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Kinetics of Site Selective Deuterium Exchange in the Substituted Pyrroles and Synthesis of Partially Deuterated Porphyrins Therefrom

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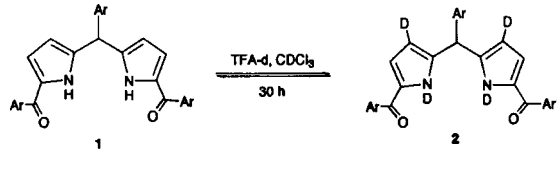
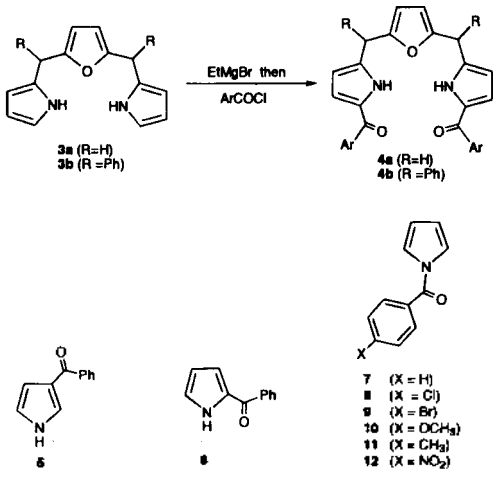
Isotopically labeled porphyrins have been important in various biological applications including interpretation of isotropic nmr shifts in heme proteins. Especially deuterated porphyrins are essential in obtaining ^2H NMR spectra of paramagnetic metal complexes,[3] ESR study of paramagnetic metalloporphyrin complexes,[3] peak assignment of various hemoproteins[3] and assignment of vibrational modes in the molecule.[4] The interpretation of resonance Raman spectra of hemes and hemoproteins also aided by the use of isotopically labeled porphyrin derivatives. Simple *meso*-tetraarylporphyrin with β-pyrrolic deuterium enrichment is readily available by simple condensation of arylaldehydes with pyrrole-d_5 or by treating *meso*-tetraphenylporphyrin (TPP) with TFA-d.[5] However these methods can not be applied in the synthesis of partial labeling of isotope at specific β-pyrrolic positions. The major obstacle in creating sophisticated models of porphyrins is the limited availability of the building subunits in most occasions. Existing synthetic routes are mainly the condensation of an aldehydes with deuterated pyrroles or pyrromethanes with aldehydes.[6,7] Thus, only symmetrically deuterated porphyrins would be available accordingly. The synthesis of porphyrins with partial labeling of deuterium at β-pyrrolic position is dependent on availability of the building subunits which can afford desired porphyrins after self-condensation. Difficulties in the synthesis of asymmetric porphyrins are also associated with construction of the dipyrromethane components bearing deuterium at specified positions. With our current studies, we report the kinetics of regioselective deuterium exchange in substituted pyrroles and the results obtained during the attempted synthesis of partially deuterated porphyrins. We also report the substituents effect on the rate of site selective deuterium exchange in the substituted pyrroles. The methods reported here will have great potentials in the synthesis of various biochemical systems and may provide an efficient synthetic method of partially deuterated porphyrins.[7]

The site selective protium-deuterium exchange in the 1,9-bisacyldipyrromethane (**1**) has been observed previously.[8] The involvement of the extended iminol-type intermediate has been proposed in the selective deuterium exchange in compound (**1**). Current studies indicate that in fact these types of exchange are very common in the acyl-substituted pyrroles. Pyrrole generally undergoes electrophilic substitution easily. The positional nucleophilicity of pyrrole is greatly influenced by substituents. For example, an α-substituted pyrrole can be electrophilically acylated at the α'-position as far as the α-substituent is not electron-withdrawing. But if electron withdrawing substituents is placed at α-position, electrophilic acylation takes place at 4-position.[9] In order to access the exchange rate and effect of substituents to the rates, we synthesized various N-substituted pyrroles and 2 or 3-substituted pyrroles.

