π electron delocalization pathway and this decreases the favorability of this species. Second, the formyl moiety is electron withdrawing and this helps to stabilize the diprotonated species. Similar trends have previously been noted for carbaporphyrin systems.[33]

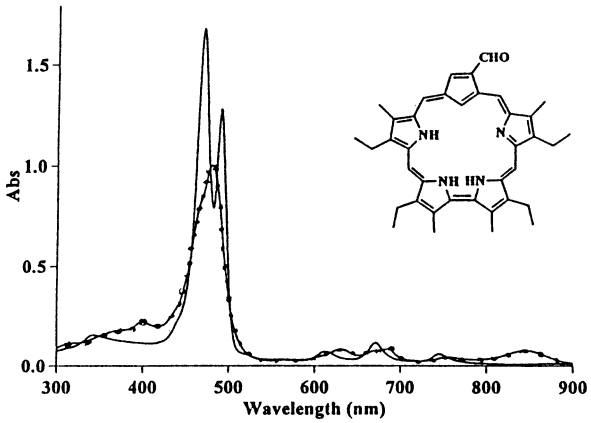


FIGURE 3. UV−vis spectra of carbasapphyrin **26**: dotted line, monocation in chloroform; bold line, C-protonated dication in 2% TFA−chloroform.

Azulene dialdehyde **27** was also reacted with **11b** in TFA−CH_2Cl_2, and following oxidation with aqueous ferric chloride, the novel azulisapphyrin system **28** was isolated as the dihydrochloride salt in 35% yield (Scheme 7). The UV−vis spectrum for **28**·2HCl in chloroform showed four absorptions in the Soret band region at 420, 455, 481, and 511 nm, and a broad absorption at 742 nm (Figure 4). This resembles the UV−vis spectrum reported for the free base form of azuliporphyrin **8**.[32] Addition of TFA led to minor shifts in these bands but the spectra appeared to correspond to the same species. In neat pyridine, essentially the same spectrum was obtained indicating that the azulisapphyrin system is considerably more basic than pyridine. However, addition of 1% triethylamine gave rise to a new species tentatively assigned as the free base form with Soret-like bands at 417 and 454 nm. This species proved to be rather unstable and after a few minutes the initially formed species disappeared and the spectrum only showed broad absorption features. Surprisingly, addition of TFA regenerated the

(55) A dicarbaporphyrin system also readily underwent C-protonation, although in this case a monocation was generated: Lash, T. D.; Romanic, J. L.; Hayes, M. J.; Spence, J. D. *Chem. Commun.* **1999**, 819.
(56) Berlin, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1820.

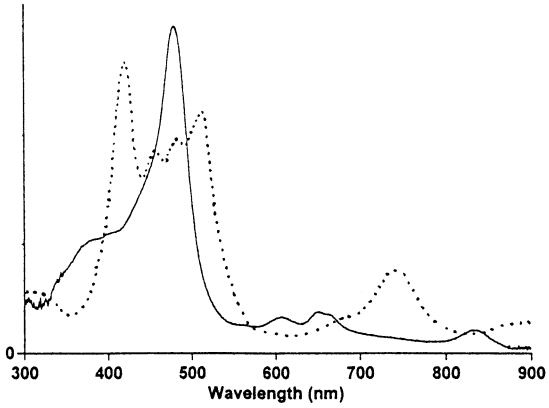
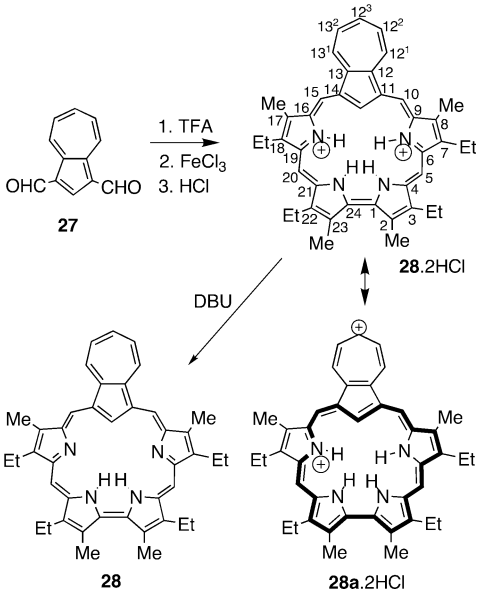


