Facile Syntheses of Modified Tripyrranes and Their Application to the Syntheses of Regioisomerically Pure Porphyrin Derivatives

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Simple conditions were discovered to afford tripyrranes by reaction of 2,5-bis(α-hydroxymethyl)furan or 2,5-bis(α-hydroxy-α-phenylmethyl)thiophene with excess pyrrole in the presence of acid catalyst. Stepwise synthesis of porphyrins with core-ligand modification and synthesis of *meso*-tetraarylporphyrins bearing two different substituents in *cis* orientation have developed as building blocks for the various porphyrin-based model systems. Consequently, 21-thia-23-oxa-10,15-diphenylporphyrin (**28**), 21-oxa-10,15-diphenylporphyrin (**29**) and 21-oxa-23-carba-12-aza-10,15-diphenylporphyrin (**30**) were synthesized by acid-catalyzed [3+1] condensation between tripyrranes and 2,5-bis(α-hydroxymethyl)pyrrole or 2,5-bis(α-hydroxy-α-phenylmethyl)thiophene. The synthetic pathway described here gave regioisomerically pure porphyrins and thus overcame the synthetic problems associated with separation and purification of regioisomeric mixture.

Introduction

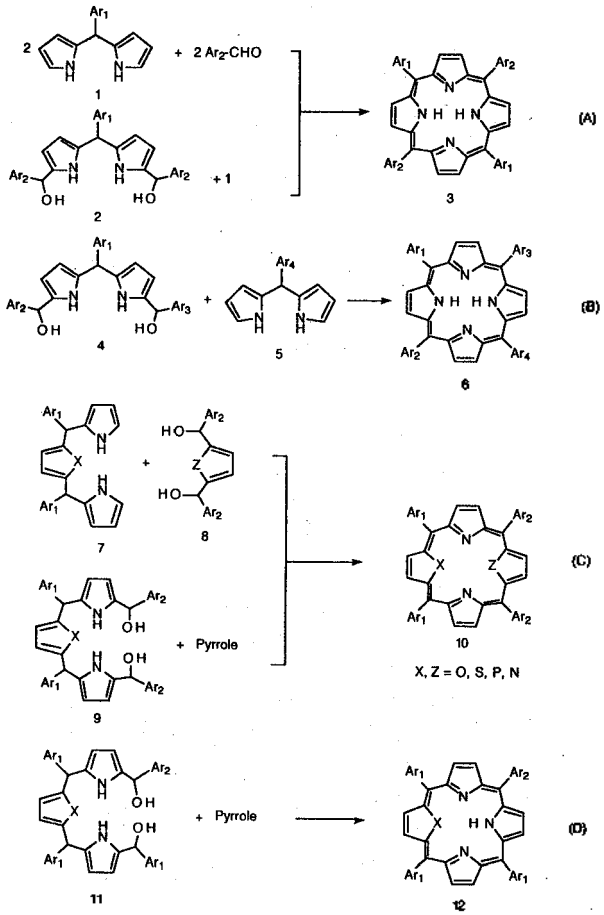
The porphyrins and related macrocyclic systems are most widely studied of all macrocyclic compounds.[1] The conveniences of *meso*-substituents as sites for functionalization, controlling the substituents geometry and the wealth of available *meso*-substituents make the *meso*-substituted porphyrins ideally suited for use in various model systems. Although porphyrin is easily obtainable from pyrroles and an aldehydes, generic methods are still limited to symmetric porphyrins because the mixed condensations usually resulted mixture of isomeric porphyrins and consequent difficulties in separation and identification. Methods currently available, have major limitation in placing different substituents selectively at four *meso*-positions or in placing different ligand-containing unit selectively at the core of the porphyrins. Thus, methods for the synthesis of *meso*-substituted porphyrins with predesignated orientation of core-ligands or *meso*-substituents still need to be developed, especially in creating sophisticated models of porphyrin-based enzymes and medicinal applications. The synthetic route in conjunction with placing four different *meso*-substituents with predesignated orientation has been developed recently.[2] But the existing methods can not be applied in the synthesis of *cis*-substituted porphyrins or those with core-ligand modification.

Interests in new porphynoid macrocycles have appeared increasingly in the past few years also.[3] In spite of increasing attention toward the chemistry of ligand-modified porphyrins, the synthetic methods for those porphyrins are not well established. A few available methods require several steps to obtain the precursors such as tripyrranes and are only applicable in the symmetric modification of two of the four nitrogen ligands.[4] Our current major concern is a selective synthesis of *cis*-substituted porphyrins and the porphynoids which have two or three different core ligands with predesignated orientation. We now report a selective synthesis of regioisomerically pure, ligand-modified porphyrins by stepwise approaches.