As shown in Scheme 2, selective introduction of acyl group at 1,14-position of 16-oxatripyrrane (**3**) was possible by utilizing the reaction of pyrrole-Grignard and acid chlorides.[10] 16-Oxatripyrrane (**3**) was treated with 2.2 equivalents of ethyl magnesium bromide in THF at room temperature and resulting tripyrromethane-Grignard reagent was



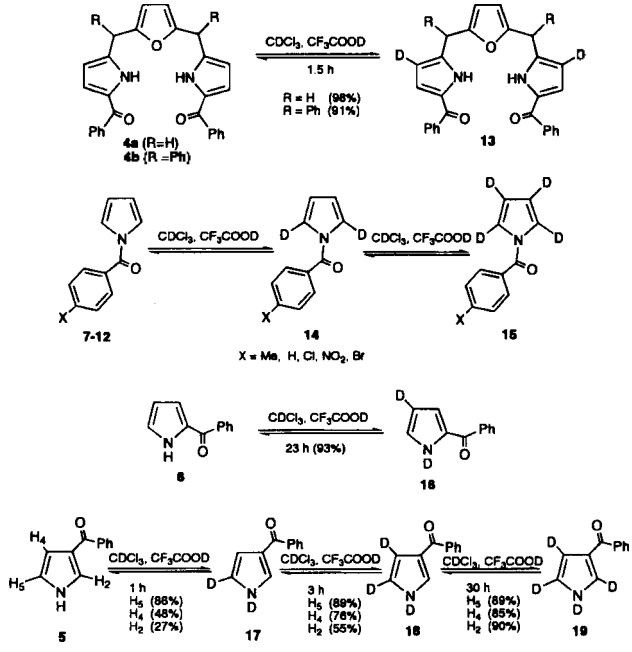
Scheme 1.



Scheme 2.

treated with 1.4 equivalent of benzoyl chlorides to afford 1, 14-bisacylated 16-oxatripyrromethane (**4**). The reaction usually gave a mixture of the mono-acylated and bis-acylated products. But compound (**4**) was usually the major product under the condition attempted. 3-Benzoylpyrrole (**5**) was easily synthesized from the Friedel-Craft acylation of N-benzenesulfonyl pyrrole and consequent desulfonylation.[11,12] 2-Benzoylpyrrole (**6**) could be synthesized from direct acylation of pyrrole[13] in the presence of Lewis acid. N-Aroylpyrroles bearing various *para*-substituents (**7**)-(**12**) in the aromatics were synthesized as reported procedure.[14]

The kinetics of proton-deuterium exchange in pyrroles and substituted pyrroles in acidic media have been investigated previously using NMR method.[15] The protonation in the pyrrole was reported to occurr both α- and β-positions of the ratio of 0.41/1.00 in this studies. Similar kinetic studies of deuterium exchange of 1-methyl pyrrole also have been investigated[16] and the results had shown that exchange was faster at β-position even though α-protonation was thermodynamically favorable in strong acid (D_2SO_4). The exchange at the α-position was rapid in weakly acidic media on the other hand. The electron donating substituents in the pyrrole ring usually induce higher reactivity toward electrophile. Although the kinetic studies have been done some extend, site selective deuterium exchange of the pyrroles bearing different substituents in various position has not been studied in detail. With these regards, we report the kinetic studies of site-selective deuterium exchange in the substituted pyrrole. The rates of proton-deuterium exchange were followed by proton NMR in deuterated chloroform in the presence of excess amount (30 equivalents) of TFA-d (trifluoroacetic acid-d) at the probe temperature. As shown in Scheme 3, treatment of (**4**) with 30 equivalents of TFA-d in $CDCl_3$ led to the exchange of the 3-proton, 12-proton and N-H protons. We found that 85% of protons are exchanged with deuteriums within 1.5 hr period. The partially deuterated 1,14-bisacyl-16-oxatripyrromethane (**4**) can be reprotonated upon exposure to normal TFA which is indicating reversible nature of the reaction. Both β-positions in the pyrrole would be equally reactive toward exchange in (**3**). But the presence of electron withdrawing acyl group causes exchange to occur exclusively at the 3,12-positions



Scheme 3.

in the 1,14-bisacylated compounds such as (**1**) and (**4**).