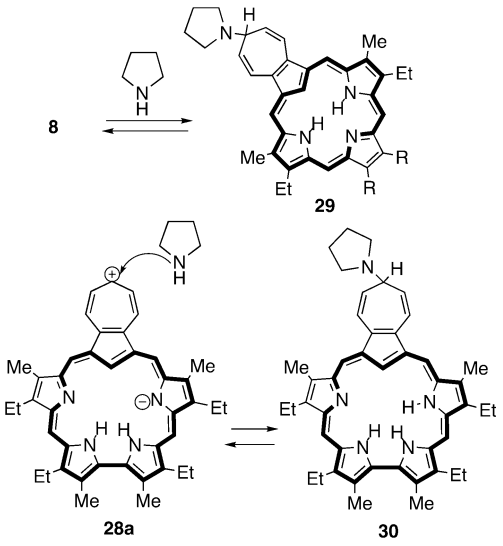
FIGURE 4. UV−vis spectra of azulisapphyrin **28**: dotted line, dication in chloroform; bold line, pyrrolidine adduct **30** in 1% pyrrolidine−chloroform.

SCHEME 7

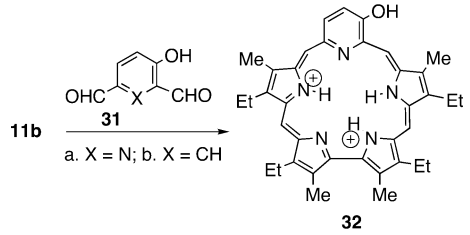


original diprotonated species. We speculate that nucleophilic attack was taking place at the *meso*-carbons and this was reversible under acidic conditions. When the spectrum was run in 1% DBU−dichloromethane, the free base species showed greater stability although degradation still occurred over a 30-min period. The free base form gave bands at 415, 457, 490, and 525 nm and a broad band centered on 781 nm. The degradation was not reversible under these conditions and addition of TFA did not produce any recognizable features in the resulting UV−vis spectrum. Azuliporphyrins **8** reversibly react with nucleophiles such as pyrrolidine to give adducts (e.g. **29**) which take on full carbaporphyrin aromaticity (Scheme 8).[37,38] This reactivity is believed to act as a trigger in oxidative rearrangements of azuliporphyrins to produce benzocarbaporphyrins.[37,38] Addition of 1% pyrrolidine to a solution of **28** in chloroform immediately gave rise to a species with a strong Soret band at 480 nm, followed by a series of Q-bands that extended to 834 nm (Figure 4). This species is assigned as the pyrrolidine−carbasapphyrin adduct **30** (Scheme 8). Unfortunately, this species undergoes irreversible decomposition over a period of about 20 min at room temperature. The NMR spectra

SCHEME 8



SCHEME 9



for **28** in various solvents were poorly resolved but these all indicated that the protonated system was highly diatropic. As is the case for protonated azuliporphyrins,[32,37] the aromatic character is believed to be derived from favorable canonical forms with a combination of tropylium and carbaporphyrinoid character (e.g. resonance contributor **28a**). In d_4-methanol, the internal CH proton resonated at −8.2 ppm, while the *meso*-protons gave two 2H singlets at 10.1 and 10.7 ppm. However, these shifts were very solvent dependent. For instance, the interior CH showed up at −3.2 ppm in d_5-pyridine−$CDCl_3$ and −4.8 ppm in TFA−$CDCl_3$. Many of the same trends are evident for azulisapphyrins and azuliporphyrins, but the instability of the free base form of **28**, as well as the difficulties in obtaining high-quality NMR spectra, has severely limited these studies.