Results and Discussion

Numerous attempts have been made to design and synthesize bioorganic model system containing porphyrins.[1] The great potentials of porphyrins in various model system led us to pursue an efficient and selective synthesis of regioisomerically pure porphyrins bearing at least two different *meso*-substituents. Direct condensation of aldehyde and pyrrole is synthetically useful when four identical *meso*-substituents are desired. Porphyrins bearing two different *meso*-substituents could be prepared by binary mixed-aldehyde condensation, but six different isomeric porphyrins could be formed and the isomeric products distribution are statistical in nature and require tedious chromatographic works. We recently reported one-flask synthesis of 1,9-unsubstituted, *meso*-substituted dipyrromethanes,[7] the regioselective synthesis of trans-substituted porphyrins and porphyrins bearing four different *meso*-substituents.[5] The acid-catalyzed reaction of an aldehyde dissolved in excess pyrrole affords the *meso*-substituted dipyrromethane in high yield. The convenience and easy availability of the dipyrromethanes by single step has prompted us to investigate methods for functionalizing and synthesizing the tripyrranes such that they can be used in rational syntheses of A_2B_2, ABAC and A_3B type porphyrins.

Scheme 1 shows a synthetic analysis of porphyrins with various *meso*-substitution. Trans-substituted porphyrin **3** can be synthesized by the route (A); porphyrins bearing four different *meso*-substituents **6** can be synthesized by route (B); *cis*-substituted porphyrins **10** can be synthesized by the approach (C) and porphyrin **12** can be synthesized by the route (D). Regardless which route is taken, the success of the synthesis solely relies on the facile construction of 1,9-substituted dipyrromethanes **2, 4** and 1,14-substituted tripyrranes **9, 11**. Introducing acyl groups to the α,α′-position of pyrrole will be a crucial step in these approaches. Pyrrole undergoes electrophilic aromatic substitution easily, but α,α′-functionalization with acyl units cannot be achieved in a direct manner. Introduction of one acyl group at the 2-position proceeds smoothly, but attempts to introduce the second acyl group result in substitution at the 4-position instead of 5-position (vide infra).[6] An α-substituted pyrrole can be acylated at the α′-position as long as the α-substituents is not

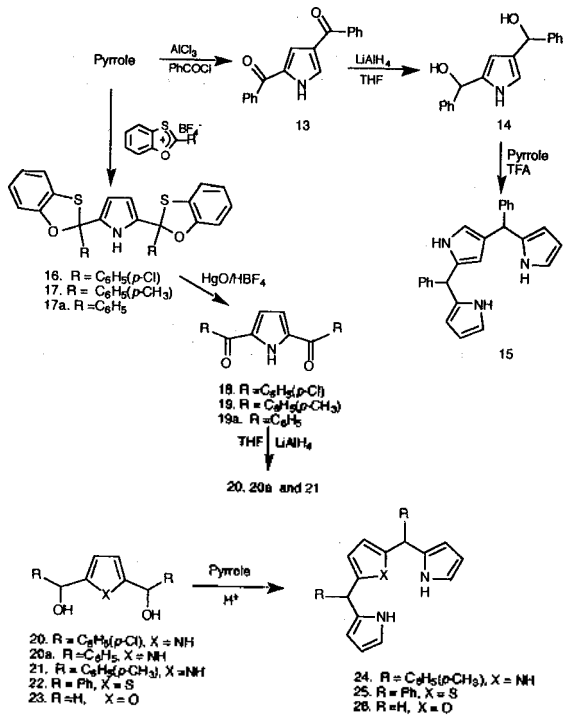


Scheme 1.

electron-withdrawing.

As shown in Scheme 2, pyrrole was treated with excess acid chloride in the presence of anhydrous aluminum chloride at room temperature to afford 2,4-bisacylated **13** in 65% yield. On the other hand, Barbero *et. al.*[8] have shown that pyrrole can be alkylated at 2- and 5- position by using benzoxathiolium salt as acyl synthon. This reaction provides a means of introducing acyl unit at the pyrrolic α- and α′-position. The treatment of pyrrole with 2.2 equivalent of 2-(*p*-chlorophenyl)-1,3-benzoxathiolium tetrafluoroborate at room temperature in dry acetonitrile gave the dialkylated product **16** in a quantitative yield. The acyl protecting group was removed by oxidative hydrolysis in the presence of HBF_4 /HgO.[8] The bisacyl compounds **13**, **18** and **19** were reduced with $LiAlH_4$ to the corresponding 2,5-bisdiol such as **14**, **20** and **21** respectively.