The similar trend was observed when 2-benzoylpyrrole (**6**) was treated with excess TFA-d. But it requires longer reaction time (~23 h) to accomplish over 93% of net exchange. In the case of N-aroylpyrroles (**7**)-(**12**), the exchange rate was varied with different para-substituents in the aromatic. For example, 89% of α-protons exchanges within 3 h in p-methoxybenzoylpyrrole (**10**) and takes longer time to accomplish upto 75% of exchange of 3-protons as shown in Scheme 3. The exchange rates are significantly varied depending on the *para*-substituents in aroyl group. As shown in Figure 1, the pseudo first order rate constants in the exchange of α-protons are significantly decreasing with different N-substituents in the pyrrole nitrogen. The observed exchange rate must be average of two α-protons and no mono-deuterated compounds were observed within the experimental time scale. The electronic effects of the substituents from *para*-nitro to *para*-methoxy group exhibit good correlation.

The observed rate constant for the exchange on p-nitrobenzoylpyrrole was 0.002/min. and 0.02/min. for the p-methoxybenzoylpyrrole respectively. The observed rate for the exchange of β-protons on p-chlorobenzoylpyrrole was 0.003/min. while that for the *para*-methoxybenzoylpyrrole was 0.0023/min. Thus the rates of exchange for the α-protons are very sensitive to the substituents but those of β-protons are relatively insensitive to the substituents. When N-benzoylpyrrole was used as substrate in the exchange experiment, all the protons in the pyrrole has been exchanged with deuterium within 1-2 min. This result is well agreed with the fact that alkyl substituents increase the reactivity of pyrrole toward electrophiles. 3-Benzoylpyrrole on the other hand showed interesting reactivity. As shown in Scheme 3, 86% of 5-proton had exchanged in 1 hr, 4-proton in 3 hr and 2-proton was exchanged in 30 hr. This result indicates that the positional reactivity of 3-benzoylpyrrole is 5 > 4 > 2

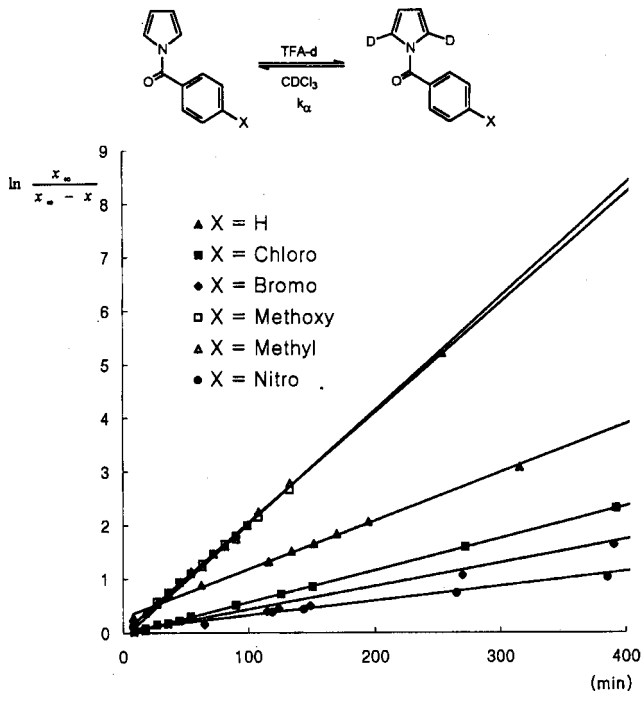


Figure 1. Plot of pseudo first order rate constant for the exchange of N-aroylpyrroles having various *para*-substituents in aryl group.