Several other dialdehydes were reacted with **11b**, but difficulties were encountered in isolating these sapphyrin products. For instance, 3-hydroxypyridine-2,6-dicarbaldehyde (**31a**)[57] reacted with **11b** to give a nonaromatic product tentatively assigned as **32** (Scheme 9). This structure was supported by high-resolution mass spectrometry, but difficulties have been encountered in obtaining NMR data for this system. The related benzene dialdehyde **31b** failed to give any macrocyclic product, even though reactions with tripyrranes afford aromatic oxybenziporphyrins.[58,59] Therefore, there appears to be some limitations to the modifications that are possible for the sapphyrin system.

(57) Lash, T. D.; Chaney, S. T. *Chem. Eur. J.* **1996**, *2*, 944.
(58) Lash, T. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2533.
(59) (a) Lash, T. D.; Chaney, S. T.; Richter, D. T. *J. Org. Chem.* **1998**, *63*, 9076. (b) Richter, D. T.; Lash, T. D. *Tetrahedron* **2001**, *57*, 3659.

Conclusions

The "4 + 1" methodology is shown to be a flexible and high-yielding route to sapphyrins, heterosapphyrins, and carbasapphyrins. These types of aromatic macrocycles have attracted considerable interest, in part due to their anion binding characteristics. The "4 + 1" route, together with the mild ferric chloride oxidation conditions, allows the synthesis of unusual carbasapphyrin structures including the first example of an azulisapphyrin system. Although the route has some limitations, it provides the means to examine whether the trends previously observed for porphyrin systems also apply to the sapphyrins.

Experimental Section

Tetrapyrrole Dibenzyl Ester 11a. Diethyl 4,4′-diethyl-3,3′-dimethyl-2,2′-bipyrroledicarboxylate[50] (1.80 g) was heated to reflux in ethylene glycol (41 mL) with NaOH (410 mg) and 8 drops of hydrazine under nitrogen for 2 h. The solution was cooled to room temperature and diluted with water, followed by extraction with chloroform and drying over sodium sulfate. After the solvent was removed under reduced pressure, the resulting residue was dissolved in ethanol (70 mL). To this solution was added 2 equiv of acetoxymethylpyrrole **13**[60] (3.15 g) and acetic acid (7 mL) and the mixture was then stirred at reflux overnight under nitrogen. The solution was then cooled to 0 °C for 1 h, and the precipitate filtered and washed with cold ethanol. The resulting light green solid was recrystallized from chloroform/hexanes to give the desired product (2.58 g, 74%) as off-white crystals, mp 168−171 °C (lit. mp[47] 163−166 °C); ^{1}H NMR ($CDCl_3$) δ 0.87 (6H, t, J = 7.1 Hz), 1.12 (6H, t, J = 7.3 Hz), 2.03 (6H, s), 2.15 (6H, s), 2.4−2.5 (8H, m), 3.73 (4H, br s), 4.62 (4H, br s), 6.92 (4H, br m), 7.19−7.27 (6H, m), 9.95 (2H, br s, NH), 11.01 (2H, br s, NH).

Tetrapyrroledicarboxylic Acid 11b. Tetrapyrrole dibenzyl ester **11a** (450 mg) was dissolved in THF (150 mL) and shaken with 10% palladium−charcoal (127 mg) under an atmosphere of hydrogen at 40 psi overnight. The solution was filtered to remove the activated charcoal and the filtrate placed on a rotary evaporator to remove the solvent. The resulting dark blue residue was further dried under vacuum overnight to remove traces of solvent. The residual dark blue powder could then be scraped from the flask, yielding the diacid (350 mg; 94%). This was used without further purification.