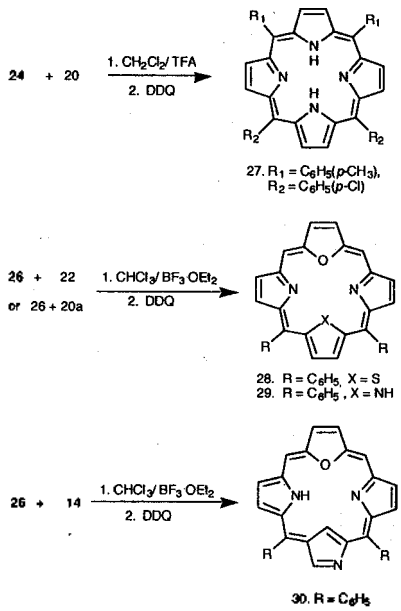
The reduction of **13** to corresponding bisdiol **14** seemed to be very sensitive to the reaction temperature; When the reaction was run at room temperature, extensive hydrogenolysis of diol was observed. The hydrogenolysis is not observed when the reaction is carried out at −10 ℃. Direct reaction of highly reactive 2-α-hydroxymethylpyrrole with pyrrole in the presence of acid catalyst resulted complex mixture of products. Due to the thermodynamic nature of the reaction, it would be possible to stop the reaction at the desired step. Indeed, this speculation turned out to be true and gave clean reaction by using one of the reactants as a solvent.



Scheme 2.

Attempted condensation of **14** and **21** with pyrrole as a solvent in the presence of boron trifluoride afforded the corresponding tripyrranes **15** and **24**. TLC analysis showed the formation of a small amount of polymeric material in origin but no other products was observed. Moreover, 16-thiatripyrrane (**25**) and 16-oxatripyrrane (**26**) were also synthesized by similar condensation. These compounds will be noble precursors to access the porphyrins with selective ligand-modification (vide infra) of porphyrin and porphynoid macrocycles with core-expansion. Scheme 3 shows the condensation between tripyrranes and 2,4- or 2,5-bisdiols, which was successful to afford porphyrins.

Attempted synthesis of porphyrins by condensation of the tripyrrane **24** with a diol **20** in the presence of trifluoroacetic acid gave *cis*-substituted porphyrin **27** in 2.5% yield. The porphyrin was readily separated by column chromatography and characterized by proton NMR spectroscopy and mass spectroscopy. Although the yield was low, the synthetic pathway afforded a regioisomerically pure *cis*-substituted porphyrin. The condensations of tripyrranes and 2,5-bisdiols were not always successful. Only a few combinations of condensation were successful and afforded porphyrins. For example, condensation of **14** with **26** in the presence of catalytic amount of $BF_3 \cdot OEt_2$ gave 12-aza-21-oxa-23-carba-10,15-diphenylporphyrin **30** in 5.4% yield. Condensation of **26** with **22** under similar condition also afforded porphyrin **28** in 8.8%. The condensation of **26** and **20a** also resulted porphyrin **29** in 17%. The yields of porphyrins was not high and did not optimized but single isomeric porpyrins were formed in each reactions. The proton NMR spectrum of **28** doesn't show any inner N-H proton indicating 22-π aromatic character of the macrocycle. The protons on the furan appeared as singlet at 9.78 ppm and protons on the thiophene at 9.86 ppm. The β-pyrrolic protons appear as a double-doublet at 9.09 and



Scheme 3.

8.80 ppm. Chemical shift of the *meso*-protons in **28** appear at 10.16 ppm which is typical for the *meso*-unsubstituted porphyrin. The proton nmr spectrum of **30** was rather complex due to unsymmetric nature of the compound. The inner C-H proton was shown at −3.1 ppm and outer β-H of the flipped pyrrole show doublet at 8.68 ppm. The inner C-H proton was not exchanged upon exposure to D_2O over 36 h period. There was no inner N-H proton observed because of aromaticity. UV-Vis spectra of the porphyrin **28** showed λ_{max} at 416 (Soret), 498, 628, and 691 nm. Porphyrin **30** showed λ_{max} at 424, 537, 574, 614, and 709 nm. This data indicates that the structure of **30** maintain planarity because there are no inner N-H hydrogen causing repulsion each other. The UV-Vis spectra of **30** is comparable with N-confused porphyrin.[9] The spectral shift and broadening was also observed when the compound was protonated. Adding excess trifluoroacetic acid in $CHCl_3$ shifted the Soret (407 nm) to 420 nm. The inner C-H signal shifted from −3.2 ppm to −1.27 ppm. The magnitude of the red shift in UV indicate that the distortion of from planarity by protonation is not severe in **30**.

The methodology described above represents the fine example of a porphyrin synthesis with ligand modification in which asymmetric array of core ligands with definitely known regiochemistry. Attempted Cu(II) and Zn(II) insertion to **28** was not successful. The difficulty in metallation is due to the breakdown of aromaticity when the metal was inserted. The scope and limitation of the condensation and metallation is currently under investigation.