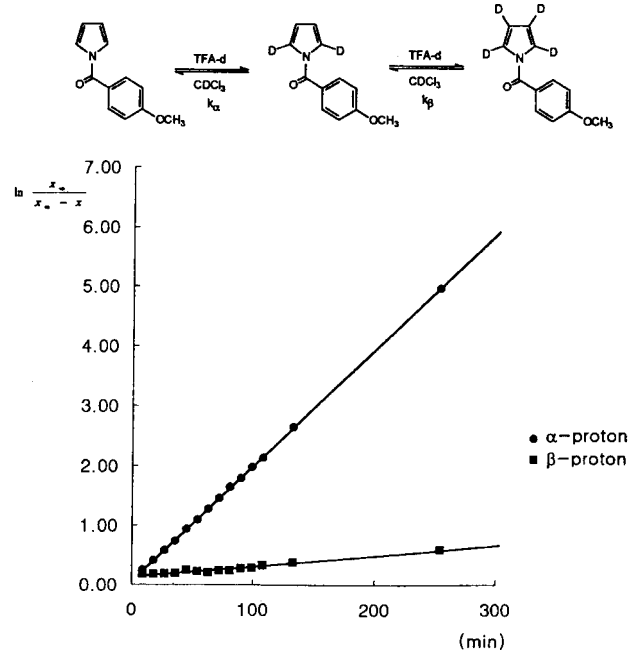


Figure 2. Plot of pseudo first order rate constant for the exchange rate of α (dot) and β (square) proton of N-(p-bromobenzoyl)pyrrole.

toward electrophiles. When the deuterium exchange experiment was performed with 2-benzoylpyrrole, only 4-proton was exchanged on the other hand and 3- and 5-protons were not exchanged regardless the reaction time and were intact after more than 48 hr. Same trend of exchange pattern was observed when the exchange was carried out with

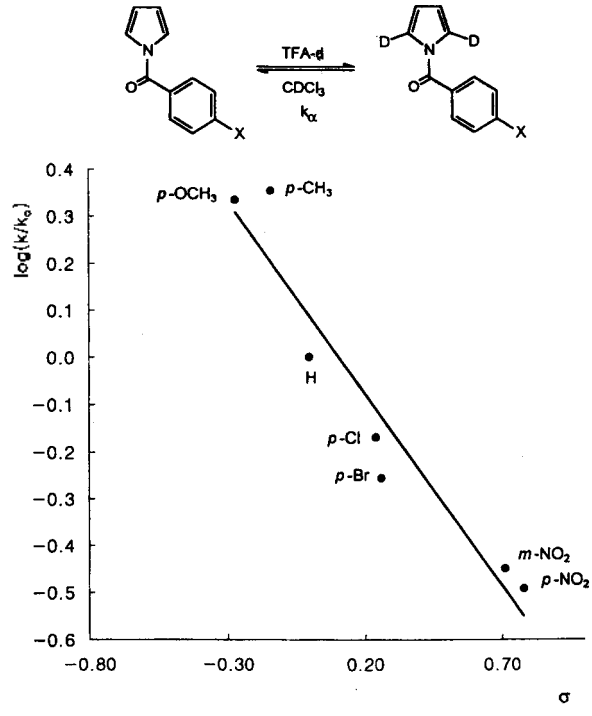
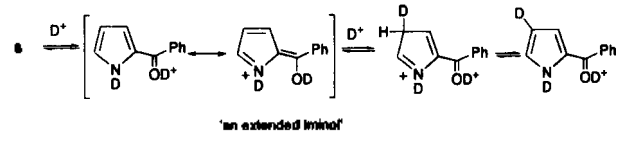


Figure 3. Hammett plot for the a-proton exchange in N-aroylpyrrole.