3,8,12,13,17,22-Hexaethyl-2,7,18,23-tetramethylsapphyrin (14). In a 100-mL round-bottom flask, tetrapyrrole **11b** (27 mg) and TFA (1 mL) were stirred under nitrogen for 2 min, after which dichloromethane (99 mL) was added, followed immediately by pyrrole dialdehyde **15**[19b,61] (9 mg) and the mixture was stirred overnight under nitrogen. The mixture was then washed with water, and then vigorously shaken with a 0.1% w/v aqueous $FeCl_3$ solution (200 mL) for 5−10 min. The organic phase was separated, adding saturated sodium chloride solution if necessary to aid phase separation, and then washed with water, saturated sodium bicarbonate solution, and 10% hydrochloric acid. At each stage, back extractions with chloroform were performed to minimize losses of sapphyrin product. The solvent was removed in vacuo, and the resulting blue residue chromatographed on silica eluting with 9% methanol−chloroform. Upon evaporation of the solvent, the product was obtained as a bright teal-blue solid. Recrystallization from chloroform−hexanes afforded the decaalkylsapphyrin **14**·2HCl as deep blue crystals (15 mg, 50%), mp >300 °C; UV−vis (1% Et_3N−$CHCl_3$) λ_{max} (log ϵ) 457 (5.45), 610 (3.88), 668 (4.11), 711 nm (3.84); UV−vis ($CHCl_3$) λ_{max} (log ϵ) 433 (4.61), 457 (5.63), 578 (3.43), 624 (4.03), 675 (4.21), 689 nm (4.13); ^{1}H NMR ($CDCl_3$) δ −4.90 (2H, s), −4.57 (1H, s), −4.29 (2H, s), 2.17−2.23 (12H, two overlapping triplets), 2.30 (6H, t, J = 7.6 Hz), 4.11 (6H, s), 4.22 (6H, s), 4.55 (4H, q, J = 7.6 Hz), 4.67−4.78 (8H, two overlapping quartets), 11.63 (2H, s), 11.70 (2H, s); hr ms calcd for $C_{40}H_{50}N_5$ 600.4066, found 600.4064.

3,7,18,22-Tetraethyl-2,8,17,23-tetramethyl-27-oxasapphyrin (16). The oxasapphyrin was prepared by the previous procedure from **11b** (25 mg) and 2,5-furandicarbaldehyde (6 mg). The crude product was chromatographed on silica with 15% methanol−chloroform and the product eluted as a blue-green fraction. Recrystallization of the dihydrochloride salt from chloroform−hexanes afforded the oxasapphyrin **16**·2HCl as blue crystals (19 mg, 68%), mp >300 °C; UV−vis (1% TFA−$CHCl_3$) λ_{max} (log ϵ) 454 (5.56), 608 (3.95), 627 (4.13), 666 (4.05), 692 nm (4.01); ^{1}H NMR ($CDCl_3$) δ −0.25 (4H, s), 1.84 (6H, t, J = 7.6 Hz), 1.98 (6H, t, J = 7.6 Hz), 3.76 (6H, s), 3.82 (6H, s), 4.17 (4H, q, J = 7.6 Hz), 4.27 (4H, q, J = 7.6 Hz), 10.03 (2H, s), 10.51 (2H, s), 10.61 (2H, s); ^{1}H NMR (TFA−$CDCl_3$) δ −6.03 (2H, s), −5.92 (2H, s), 2.11 (6H, t, J = 7.8 Hz), 2.20 (6H, t, J = 7.8 Hz), 4.16 (6H, s), 4.27 (6H, s), 4.55 (4H, q, J = 7.6 Hz), 4.79 (4H, q, J = 7.6 Hz), 11.02 (2H, s), 11.82 (2H, s), 11.88 (2H, s); fab hr ms calcd for $C_{36}H_{41}N_4O$ 545.3280, found 545.3280.