Conclusion

A few core-modified porphyrins were synthesized by the reaction between tripyrranes and 2,4-bis(hydroxymethyl)pyrrole or 2,5-bis(hydroxymethyl)thiophene derivatives. The porphyrin was obtained by applying the conditions of high dilution. The reaction was catalyzed by BF_3. OEt_2 or trifluoroacetic acid. The yields of porphyrins were not high, but the reaction gave specifically single isomeric porphyrins with desired regiochemistry. The mild reaction condition will allow to prepare any porphyrins with specific core-modification. In order to establish synthetic generality for the preparation of porphyrin building blocks with core-ligand modification, extensive adjustment is under investigation.

Experimental

^1H NMR spectra (200 MHz, Varian Gemini 200), IR spectra (Perkin Elmer 1430), and absorption spectra (Kontron 941 and Hitachi U-3200) were collected routinely. Mass spectra was obtained by electron impact and matrix assisted laser desorption mass spectra (MALDI) were obtained at Argonne National laboratory in NM. High resolution mass spectra were obtained from KRICT. Column chromatography was performed on silica (Merck, 230-400 mesh) or alumina (Fisher A540, 80-200 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. CH_2Cl_2 (Fisher, reagent grade) was distilled from K_2CO_3. $CHCl_3$ (Fisher certified A.C.S.) containing 0.75% ethanol was distilled from K_2CO_3. Trifluoroacetic acid and $BF_3 \cdot OEt_2$ were used as obtained from Aldrich. All other reagents were obtained from Aldrich unless noted otherwise. The 2,5-bis[(α-hydroxy-α-phenyl)methyl]thiophene (**22**) was synthesized by reported method[10] and 2,5-furandimethanol were purchased from Aldrich.

2,4-Dibenzoylpyrrole (13). A solution of dry benzoyl chloride (1.57 g, 11.2 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of pyrrole (3.4 mg, 5 mmol) and anhydrous $AlCl_3$ (1.60 g, 12 mmol) in dry methylene chloride (20 mL) at room temperature over period of 20 min. Then the reaction mixture was heated until reflux, and reflux was maintained for 72 hour. When TLC showed the reaction had stopped (chloroform/ethylacetate=9/1). The reaction mixture was quenched with ice and saturated aqueous sodiumbicarbonate. The organic phase was separated and combined with the methylene chloride. The mixture was extracted (3×50 mL) and the combined organic phase was washed with water (2×25 mL), dried on anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was separated by column chromatography on a silica (methylene chloride). Yield 2.0 g (65%); mp 141.1-141.7 ℃; ^1H NMR ($CDCl_3$) δ 10.45 (m, 1H, N-H), 7.98-7.83 and 7.63-7.45 (m, 10H, Ar-H), 7.70 (dd, 1H, pyrrole-5-H), 7.43 (dd, 1H, pyrrole-3-H).

2,4-Bis(α-hydroxy-α-phenyl)methylpyrrole (14). To a suspension of $LiAlH_4$ (0.76 g, 40.0 mmol) in dry THF (60 mL) was added 2,4-dibenzoylpyrrole(0.55 g, 2.0 mmol) in dry THF (20 mL) cooled in ice bath. The dark yellow solution was stirred under nitrogen for 2 hr keeping temperature 0 ℃. The progress of reaction was followed by TLC (chloroform/ethylacetate=1/1). A water/methylene chloride (20 mL/60 mL) mixture was carefully added at 0 ℃, and the layers were separated. The organic layer was washed with water (3×20 mL), dried (anhydrous Na_2SO_4). Evaporation of solvent afforded dark yellow solid which was separated by chromatography on silica (chloroform/ethyl acetate=7/3). Yield 0.5 g (90%).; ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H, N-H), 7.25 (m, 10H, Ar-H), 6.27 (d, 1H), 5.78 (d, 1H), 5.57 (d, 1H, *meso*-H), 5.58 (s, 1H, *meso*-H), 3.65 (bs, 1H, OH), 2.92 (bs, 1H, OH).

7-Aza-5,10-diphenyl-15,17-dihydro-18-carba-tripyrrin (15). To the mixture of 2,4-Bis(α-hydroxy-α-phenyl methyl) pyrrole (0.42 g, 1.50 mmol) and pyrrole (2.0 g, 30.0 mmol) was added boron trifluoride-etherate ($BF_3 \cdot OEt_2$, 21.3 mg, 0.15 mmol). The reaction mixture was stirred for 25 min then the mixture was diluted with methylene chloride (30 mL) then washed with 0.1 N aqueous NaOH (10 mL), water (10 mL) and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure and unreacted pyrrole was removed by vacuum distillation at room temperature. The remaining solid was purified by flash column chromatography on silica (methylene chloride). Yield 0.18 g (34%); mp 68.7-69.5 ℃; ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H, N-H), 7.72 (m, 1H, N-H), 7.33-7.15 (m, 10H, Ar-H), 6.66 (m, 2H), 6.33 (s, 1H), 6.14 (m, 2H), 5.87 (m, 2H), 5.42 (s, 1H, *meso*-H), 5.30 (s, 1H, *meso*-H), MALDI Calcd. for $C_{26}H_{23}N_3$ 377.2, Found 376.2 (M^+-H).