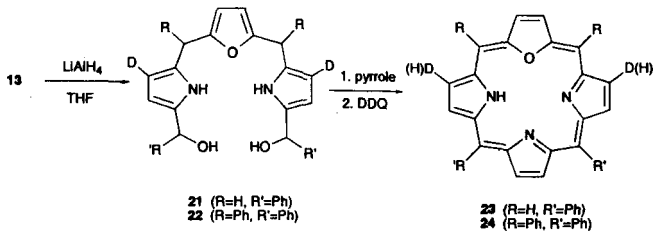
1,14-bisbenzoyl-16-oxatripyrromethane (**4a, 4b**). The results indicate that the most nucleophilic site in 3-benzoylpyrrole is 5-position and 4-position in 2-benzoylpyrrole. *Meta*-position from the carbonyl function is most reactive toward electrophile in 2-benzoylpyrrole. The fact that deuterated 2-benzoylpyrrole can be re-protonated upon exposure to trifluoroacetic acid is good indication of reversible nature of the exchange reaction.

Hammett plot for the exchange rate with σ value show fair linear relationship with the slope of −0.81 (Figure 3). This result indicates that slightly positive charge is developing in the reaction center and the substituents on the benzoyl group influence the exchange rates electronically. As shown in Scheme 4, the site-selective exchange can be viewed as involving resonance of the extended iminol form which could allow the extended conjugation of the two aromatics each other. Thus, the most probable position for the protonation should be meta from the carbonyl function.[9]

Attempted synthesis of the partially deuterated porphyrin by condensing carbonyl-reduced (**13**) with pyrrole in the presence of acid catalyst seems to result in re-exchange of most deuterium with protium. Deuterated 1,14-bisacyl compounds (**13**) was quantitatively reduced to corresponding diols (**21, 22**) with $LiAlH_4$ in THF and the condensation of diols with pyrrole in the presence of acid catalyst afforded



Scheme 4.



Scheme 5.

porphyrins (**23, 24**). The proton NMR spectrum of the porphyrin (**23**) shows re-exchange of most deuterium in the β-pyrrolic region with protium. The integration of 1 and 14-pyrrolic protons after condensation were just ~10% less than those of 2- and 12-protons indicating only 10% of deuterium is intact. Mass spectral analysis show molecular ion peak corresponding to two deuterium attached in the products.

The results obtained with this studies indicates that partially deuterated tripyrranes such as (**21**) and (**22**) is not good precursor in the synthesis of corresponding partially deuterated porphyrins. But partially deuterated dipyrromethanes could be used in the synthesis of corresponding partially deuterated porphyrins under carefully controlled condition. In conclusion, Deuterium enriched porphyrins at β-pyrrolic carbon with two or three different *meso*-substituents can be synthesized regioselectively. The synthesis utilizes the condensation of 3,7-dideuterated-1,9-bisacylated dipyrromethanes and 1,9-unsubstituted dipyrromethanes. This synthetic methodology will have variety of utilities in conjunction with a synthetic method toward isotopically labeled porphyrins. In order to establish their generality and exploit them for the preparation of deuterated porphyrin building blocks, wide applicable approaches are under investigation.

Experimental

Absorption spectra (Kontron 941 and Hitachi U-3200) were collected routinely. Mass spectra were obtained by electron impact or FAB. Column chromatography was performed on silica (Merck, 230-400 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. All other reagents were obtained from Aldrich unless noted otherwise. The kinetic studies were performed using Bruker AM-400 NMR spectrometer at probe temperature. The rate constants were obtained by monitoring the disappearance of a signal at known ppm. The pseudo first order rate constants were calculated from the equation $\ln (A_t-A_\infty/A_{inf}-A_t)=\exp(-kt)$. 2-Benzoly pyrrole,[13] N-aroyl pyrroles[14] and 1,14-bisbenzoyl-16-oxatripyrromethane[10b] were synthesized as reported.

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