3,7,18,22-Tetraethyl-2,8,17,23-tetramethyl-27-thiasapphyrin (17). The thiasapphyrin was prepared by the previous procedure from **11b** (26 mg) and 2,5-thiophenedicarbaldehyde (7 mg). The crude product was chromatographed on silica eluting with 15% methanol−chloroform and the product collected as the bright blue-green fraction. Recrystallization from chloroform−hexanes yielded the thiasapphyrin dihydrochloride salt as bluish-purple crystals (27 mg, 90%), mp >300 °C; UV−vis (1% TFA−$CHCl_3$) λ_{max} (log ϵ) 464 (5.51), 644 (3.95), 689 nm (4.10); ^{1}H NMR ($CDCl_3$) δ 1.77 (6H, t, J = 7.6 Hz), 1.96 (6H, t, J = 7.6 Hz), 3.63 (6H, s), 3.74 (6H, s), 4.10 (4H, q, J = 7.6 Hz), 4.19 (4H, q, J = 7.5 Hz), 10.36 (2H, s), 10.45 (2H, s), 11.12 (2H, s); ^{1}H NMR (TFA−$CDCl_3$) δ −6.80 (2H, s), −5.51 (2H, s), 1.97 (6H, t, J = 7.8 Hz), 2.19 (2H, t, J = 7.8 Hz), 4.09 (6H, s), 4.25 (6H, s), 4.56 (4H, q, J = 7.7 Hz), 4.75 (4H, q, J = 7.7 Hz), 11.36 (2H, s), 11.92 (2H, s), 12.48 (2H, s); fab hr ms calcd for $C_{36}H_{41}N_4S$ 561.3052, found 561.3053.

3,7,18,22-Tetraethyl-2,8,17,23-tetramethylphenanthro[9,10-*l*]sapphyrin (19). The phenanthrosapphyrin was prepared by the previous procedure from **11b** (31 mg), phenanthropyrrole dialdehyde **21**[44b] (24 mg), TFA (1 mL), and dichloromethane (99 mL). Following the previous extraction sequence, the resulting blue residue was chromatographed on silica eluting with 8% methanol−chloroform and the product collected as a bright teal-blue fraction. Recrystallization from chloroform−hexanes afforded the phenanthrosapphyrin **19**·2HCl as blue crystals (33 mg, 75%), mp >300 °C; UV−vis (1% Et_3N−$CHCl_3$) λ_{max} (log ϵ) 473 (5.45), 607 (3.91), 626 (3.89), 659 (4.27), 686 (4.20), 726 (3.77), 750 nm (3.86); UV−vis ($CHCl_3$) λ_{max} (log ϵ) 474 (5.75), 589 (3.68), 639 (4.14), 697 nm (4.57); ^{1}H NMR ($CDCl_3$) δ −2.82 (5H, br s), 1.87 (6H, t, J = 7.5 Hz), 1.97 (6H, t, J = 7.6 Hz), 3.74 (6H, s), 3.98 (6H, s), 4.20 (4H, q, J = 7.5 Hz), 4.42 (4H, q, J = 7.4 Hz), 8.01 (2H, t, J = 7.5 Hz), 8.24 (2H, t, J = 7.2 Hz), 9.26 (2H, d, J = 8.2 Hz), 10.10 (2H, d, J = 7.7 Hz), 10.35 (2H, s), 11.35 (2H, s); ^{1}H NMR (TFA−$CDCl_3$) δ −5.61 (2H, s), −5.50 (2H, s), −5.02 (1H, s), 2.07 (6H, t, J = 7.8 Hz), 2.15 (6H, t, J = 7.5 Hz), 4.11 (6H, s), 4.26 (6H, s), 4.53 (4H, q, J = 7.6 Hz), 4.69 (4H, q, J = 7.7 Hz), 8.26 (2H, t, J = 7.5 Hz), 8.47 (2H, t, J = 7.2 Hz), 9.44 (2H, d, J = 8.2 Hz), 10.38 (2H, d, J = 7.6 Hz), 11.62 (2H, s), 12.57 (2H, s); ^{13}C NMR ($CDCl_3$) δ 12.9, 16.0, 17.9, 18.0, 20.7, 20.8, 30.0, 95.3, 95.8, 124.7, 126.1, 127.1, 128.1, 128.5, 129.6, 132.2, 132.3, 133.3, 134.6, 135.2, 136.2, 140.3, 141.6; ^{13}C NMR (TFA−$CDCl_3$) δ 13.1, 15.6, 17.4, 17.6, 21.0, 21.2, 94.1, 98.5, 125.2, 128.2, 128.5,

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128.7, 129.4, 129.5, 130.8, 131.0, 132.6, 132.7, 133.5, 136.1, 136.9, 143.2, 144.9; hr ms calcd for $C_{48}H_{49}N_5$ 695.3988, found 695.3979.