2,5-Bis-[α-(*p*-chlorophenyl)-α-(1,3-benzoxathiolyl)] pyrrole (16). 2-(*p*-chlorophenyl)-1,3-benzoxathiolium tetrafluoroborate (2.34 g, 7 mmol), pyrrole (0.19 g, 2.8 mmol), pyridine (0.55 g, 7 mmol) was reacted in acetonitrile (4 mL) under identical condition as described above. Yield 1.51 g (98 %); ^{1}H NMR ($CDCl_3$), δ 9.16 (bs, 1H, N-H), 7.58 (d, 4H, Ar-H, J=8.0 Hz), 7.31 (d, 4H, Ar-H, J=8.0 Hz), 6.69-7.09 (m, 8H, Ar(oxathiolyl)-H), 5.74 and 5.73 (2s, 2H, pyrrole-H).

2,5-Bis-[α-(*p*-toluyl)-α-(1,3-benzoxathiolyl)]pyrrole (17). The 2-tolyl-1,3-benzoxathiolium tetrafluoroborate (0.94 g, 3.0 mmol) was added to a solution of pyrrole (0.08 g, 1.20 mmol), dry pyridine (0.24 g, 3.0 mmol) and dry acetonitrile (2 mL) in one portion with stirring. The reaction was exothermic and the salt dissolved at once. The mixture was stirred for 30 min at room temperature. Then the mixture was combined with water (10 mL) and extrated with chloroform (3×30 mL). The organic layer was washed with aqueous sodium hydroxide solution (5%, 10 mL) and with water. The layer was dried (anhyd. Na_2SO_4) and the solution was concentrated to dryness and the crude product was washed with hot methanol (2×2 mL) to afford pure product. Yield 1.54 g (99%); ^{1}H NMR ($CDCl_3$) δ 8.67 (bs, 1H, N-H), 7.54 (d, 4H, Ar(tolyl)-Hs, J=8.11 Hz), 7.15 (d, 4H, Ar(tolyl)-Hs, J=8.11 Hz), 6.84-7.10 (m, 8H, Ar (oxathiolyl)-Hs), 6.11 (d, 1H, pyrrole-H), 5.99 (d, 2H, pyrrole-H), 2.34 (s, 6H, methyl).

2,5-Bis(*p*-chlorobenzoyl)pyrrole (18). 2,5-Bis-[α-(*p*-chlorophenyl)-α-(1,3-benzoxathiolyl)]pyrrole (1.40 g, 2.5 mmol) was added to the solution constituting mercury(II) oxide (red, 0.65 g, 3.0 mmol) dissolved in THF (3.0 mL) and 48% aqueous tetrafluoroboric acid (0.44 mL). The reaction was exothermic, and mercury(II) oxide dissolved at once. The mixture was heated at 50 ℃ for 3 hr. until the disappearance of the starting materiel on TLC (petroleum ether/ethyl ether=9.5/0.5). The reaction mixture were diluted with 200 mL of methylene chloride. The reaction mixture then was washed successively with 10% potassium iodide solution (2× 10 mL), 5% sodium hydroxide solution (10 mL), and dried (Na_2SO_4). The solution was concentrated by rotary evaporation. Pure 2,5-bis(p-chlorobenzoyl)pyrrole was obtained in quantitative yield. Yield 0.82 g (95%); mp 244.7-245.4 ℃. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 4H, Ar-H, J=6.8 Hz), 7.52 (d, 4H, Ar-H, J=6.8 Hz), 6.88 (s, 2H, pyrrole-H), 3.66 (bs, 1H, NH).

2,5-Bis(4-methylbenzoyl)pyrrole (19). 2,5-Bis-[α-(tolyl)-α-(1,3-benzoxathiolyl)]pyrrole (0.31 g, 0.6 mmol) was added to the solution containing mercury(II) oxide (0.26 g, 1.2 mmol), THF (3.0 mL) and 48% aqueous tetrafluoroboric acid (0.44 mL). The reaction was exothermic and mercury(II) oxide dissolved at once. The mixture was heated at 50 ℃ with stirring for 3 hr. The progress of reaction was monitored by following disappearance of the starting material in TLC (petroleum ether/diethyl ether=9.5/0.5). The reaction mixture was diluted with methylene chloride (100 mL) when no more starting material was remaining. The reaction mixture was washed successively with 10% potassium iodide solution (2×10 mL), 5% sodium hydroxide solution (10 mL), and dried (anhydrous Na_2SO_4). The solution was concentrated under reduced pressure to give pure product. Yield 0.17 g (96%); mp 193.9-194.2 ℃. ^{1}H NMR ($CDCl_3$) δ 10.25 (br, 1H, N-H), 7.86 (d, 4H, Ar-H, J=8.0 Hz), 7.32 (d, 4H, Ar-H, 8.0 Hz), 6.89 (s, 2H, pyrrole-H), 2.46 (s, 6H, methyl).

2,5-Bis[α-hydroxy-α-(*p*-chlorophenyl)]methylpyrrole (20). To a suspension of $LiAlH_4$ (0.19 g, 5.0 mmol) in dry THF (20 mL) was added 2,5-Bis(*p*-chlorobenzoyl)pyrrole (0.17 g, 0.48 mmol) in dry THF (10 mL). The dark yellow solution was stirred at room temperature under nitrogen for 2 hour. A water and methylene chloride (10 mL/50 mL) mixture was carefully added, and then the layers were separated. The organic layer was washed three times with water (3×10 mL) dried over anhydrous Na_2SO_4 and evaporated to give a dark yellow oil. This crude material was used for the condensation without further purification. Yield 0.17 g (97%).

2,5-Bis[α-hydroxy-α-(*p*-tolyl)]methylpyrrole (21). To a suspension of $LiAlH_4$ (0.33 mg, 8.6 mmol) in dry THF (20 mL) was added 2,5-bis(*p*-methylbenzoyl)pyrrole (0.26 mg, 0.846 mmol) in dry THF (20 mL). The dark yellow solution was stirred at room temperature under nitrogen for 2 hour. Then water/methylene chloride (10 mL/50 mL) mixture was carefully added. The organic layer was washed three times with water (3×10 mL) dried over anhydrous Na_2SO_4 and evaporation of solvent resulted a dark yellow oil. This crude diol was verified by IR and went to the next step without further purification. Yield 0.25 g (98%); mp 101.7-102-7 ℃. ^{1}H NMR ($CDCl_3$) δ 8.60 (br, 1H, N-H), 7.26 (d, 4H, Ar-H, J=7.6 Hz), 7.17 (d, 4H, Ar-H, J=7.6 Hz), 7.08 (s, 2H, pyrrole-H), 5.74-5.82 (m, 2H, *meso*-H), 3.86 (s, 2H, OH), 2.34 (s, 6H, methyl).

5,10-Ditolyl-15,17-dihydrotripyrrin (24). To a solution of 2,5-Bis(α-hydroxy-α-tolyl)pyrrole (0.17 g, 0.55 mmol) and pyrrole (1.48 g, 22 mmol) was added trifluoroacetic acid (4.23 mL, 0.055 mmol). The mixture was stirred for 15 min, then diluted with methylene chloride (50 mL). The mixture was washed with 0.1 N aqueous sodium hydroxide (10 mL), water (10 mL) and dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure and unreacted pyrrole was removed by vacuum distillation. The resulting solid was purified by flash chromatography (silica, cyclohexane/ethyl acetate/triethylamine=80/15/1). Yield 0.1 g (45%); ^{1}H NMR ($CDCl_3$) δ 7.86 (br, 2H, N-H), 7.69 (br, 1H, N-H), 7.02-7.12 (m, 8H, Ar-H), 6.64 (m, 2H), 6.11 (m, 2H), 5.95 (br, 2H), 5.74 (2s, 2H, pyrrole-H), 5.31 (s, 2H, *meso*-H), 2.34 (s, 6H, methyl).

5,10-Diphenyl-16-thia-15,17-dihydrotripyrrin (25). To a solution of 2,4-Bis[(α-hydroxy-α-phenyl)methyl]thiophene (0.1 g, 0.34 mmol) and pyrrole (0.9 g, 13.5 mmol) was added $BF_3 \cdot OEt_2$ (47.3 mg, 0.34 mmol). The reaction mixture was stirred for 30 min at room temperature. Then the mixture was diluted with methylene chloride (130 mL) and washed with 0.1 N aqueous sodium hydroxide (10 mL), water (2×10 mL) and dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure and unreacted pyrrole was removed by vacuum distillation at room temperature. Yield 0.13 g (98%); mp 40.9-42 ℃; ^1H NMR ($CDCl_3$) δ 7.89 (bs, 2H, N-H), 7.36-7.25 (m, 10H, Ar-H), 6.83 (m, 2H, pyrrole-H), 6.69 (s, 2H, thiophene-H), 6.15 (m, 2H, pyrrole-H), 5.93 (m, 2H, pyrrole-H), 5.57 (s, 2H, *meso*-H).