3,7,18,22-Tetraethyl-2,8,17,23-tetramethylacenaphtho-[1,2-*l*]sapphyrin (20). The acenaphthosapphyrin was prepared by the previous procedure from **11b** (53 mg), acenaphthopyrrole dialdehyde **22**[44b] (24 mg), TFA (1 mL), and dichloromethane (99 mL). Following the previous extraction sequence, the blue residue was chromatographed on silica eluting with 8% methanol−chloroform and the product collected as a bright teal-blue fraction. Recrystallization from chloroform−hexanes afforded the acenaphthosapphyrin as blue crystals (55 mg, 74%), mp >300 °C; UV−vis (1% Et_3N−$CHCl_3$) λ_{max} (log ϵ) 500 (5.25), 677 (4.17), 709 (4.46), 744 nm (4.27); UV−vis ($CHCl_3$) λ_{max} (log ϵ) 486 (5.53), 595 (3.70), 647 (4.07), 710 nm (4.81); ^{1}H NMR ($CDCl_3$) δ −3.36 (5H, br s), 1.92−1.99 (12H, two overlapping triplets), 3.73 (6H, s), 3.87 (6H, s), 4.27−4.34 (8H, two overlapping quartets), 7.80 (2H, t), 7.89 (2H, d, J = 7.8 Hz), 8.75 (2H, d, J = 5.3 Hz), 10.39 (4H, s); ^{1}H NMR (TFA−$CDCl_3$) δ −6.20 (2H, s), −5.80 (2H, s), −5.55 (1H, s), 2.10 (6H, t, J = 7.7 Hz), 2.22 (6H, t, J = 7.7 Hz), 4.15 (6H, s), 4.40 (6H, s), 4.57 (4H, q, J = 7.7 Hz), 4.79 (4H, q, J = 7.7 Hz), 8.26 (2H, t, J = 7.4 Hz), 8.37 (2H, d, J = 7.7 Hz), 9.58 (2H, d, J = 7.1 Hz), 11.74 (2H, s), 12.25 (2H, s); ^{13}C NMR ($CDCl_3$) δ 11.7, 16.5, 17.7, 17.9, 18.0, 20.4, 20.7, 91.4, 95.7, 121.6, 122.0, 126.4, 127.0, 127.2, 127.9, 129.3, 133.3, 133.9, 134.5, 135.5, 136.2, 141.2, 141.8, 142.2; ^{13}C NMR (TFA−$CDCl_3$) δ 13.0, 15.7, 17.4, 17.7, 21.1, 21.3, 94.9, 98.0, 125.5, 129.3, 129.7, 130.1, 131.3 (2), 133.2, 133.5, 136.4, 136.5, 137.3, 143.3, 145.1, 145.3; hr ms calcd for $C_{46}H_{47}N_5$ 669.3831, found 669.3819.