16-Oxa-5,10,15,17-tetrahydrotripyrrin (26). To a mixture of furandimethanol (0.41 g, 3.2 mmol) and pyrrole (5 mL) was added $BF_3 \cdot OEt_2$ (2.5 M solution in methylene chloride) under nitrogen atmosphere. The mixture was stirred for 20 min at 25 ℃ then diluted with methylene chloride (100 mL). The dark black mixture was washed with aqueous sodium hydroxide (0.1 N), water and dried (anhydrous Na_2SO_4). Evaporation of the solvent to dryness and column chromatographic separation on silica afforded pure product. Yield 0.3 g (42%); mp 81.3-82.2 ℃; ^1H NMR ($CDCl_3$) δ 7.91 (bs, 2H, N-H), 6.63 (m, 2H, pyrrole-H), 6.11 (m, 2H, pyrrole-H), 5.98 (s, 2H, pyrrole-H), 5.92 (s, 2H, furan-H), 3.89 (s, 4H, *meso*-H).

5,10-Di(4-chlorophenyl)-15,20-di(*p*-tolyl)porphyrin (27). A solution of trypyrrane (90.6 mg, 0.22 mmol) and 2,5-bis[α-(*p*-chlorophenyl)-α-hydroxyl] pyrrole (76.6 mg, 0.22 mmol) in methylene chloride (22 mL) was stirred then trifluoroacetic acid (5.1 mL, 0.066 mmol) was injected. The reaction mixture was stirred for 20 min at room temperature then DDQ (199.8 mg, 0.88 mmol) was added . The mixture was stirred at room temperature for additional 2 hour, then the solvent was removed. Column chromatography on silica (methylene chloride) gave crude porphyrin. Repeated column chromatography (CH_2Cl_2/Hexanes=1/1) gave pure porphyrin product. Yield 3.2 mg (2.5%); ^1H NMR ($CDCl_3$) δ 8.64 (m, 8H, Ar-H), 8.12 (m, 8H, Ar-H), 7.74 (m, 4H), 7.56 (m, 4H), 2.71 (s, 12H, methyl), −2.82 (s, 2H, N-H). UV-vis (CH_2Cl_2) λ_{max} (ε×10³); 418 (497), 515 (19), 550 (9), 590 (6), 646 (4), MALDI Calcd for $C_{46}H_{32}N_4O_2$ 711.69, Found 711.9.

21-Thia-23-oxa-10,15-diphenylporphyrin (28). A solution of 16-oxatripyrrane (0.136 g, 0.6 mmol) and 2,5-bis(α-hydroxy-α-phenyl)thiophene (0.178 g, 0.6 mmol) in chloroform (60 mL) was stirred then $BF_3 \cdot OEt_2$ (150 μL, 1.2 mmol) was injected. The reaction mixture was stirred for 30 min at room temperature then the reaction was quenched by adding triethylamine (170 μL, 1.2 mmol). After adding DDQ (0.54 g, 2.4 mmol), the mixture was stirred for 2 hr at room temperature. Then the solvent removed. Column chromatography on silica (chloroform/ethylacetate=1/1 then change eluent to methylene chloride/ethylacetate=9/1) gave the crude porphyrin. Repeated column chromatography (chloroform/ethylacetate=9/1) gave the pure porphyrin. Yield 25.4 mg (8.8%). ^1H NMR ($CDCl_3$) δ 10.16 (s, 2H, *meso*-H), 9.86 (s, 2H, thiophene-H), 9.78 (s, 2H, furan-H), 9.09 (d, 2H, pyrrole-H), 8.80 (d, 2H, pyrrole-H), 8.27-8.23 (m, 4H, Ar-H), 7.86-7.80 (m, 6H, Ar-H), UV-vis (CH_2Cl_2) λ_{max} (ε×10³), 416 (121), 498 (17), 628 (1), 691 (3), MALDI Calcd for $C_{32}H_{20}N_2SO$ 480.5, Found 480.5.

21-Oxa-10,15-diphenylporphyrin (29). A solution of 16-oxatripyrrane (0.077 g, 0.34 mmol) and 2,5-bis(α-hydroxy-α-phenyl)pyrrole (0.96 g, 0.6 mmol) in $CHCl_3$ (34 mL) was stirred at room temperature, then trifluoroacetic acid (84 μL, 0.68 mmol) was added. The mixture was stirred for 30 min then triethylamine (95 μL, 0.68 mmol) followed by addition of DDQ (0.232 g, 1.02 mmol). Resulting black solution was stirred for 2 hr. Solvent was evaporated and the remaining solid was separated by column chromatography on silica (chloroform/ethanol=19/1). Yield 26 mg (17%); ^1H NMR ($CDCl_3$) δ 10.22 (s, 2H, *meso*-H), 9.88 (s, 2H, furan-H), 9.16 (d, 2H, pyrrole-H), 8.97 (s, 2H, pyrrole-H), 8.85 (d, 2H, pyrrole-H), 8.23-8.19 (m, 4H, Ar-H), 7.81-7.74 (m, 6H, Ar-H), −2.01 (bs, 1H, inner N-H); UV-vis (CH_2Cl_2) λ_{max} (ε×10³), HRMS Calcd for $C_{32}H_{21}N_3O$ 463.1685, Found 463.1706.

12-aza-21-Oxa-23-carba-10,15-diphenylporphyrin (30). A solution of 16-oxatripyrrane (0.23 g, 1.1 mmol) and 2,5-bis(α-hydroxy-α-phenyl)pyrrole(0.31 g, 1.1 mmol) in chloroform (106 mL) was stirred then $BF_3 \cdot OEt_2$ (260 μL, 2.1 mmol) was injected. The reaction mixture was stirred for 30 min at room temperature then triethylamine (290 μL, 2.1 mmol) was added. After adding DDQ (0.72 g, 3.1 mmol), the mixture was stirred at room temperature for additional 2 hour. and then the solvent was removed. Column chromatography (silica, ethylacetate) gave the crude porphyrin. Repeated column chromatography (chloroform/ethanol=19/1) gave the pure porphyrin. Yield 27 mg (5.4%). ^1H NMR ($CDCl_3$) δ 9.44 (d, 2H), 8.76 (bs, 1H, N-H), 8.72 (dd, 2H), 8.27-8.19 (m, 4H), 7.87-7.77 (m, 6H, Ar-H), −3.10 (bs, 1H, inner C-H). UV-vis (CH_2Cl_2) λ_{max} (ε×10³); 424 (25.4), 537 (2.6), 574 (1.8), 614 (0.2), 709 (0.8), MALDI Calcd for $C_{32}H_{21}N_3O$ 463.54, Found 464.2.

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Stoichiometric Solvation Effects. Product-Rate Correlation for Solvolyses of Phenyl Chloroformate in Alcohol-Water Mixtures

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Solvolyses of phenyl chloroformate in water, D_2O, CH_3OD, 50% D_2O-CH_3OD, and in aqueous binary mixtures of acetone, ethanol and methanol are investigated at 25.0 ℃. Product selectivities are reported at 25 ℃ for a wide range of ethanol-water and methanol-water solvent compositions. The Grunwald-Winstein plots of first-order rate constants for phenyl chloroformate with Y_{Cl} (based on 2-adamantyl chloride) show marked dispersions into three separate lines for the three aqueous mixtures with a small m value ($m<0.2$) and a rate maximum for aqueous alcohol solvents. Third-order rate constants, k_{www}, k_{aww}, k_{wwa} and k_{aa} were calculated from the observed k_{www} and k_{aa} values together with k_{aw} and k_{wa} calculated from the intercept and slope of the plot of $1/S$ *vs.* [alcohol]/[water]. The calculated rate constants, k_{calc} and mol % of ester agree satisfactorily with those of the observed rate constants, k_{obs} and mol % of ester, supporting the stoichiometric solvation effect analysis. The kinetic solvent isotope effects determined in water and methanol are consistent with the proposed mechanism of the general base catalyzed and/or carbonyl addition for phenyl chloroformate solvolyses based on mass law and stoichiometric solvation effect studies.

Introduction

Many acyl transfer reactions in protic solvents involving esters,[1] amide derivatives[2] and acid chlorides[3] are third order overall, and it is thought that one molecule of solvent acts as a nucleophile and a second molecule acts as a general base.[4] In the third order process, methanol probably acts as both nucleophile and general base, because large rate enhancements are observed when chloride ion (a base in acetonitrile) is added while only minor rate enhancements are observed when phenol is added.[3]

The other process may be pseudo second order, and may involve methanol as nucleophile with acetonitrile, present in large excess, acting as general base.[3b] Similar results have been obtained for aminolyses involving primary and secondary amines.[5] According to change of reaction condition as variation of substituent or solvent composition, nucleophilic reactions of acyl halides were reported as an addition-elimination, S_N1 or S_N2 reaction mechanism.[6,7] Based on product-rate study, benzoyl chloride (I) solvolyzes by an S_N2 mechanism in high polarity solvents, whereas it favors general-base catalyzed or possible addition-elimination pathway (S_AN) in less polar media.[8,9]

Nucleophilic substitution reactions of furoyl chloride (II) and thenoyl chloride (III) were reported to proceed *via* different reaction mechanisms, the former by an addition-elimination and the latter by an S_N2 mechanism based on a product-rate study.[10] Though the only difference between two substrates is sulfur atom in thenoyl chloride which is replaced by an oxygen atom in furoyl, two substrates show a remarkable change in reaction mechanism.[5]

Therefore, it will be very interesting to test product-rate behaviors for solvolyses of IV, which has an oxygen atom adjacent to carbonyl group, in alcohol-water mixtures.

Competing nucleophilic substitution reactions in alcohol-water mixtures are interpreted in terms of product selectivities, S, defined from molar ratios of products and of solvents [equation (1)]. If these reactions simply involved competitive