3,7,18,22-Tetraethyl-2,8,17,23-tetramethyl-27-carba-benzo[*l*]sapphyrin (24). 24 was prepared by the foregoing procedure from tetrapyrrole **11b** (52 mg), diformylindene **23**[62] (16 mg), TFA (1 mL), and CH_2Cl_2 (99 mL). Following extraction, as above, and evaporation of the organic solvents, the resulting blue residue was chromatographed over Grade III alumina eluting with 5% methanol−chloroform and then on a silica column eluting with 10% methanol−chloroform. The product eluted as a bright teal-blue fraction. Recrystallization from chloroform−hexanes afforded the carbasapphyrin **24**·HCl as blue crystals (23 mg, 36%), mp >300 °C; UV−vis (1% DBU−$CHCl_3$; free base) λ_{max} (log ϵ) 377 (4.51), 470 (5.33), 596 (4.20), 645 (4.32), 710 (3.94), 793 nm (4.12); UV−vis ($CHCl_3$; monocation) λ_{max} (log ϵ) 374 (4.49), 476 (5.40), 496 (5.08), 613 (4.09), 669 (4.40), 708 (3.95), 788 nm (4.33); UV−vis (5% TFA−$CHCl_3$; dication) λ_{max} (log ϵ) 351 (4.60), 482 (5.55), 527 (4.22), 601 (3.98), 652 (4.18), 722 nm (4.43); ^{1}H NMR ($CDCl_3$; monocation) δ −7.88 (1H, br s), −5.08 (2H, br s), −4.43 (2H, br s), 2.06 (6H, t, J = 7.6 Hz), 2.12 (6H, t, J = 7.6 Hz), 4.08 (6H, s), 4.13 (6H, s), 4.51 (4H, br q), 4.63 (4H, br q), 7.94−7.97 (2H, m), 9.33−9.37 (2H, m), 11.13 (2H, s), 11.32 (2H, s); ^{1}H NMR (TFA−$CDCl_3$; dication) δ −3.75 (2H, br s), −0.56 (2H, br s), 0.67 (2H, br s), 1.76 (6H, t, J = 7.7 Hz), 1.89 (6H, t, J = 7.7 Hz), 3.43 (6H, s), 3.66 (6H, s), 3.93 (4H, q, J = 7.7 Hz), 4.12 (4H, q, J = 7.8 Hz), 8.70−8.74 (2H, m), 9.99−10.04 (2H, m), 10.37 (2H, s), 11.05 (2H, s); ^{13}C NMR (TFA−$CHCl_3$) δ 11.8,13.9,16.9, 17.2, 20.3, 20.7, 30.6, 104.6, 109.2, 123.0, 123.1, 127.0, 129.5, 130.9, 131.6, 132.8, 133.2, 144.6, 144.7, 145.2, 148.9; hr ms calcd for $C_{41}H_{45}N_4$ 593.3644, found 593.3645. Anal. Calcd for $C_{41}H_{44}N_4$·HCl·0.2$CHCl_3$: C, 75.76; H, 6.98; N, 8.58. Found: C, 75.79; H, 7.17; N, 8.58.

3,7,18,22-Tetraethyl-12-formyl-2,8,17,23-tetramethyl-27-carbasapphyrin (26). Following the procedure described above, the carbasapphyrin was prepared from tetrapyrrole dicarboxylic acid **11b** (25 mg) and 1,3,4-triformylcyclopentadiene[63] (7 mg) with TFA (1 mL) in CH_2Cl_2 (99 mL). After the solvent was removed under reduced pressure, the resulting dark residue was chromatographed on silica eluting with 5% methanol−chloroform and the product collected as a green fraction. Recrystallization from chloroform−hexanes afforded the formylcarbasapphyrin hydrochloride salt (4−5 mg, 7−12%) as blue crystals, mp >300 °C; UV−vis ($CHCl_3$; HCl−salt monocation) λ_{max} (log ϵ) 400 (4.53), 480 (5.18), 612 (4.06), 671 (4.26), 755 (3.85), 844 nm (4.09); UV−vis (2% TFA−$CHCl_3$; dication) λ_{max} (log ϵ) 343 (4.45), 469 (5.41), 490 (5.29), 632 (4.12), 685 (4.13), 745 nm (3.98); ^{1}H NMR ($CDCl_3$) δ −8.10 (1H, br s), −5.20 (2H, br s), −4.40 (1H, br s), −4.30 (1H, br s), 2.0−2.1 (12H, four overlapping triplets), 4.02 (3H, s), 4.07 (3H, s), 4.09 (3H, s), 4.10 (3H, s), 4.47−4.54 (4H, two overlapping quartets), 4.56−4.64 (4H, two overlapping quartets), 9.72 (1H, s), 10.93 (1H, s), 11.04 (1H, s), 11.09 (1H, s), 11.26 (1H, s), 12.46 (1H, s); ^{1}H NMR (TFA−$CDCl_3$) δ −7.06 (2H, s), −4.31 (1H, s), −4.21 (1H, s), −2.67 (2H, s), 1.89−1.96 (6H, two overlapping triplets), 2.06−2.11 (6H, two overlapping triplets), 3.85 (3H, s), 3.86 (3H, s), 4.04 (3H, s), 4.06 (3H, s), 4.30−4.36 (4H, two overlapping quartets), 4.50−4.57 (4H, two overlapping quartets), 11.39 (1H, s), 11.40 (1H, s), 11.65 (1H, s), 11.99 (1H, s), 12.10 (1H, s), 12.85 (1H, s); hr ms calcd for $C_{38}H_{42}N_4O$ 570.3359, found 570.3365.

Azulisapphyrin 28. 28 was prepared as above from tetrapyrrole dicarboxylic acid **11b** (50 mg), 1,3-azulenedicarbaldehyde[64] (17 mg), TFA (1 mL) ,and dichloromethane (99 mL). After the solvent was removed under reduced pressure the resulting dark brown residue was chromatographed on silica and the product eluted as an orange fraction with 15% methanol−chloroform. Recrystallization from chloroform−trace methanol−hexanes yielded the azulene derivative **28**·2HCl as a dark blue powder (19 mg, 35%), mp >300 °C; UV−vis ($CHCl_3$) λ_{max} (log ϵ) 420 (4.94), 455 (4.78), 481 (4.80), 511 (4.86), 742 nm (4.41); UV−vis (1% TFA−$CHCl_3$) λ_{max} (log ϵ) 416 (5.00), 449 (4.83), 478 (4.86), 505 (4.95), 736 nm (4.54); UV−vis (5% TFA−$CHCl_3$) λ_{max} (log ϵ) 413 (5.00), 449 (4.84), 475 (4.87), 504 (4.97), 734 nm (4.57); UV−vis (pyridine) λ_{max} (log ϵ) 421 (4.90), 452 (4.79), 482 (4.82), 508 (4.83), 673 (sh, 4.00), 740 nm (4.41); UV−vis (1% DBU−$CHCl_3$; free base) λ_{max} (log ϵ) 415 (4.85), 457 (4.79), 490 (sh, 4.63), 525 (4.62), 609 (sh, 3.92), 704 (sh, 3.92), 781 nm (4.18); UV−vis (1% pyrrolidine−$CHCl_3$) λ_{max} (log ϵ) 480 (5.09), 606 (4.14), 651 (4.21), 834 nm (4.08); ^{1}H NMR (d_5-pyridine−$CDCl_3$, 20 °C) δ −3.25 (1H, br s), −1.45 (1H, br s), −0.55 (1H, br s), 1.94−2.06 (12H, br m), 3.83 (6H, s), 3.89 (6H, s), 4.28 (4H, br q), 4.40 (4H, br q), 8.30 (1H, t, J = 8 Hz), 8.36−8.48 (2H, br m), 10.6 (2H, v br s), 10.66 (2H, br d), 11.1 (2H, v br s); ^{1}H NMR (TFA−$CDCl_3$, 50 °C) δ −4.8 (1H, br s), −3.4 (4H, br s), 1.95 (6H, t, J = 7.4 Hz), 2.01 (6H, t, J = 7.4 Hz), 3.88 (6H, br s), 3.98 (6H, br s), 4.18−4.28 (4H, m), 4.37 (4H, q), 8.51 (1H, br), 8.63 (2H, br), 10.5 (2H, v br s), 10.55 (2H, br d), 11.1 (2H, v br s); ^{13}C NMR (d_5-pyridine−$CDCl_3$) δ 15.2,29.8, 35.3, 36.9, 101.6, 104.0, 119.9, 122.1, 126.5, 127.5, 128.6, 131.9, 132.7, 136.3, 136.7, 139.1, 140.5, 145.8; fab hr ms calcd for $C_{42}H_{45}N_4$ 605.3644, found 605.3646.

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